BERKELEY TECHNOLOGY LAW JOURNAL

VOLUME 39, SPECIAL ISSUE

LIFE SCIENCES INNOVATION CASE STUDY

2024

Pages

345–680

Production: Produced by members of the *Berkeley Technology Law Journal.* All editing and layout done using Microsoft Word.

Printer: Joe Christensen, Inc., Lincoln, Nebraska.
Printed in the U.S.A.
The paper used in this publication meets the minimum requirements of American National Standard for Information Sciences—Permanence of Paper for Library Materials, ANSI Z39.48—1984.

Berkeley Technology Law Journal
University of California
School of Law
3 Law Building
Berkeley, California 94720-7200
editor@btlj.org
https://www.btlj.org

BERKELEY TECHNOLOGY LAW JOURNAL

VOLUME 39 SPECIAL ISSUE 2024

ARTICLES

SUBSCRIBER INFORMATION

The *Berkeley Technology Law Journal* (ISSN1086-3818), a continuation of the *High Technology Law Journal* effective Volume 11, is edited by the students of the University of California, Berkeley, School of Law and is published in print three times each year (March, September, December), with a fourth issue published online only (July), by the Regents of the University of California, Berkeley. Periodicals Postage Rate Paid at Berkeley, CA 94704-9998, and at additional mailing offices. POSTMASTER: Send address changes to Journal Publications, Law Library, LL123 South Addition, Berkeley Law, University of California, Berkeley, Berkeley, CA 94720-7210.

Correspondence. Address all correspondence regarding subscriptions, address changes, claims for non-receipt, single copies, advertising, and permission to reprint to Journal Publications, Law Library, LL123 South Addition, Berkeley Law, University of California, Berkeley, Berkeley, CA 94720-7210; (510) 643-6600; JournalPublications@law.berkeley.edu. *Authors*: see section titled Information for Authors.

Subscriptions. Annual subscriptions are $65.00 for individuals and $85.00 for organizations. Single issues are $30.00. Please allow two months for receipt of the first issue. Payment may be made by check, international money order, or credit card (MasterCard/Visa). Domestic claims for non-receipt of issues should be made within 90 days of the month of publication; overseas claims should be made within 180 days. Thereafter, the regular back issue rate ($30.00) will be charged for replacement. Overseas delivery is not guaranteed.

Form. The text and citations in the *Journal* conform generally to THE CHICAGO MANUAL OF STYLE (16th ed. 2010) and to THE BLUEBOOK: A UNIFORM SYSTEM OF CITATION (Columbia Law Review Ass'n et al. eds., 21st ed. 2020). Please cite this issue of the *Berkeley Technology Law Journal* as 39 BERKELEY TECH. L.J. ___ (2024).

BTLJ ONLINE

The full text and abstracts of many previously published *Berkeley Technology Law Journal* articles can be found at https://www.btlj.org. Our site also contains a cumulative index; general information about the *Journal*; the *BTLJ Blog*, a collection of short comments and updates about new developments in law and technology written by BTLJ members; and *BTLJ Commentaries*, an exclusively online publication for pieces that are especially time-sensitive and shorter than typical law review articles.

INFORMATION FOR AUTHORS

The Editorial Board of the *Berkeley Technology Law Journal* invites the submission of unsolicited manuscripts. Submissions may include previously unpublished articles, essays, book reviews, case notes, or comments concerning any aspect of the relationship between technology and the law. If any portion of a manuscript has been previously published, the author should so indicate.

Format. Submissions are accepted in electronic format through Scholastica online submission system. Authors should include a curriculum vitae and resume when submitting articles, including his or her full name, credentials, degrees earned, academic or professional affiliations, and citations to all previously published legal articles. The Scholastica submission website can be found at https://btlj.scholasticahq.com/for-authors.

Citations. All citations should conform to THE BLUEBOOK: A UNIFORM SYSTEM OF CITATION (Columbia Law Review Ass'n et al. eds., 21st ed. 2020).

Copyrighted Material. If a manuscript contains any copyrighted table, chart, graph, illustration, photograph, or more than eight lines of text, the author must obtain written permission from the copyright holder for use of the material.

SPONSORS
2023–24

The *Berkeley Technology Law Journal* and the Berkeley Center for Law & Technology acknowledge the following generous sponsors of Berkeley Law's Law and Technology Program:

ALLEN & OVERY LLP

ARENTFOX SCHIFF LLP

AXINN, VELTROP & HARKRIDER LLP

BAKER BOTTS L.L.P.

CHARLES RIVER ASSOCIATES

COOLEY LLP

CORNERSTONE RESEARCH

COVINGTON & BURLING LLP

CROWELL & MORING LLP

DESMARAIS LLP

DLA PIPER

DURIE TANGRI LLP

FENWICK & WEST LLP

FISH & RICHARDSON P.C.

GENENTECH, INC.

GEN LAW FIRM

GIBSON, DUNN & CRUTCHER LLP

GILEAD SCIENCES, INC.

GOODWIN PROCTER LLP

GREENBERG TRAURIG, LLP

GTC LAW GROUP PC

HAYNES AND BOONE, LLP

HOGAN LOVELLS

IRELL & MANELLA LLP

JINGTIAN & GONGCHENG

JONES DAY

KEKER, VAN NEST & PETERS LLP

KILPATRICK TOWNSEND & STOCKTON LLP

KING & SPALDING LLP

KING & WOOD MALLESONS

SPONSORS
2023–24

KIRKLAND & ELLIS LLP

KNOBBE MARTENS

LATHAM & WATKINS LLP

MARKS & CLERK

MCDERMOTT WILL & EMERY

MICROSOFT

MORGAN, LEWIS & BOCKIUS LLP

MORRISON & FOERSTER LLP

MUNGER, TOLLES & OLSEN LLP

OCEAN TOMO

ORRICK HERRINGTON & SUTCLIFFE LLP

PAUL HASTINGS, LLP

QUALCOMM TECHNOLOGIES, INC.

QUINN EMANUEL URQUHART & SULLIVAN, LLP

ROBINS KAPLAN LLP

ROPES & GRAY LLP

SIDLEY AUSTIN LLP

TENSEGRITY LAW GROUP LLP

VAN PELT, YI & JAMES LLP

VIA LICENSING CORPORATION

WANHUIDA INTELLECTUAL PROPERTY

WEIL, GOTSHAL & MANGES LLP

WESTERN DIGITAL CORPORATION

WHITE & CASE LLP

WILMER CUTLER PICKERING HALE AND DORR LLP

WILSON SONSINI GOODRICH & ROSATI

WINSTON & STRAWN LLP

WOMBLE BOND DICKINSON

BOARD OF EDITORS
2023–24

Executive Board

BOARD OF EDITORS
2023–24

Editorial Board

Articles Editors

GULNUR BEKMUKHANBETOVA
XUEJIAO CAO
ALEX CHOI
MICHELLE D'SOUZA
GARIMA KEDIA
JOSHUA KUHN
SARAH LUNT
MARLEY MACAREWICH
JOSH MIMURA
BANI SAPRA
SANDEEP STANLEY
NICOLE ZEINSTRA

Notes & Comments Editor
NINA ZHANG

Student Publication Editors
MAYA DARROW
JOHN MOORE

Submissions Editors
WILLY ANDERSON
JENNIFER CHENG
VERNON ESPINOZA VALENZUELA
HYEMI PARK

Technical Editors
ASHLEY FAN
EDLENE MIGUEL
BEN PEARCE
ANDREW STONE
CARESSA TSAI

Alumni Relations Editor
EMMA BURKE

External Relations Editor
HUNTER KOLON

Member Relations Editors
JAEYOUNG CHOI
CYRUS KUSHA

Podcast Editors
ERIC AHERN
JULIETTE DRAPER
MEGHAN O'NEILL

Symposium Editors
MARIT BJÖRNLUND
NICOLE BOUCHER

Life Sciences Articles Editors
TIM DABROWSKI
DUANE YOO

Web & Technology Editors
EMILY WELSCH
LISA YOUNES

Production Editors
BEN CLIFNER
SARAH DAVIDSON
KELSEY EDWARDS
LAUREL MCGRANE

LLM Editor
FERNANDA GONZAGA

MEMBERSHIP
2023–24

Members

SANSKRITI AGARWAL	AYESHA AHUJA	NOOSHA ALIABADI
REEM ALMUAITHER	AYESHA ASAD	AISHWARYA ATHAVALE
CEREN AYTEKIN	DAVID BERNSTEIN	HANNAH BORROWS
OSMANE CAILLEMER	ALYSON CHIE	ANGELA CHUNG
WILLIAM CIEL	SKYLAR CUSHING	EVELINA DASH
HALA EL SOLH	IMAN ESLAMI	PAYTON FONG
MAX FRIEND	DAN GRUSHKEVICH	ANANT GUPTA
RUI HAN	ANNIKA HANSEN	MARIA HARRAST
ANGELA HERBOSA	MENGRUO HUANG	ROGER HUANG
NAMAMI JAIN	MONICA JEUNG	CORINNE JOHNSTON
YASAMEEN JOULAEE	AARON KAMATH	NAT KAVALER
SRISHTI KHEMKA	TYLER KOTCHMAN	DHANYA SETLUR KRISHNAN
JOSEPH KYBURZ	JOSHUA LEE	KARISSA LIN
WANYI LIN	WENHUI LIU	LILLY MAXFIELD
MAXWELL MELNIK	MARIA MILEKHINA	AUDREY MITCHELL

MEMBERSHIP
2023–24

Members (continued)

LEA MOUSTAKAS	GRACE MURPHY	SAIAISWARYA NAGENDARA
NIYATI NARANG	NICHOLAS NAVARRO	TUONG-VI NGUYEN
ANTONY NOVAK	NADIA ORCHID GHAFFARI	ALLEN PARK
YUNFEI QIANG	DEVANGINI RAI	UDAYVIR RANA
SANIDHYA RAO	EMILY REHMET	KARINA SANCHEZ
ABBY SANDERS	JULIAN SANGHVI	PRIYADARSINI SHANMUGAM
GAYATHRI SINDHU	ANKUR SINGHAL	MATT SIOSON
SARAH SISNEY	HAILEY STEWART	LORENZ STRUB
LESLEY SUN	AMANDA SUZUKI	TRISTAN THREATT
ERIC TING	ITAI TISMANZKY	AYA TOYA
SIMON WAGNER	JESSE WANG	SOPHIA WANG
TIANA WANG	XINRUI WANG	DANIEL WARNER
TIANQI WEI	ETHAN WISEMAN	PAUL WOOD
LUCAS WU	TWINKLE YE	LISA YOUNES
VINCENT ZHAI	TERRY ZHAO	FAYE ZOU

BERKELEY CENTER FOR LAW & TECHNOLOGY
2023–24

WAYNE STACY
Executive Director

Staff

ALLISON SCHMITT
Director, BCLT Life Sciences Law & Policy Center and Senior Fellow

JANN DUDLEY
Associate Director

RICHARD FISK
Assistant Director, Events & Communications

JUSTIN TRI DO
Media Coordinator

ABRIL DELGADO
Events Specialist

ALEXIS GOETT
Office Administrator

Fellow

RAMYA CHANDRASEKHAR
Biometric Regulatory Fellow

YUAN HAO
Senior Fellow

KATHRYN HASHIMOTO
Copyright Law Fellow

MIRIAM KIM
Practitioner Fellow, Generative AI

ROBERT BARR
BCLT Executive Director Emeritus

BERKELEY CENTER FOR LAW & TECHNOLOGY
2023–24

Faculty Directors

KENNETH A. BAMBERGER
Rosalinde and Arthur Gilbert Foundation Professor of Law

ELENA CHACHKO
Assistant Professor of Law

COLLEEN CHIEN
Professor of Law

CATHERINE CRUMP
Director, Samuelson Law, Technology & Public Policy Clinic and Clinical Professor of Law

CATHERINE FISK
Barbara Nachtrieb Armstrong Professor of Law

CHRIS JAY HOOFNAGLE
Professor of Law in Residence

SONIA KATYAL
Roger J. Traynor Distinguished Professor of Law

ORIN S. KERR
William G. Simon Professor of Law

PETER S. MENELL
Koret Professor of Law

ROBERT P. MERGES
Wilson Sonsini Goodrich & Rosati Professor of Law

DEIRDRE K. MULLIGAN
Professor in the School of Information and School of Law

TEJAS N. NARECHANIA
Robert and Nanci Corson Assistant Professor of Law

BRANDIE NONNECKE
Associate Research Professor at the Goldman School of Public Policy

OSAGIE K. OBASOGIE
Haas Distinguished Chair and Professor of Law

ANDREA ROTH
Professor of Law

PAMELA SAMUELSON
Richard M. Sherman Distinguished Professor of Law and Information

PAUL SCHWARTZ
Jefferson E. Peyser Professor of Law

ERIK STALLMAN
Associate Director, Samuelson Law, Technology & Public Policy Clinic and Assistant Clinical Professor

JENNIFER M. URBAN
Director, Samuelson Law, Technology & Public Policy Clinic and Clinical Professor of Law

MOLLY SHAFFER VAN HOUWELING
Harold C. Hohbach Distinguished Professor of Patent and IP Law

REBECCA WEXLER
Assistant Professor of Law

INTRODUCING THE LIFE SCIENCES INNOVATION CASE STUDY PROJECT

Allison A. Schmitt[†]

ABSTRACT

This Issue of the *Berkeley Technology Law Journal* presents the results from an ambitious and broad pilot study of the institutions, funders, patent, and regulatory regimes that shape biomedical innovation. This study relies on a comparative analysis of real-world case study examples of breakthrough inventions in the life sciences ecosystem to facilitate evidence-based policy recommendations for allocation of scarce IP, regulatory, and funding resources grounded in real life sciences inventive pathways.

Over the 2022–23 academic year, students enrolled in Berkeley Law's Life Sciences & Innovation Workshop drafted the five case studies published in this Issue. The case studies range from small-molecule therapeutics (Lyrica, Truvada, and Spravato) to biological products (Yescarta) and platform technologies (next-generation sequencing). In each case study, the author examined the scientific background, development history, and innovation "drivers" and "impediments" that led to successful commercialization of the invention.

This Article describes the methodology used to develop each case study and provides key comparative insights on the innovation drivers and impediments most critical to successful commercialization for these examples. Even at this preliminary stage of the project, the case studies highlight the importance of early-stage serendipitous discovery and the key role of the Bayh-Dole Act in facilitating later-stage commercialization efforts—whether through startup companies or large pharmaceutical companies. The case studies also illustrate the incentive structures that IP rights create for manufacturers and the important role of the U.S. regulatory framework in shaping innovation. And several case studies highlight ethical, moral, and political considerations that helped to develop environments conducive to scientific research. Expanding the case study universe in future work will lead to further development of the evidence-based policies and resource allocations offered here—and identification of additional policies to advance life science innovation.

DOI: https://doi.org/10.15779/Z384B2X61J

† Fellow, Berkeley Law; Director, Berkeley Center for Law & Technology's Life Sciences Law & Policy Center. This Article benefitted from thoughtful feedback from Tim Dabrowski, D. Shayon Ghosh, Vincent Joralemon, William P. Kasper, Peter S. Menell, Christine R. O'Brien Laramy, Caressa N. Tsai, Yuhan Wu, Duane Yoo, and Kaidi (Ted) Zhang, and from research support from Vincent Joralemon, William P. Kasper, Christine R. O'Brien Laramy, Allyson Malecha, Nayan Pallegar, Caressa N. Tsai, Yuhan Wu, Andrea Zachrich, and Kaidi (Ted) Zhang. The contributions of each member of the 2022–23 Berkeley Law Life Sciences & Innovation Workshop class to the course and project were essential to the pilot project's success. Finally, this Article, Issue, and project would not have been possible without the collaboration and support of Peter S. Menell, the Berkeley Center for Law & Technology, and the *Berkeley Technology Law Journal*.

TABLE OF CONTENTS

I. INTRODUCTION

In recent years, the life sciences sector has generated a multitude of remarkable inventions (gene editing, personalized medicine applications, and immunological cancer therapeutics, among countless others) with inestimable societal value. Life sciences inventions differ from other scientific inventions for several reasons. First, these inventions often save lives, or at least significantly impact patients' quality of life—the importance of these inventions to society cannot be overestimated. Second, these inventions typically require significant research and development (R&D) investment well in advance of any recoupment via sales of a commercialized product (although the overall costs of such R&D are a subject of considerable debate).[1] Third, these inventions have a high rate of failure; only a small percentage of potential therapeutics, platform technologies, or diagnostics identified in early-stage research ever make it to market.[2]

Society's understanding of the various factors that drive and impede life sciences breakthroughs has not kept pace with the rapid progress in developing new life sciences inventions or understanding the scientific principles that make those inventions work. Significant investment from scarce public and private resources (in the form of funding, labor, intellectual property (IP) rights, regulatory exclusivities, and more) flows to individuals and companies innovating in this sector. But currently available economic and policy analysis tools have not allowed for optimally calibrated distribution of these resources to maximize innovative activities in this sector at the lowest possible social cost.

Calibrating innovative investment levels is difficult, given the number and complexity of the interactions between the various innovation policy levers,

1. *Compare, e.g.*, Joseph A. DiMasi, Henry G. Grabowski & Ronald W. Hansen, *Innovation in the Pharmaceutical Industry: Estimates of R&D Costs*, 47 J. HEALTH. ECON. 20, 23–27 (2016) (estimating clinical trial costs per new approved drug at $965 million in 2013 dollars, and overall R&D costs at $1.395 billion per new approved drug) *with* Thomas J. Moore, Hanzhe Zhang, Gerard Anderson, & G. Caleb Alexander, *Estimated Costs of Pivotal Trials for Novel Therapeutic Agents Approved by the US Food and Drug Administration, 2015-2016*, 178 JAMA INTERN MED. 1451, 1451–57 (2018) (estimating costs from pivotal efficacy trials supporting FDA approval of new drugs from 2015–16 as $19.0 million (median cost)).

2. *See, e.g.*, DELOITTE, EARLY VALUE ASSESSMENT 2 (2020), https://www2.deloitte.com/content/dam/Deloitte/be/Documents/life-sciences-health-care/Deloitte%20Belgium_Early%20Value%20Assessment.pdf (estimating that for every 5,000 to 10,000 compounds that enter the development pipeline, only one compound will eventually receive FDA approval; explaining that "medicines that reach clinical trials only have a 16% chance of being [FDA] approved").

entities, and processes required to develop new inventions in the life sciences space. A non-exhaustive list of these levers, entities, and processes includes:

- University- and government-based research (and the key role of privatization of that research towards commercialization);
- Use and availability of the IP regimes most commonly used by life science innovators (patents and trade secrets);
- Funding sources, including government grants, philanthropic support, and later-stage investments (through venture capital, private equity, and large pharmaceutical and biotechnology companies);
- The medical profession's key role in fostering these inventions, including clinician engagement in clinical testing and prescribing processes;
- Regulation of eligible products through clinical testing, standard regulatory approval, and accelerated regulatory approval mechanisms; and
- The insurance approval and reimbursement regimes.

The optimal role for each of these features of the life sciences ecosystem is the subject of heated debate, fueled by the significant upfront investment required to bring life sciences inventions to market (and the business risk that such investment entails). Scholars, practitioners, government officials, and life sciences companies extensively dispute the proper role of innovation levers like IP protection and regulatory exclusivity in fostering life sciences innovation.

For example, in the past sixty years, patent exclusivity in the pharmaceutical and biotechnology industries has been the subject of significant debate and study.[3] Pharmaceutical and biotechnology companies (and many policymakers) assert a need for patent exclusivity to recover R&D costs, including for human clinical trials to obtain marketing approval.[4] But others criticize the extensive use of patents in the pharmaceutical and

3. *See, e.g.*, Sam F. Halabi, *The Drug Repurposing Ecosystem: Intellectual Property Incentives, Market Exclusivity, and the Future of "New" Medicines*, 20 YALE L.J. & TECH. 1, 6–23 (2018); Arti K. Rai, *Fostering Cumulative Innovation in the Biopharmaceutical Industry: The Role of Patents and Antitrust*, 16 BERKELEY TECH. L.J. 813, 828–29 (2001); Heidi L. Williams, *How Do Patents Affect Research Investments?*, 9 ANN. REV. ECON. 441, 441–69 (2017). *See generally* Fritz Machlup, *An Economic Review of the Patent System*, Study No. 15, Subcomm. on Patents, Trademarks, and Copyrights of the Senate Committee on the Judiciary, 85th Cong. 2d Sess. 1 (1958); Keith E. Maskus, *Intellectual Property Rights and Economic Development*, 32 CASE W. RES. J. INT'L L. 471 (2000); Keith E. Maskus, Sahar Milani & Rebecca Neumann, *The Impact of Patent Protection and Financial Development on Industrial R&D*, 48 RES. POLICY 355 (2019).

4. *See, e.g.*, Arti K. Rai, *Fostering Cumulative Innovation in the Biopharmaceutical Industry: The Role of Patents and Antitrust*, 16 BERKELEY TECH. L.J. 813, 828–29 (2001).

biotechnology industries. They argue patents increase the price of new drugs during the exclusivity term,[5] clog cumulative innovation, and hinder collaboration (the "tragedy of the anticommons").[6]

Many scholars have commented on the failure of previous work to elucidate an optimal allocation of the scarce IP, regulatory exclusivity, and government and private funding resources that maximizes innovation across the life sciences ecosystem.[7] Challenges in collecting comparative, broad, empirical data studying the impacts of the IP and regulatory systems on the life sciences innovation ecosystem (and the wider economy) hinder this analysis and policymaking.[8] A complicating factor is that life sciences companies often generate the relevant data (e.g., expenses incurred as part of research and development efforts), but treat it as proprietary.

Policymakers and stakeholders require a new approach to answer these complex, ecosystem-wide questions. Effective policymaking to maximize breakthroughs requires a detailed, holistic, and evidence-based understanding of life sciences' regulatory, IP, and funding systems and how they relate. This understanding can only flow from non-politicized data focused on actual life sciences inventive pathways, where the data derives from actual life science invention processes.

This Article and Issue of the *Berkeley Technology Law Journal* present an ambitious new methodology to study the institutions, funders, patent and regulatory regimes impacting innovation of biomedical products and techniques. The methodology relies on real-world case study examples of breakthrough inventions in the life sciences space. The Issue presents results from a pilot study of this methodology designed to study the complex ecosystem of life sciences innovation drivers. Allison A. Schmitt (Berkeley Law Fellow and Director of the Berkeley Center for Law & Technology's Life Sciences Law & Policy Center) and Professor Peter S. Menell at Berkeley Law (together, "study project leaders") developed this approach and initiated its implementation in the Berkeley Law Life Sciences & Innovation Workshop ("LSI Workshop") course held during the 2022–23 academic year.

5. *See, e.g.*, I-MAK, OVERPATENTED, OVERPRICED: HOW EXCESSIVE PATENTING IS EXTENDING MONOPOLIES AND DRIVING UP DRUG PRICES (2022), https://www.i-mak.org/wp-content/uploads/2023/01/Overpatented-Overpriced-2023-01-24.pdf; *see also* Robin Feldman, *May Your Drug Price be Evergreen*, J.L. BIOSCIENCES 590 (2018).

6. *See, e.g.*, Michael A. Heller & Rebecca S. Eisenberg, *Can Patents Deter Innovation? The Anticommons in Biomedical Research*, 280 SCI. 698, 698–99 (1998).

7. *See, e.g.*, JOHN R. THOMAS, MARCH-IN RIGHTS UNDER THE BAYH-DOLE ACT 3–5 (2016); Williams, *supra* note 3.

8. *See, e.g.*, THOMAS, *supra* note7; Williams, *supra* note 3.

Following this Article, the Issue includes five case study Articles drafted by Berkeley J.D. and Ph.D. students who participated in the LSI Workshop. Each case study Article serves as a single data point in which the author explores the scientific background, development history, and innovation "drivers" and "impediments" underpinning successful commercialization of the invention. Part II of this Article describes the methodology in more detail, and Part III provides a summary of the five case study Articles included in the Issue.

Part IV of this Article provides an initial analysis from the comparative case study methodology to demonstrate its effectiveness in tackling the largest and most pressing questions facing lawmakers, administrators, and others engaged in life sciences policymaking. Comparison across the disparate case studies reveals common innovation drivers and impediments. These conclusions provide real world evidence-based policy recommendations to incentivize life sciences innovation and to tailor various exclusivities (IP, regulatory) to optimize the use of scarce resources such as public funding.

Comparisons across the first set of case studies reveal several initial lessons. For example, the case studies emphasize the importance of serendipitous discovery during early-stage research at universities and research institutions. Each case study also reflected the importance of the Bayh-Dole Act (or similar mechanisms) to facilitate later-stage commercialization through privatization of early-stage, university-based research efforts. Multiple case studies demonstrated the significant role that life sciences startup companies play in fostering breakthrough innovation to commercialization. Additionally, manufacturers viewed IP rights as important (perhaps even critical) incentives for commercialization efforts. Several case studies emphasized the important role of accelerated regulatory approval mechanisms, regulatory exclusivity, and shortened clinical trial processes to incentivize development of eligible pharmaceutical products. One case study highlighted the challenges arising from U.S. Food and Drug Administration (FDA) approval as a prerequisite to insurance reimbursements. Finally, ethical, moral, and political considerations impacted innovation in several case studies—in particular, patient advocacy can play a crucial role in overcoming barriers to innovation like disease stigma, therein helping to develop environments conducive to scientific R&D.

II. COMPARATIVE CASE STUDIES: A NOVEL METHODOLOGY FOR STUDYING LIFE SCIENCES INNOVATION

Part II of this Article introduces the case study methodology underlying the pilot study presented in this Issue. Section II.A explains the advantages of

a comparative case study approach for studying the complex life sciences space. This approach offers an evidence-based method for detailed examination of successful innovation pathways to develop policy recommendations based on real world evidence. Section II.B provides a brief historical background for the case studies. Section II.C explains the methodology beyond the comparative case study approach, including a detailed framework of innovation drivers, impediments, and inquiries. Section II.D explains the initial implementation of the new comparative case study methodology as part of a new year-long course at Berkeley Law.

A. WHY COMPARATIVE CASE STUDIES?

This Issue describes the development of a comparative case study framework, intended to span the wide range of life sciences innovations. Under this approach, study project leaders and authors identify life sciences breakthroughs and inventions representative of common life sciences development pathways (e.g., certain small molecule drugs, biologic drugs, and medical devices). Authors then engage in a "deep dive" exploration of the invention's development history to identify key innovation "drivers" (factors that promoted successful innovation) and "impediments" (factors that impeded successful innovation, or factors that required the inventors to detour from their original innovation plan). Eventually, with a large enough number of case studies, this method will allow scholars and policymakers to compare innovation drivers and impediments across a wide range of life sciences inventions to draw system-wide insights and recommendations to promote innovation in this complex space.

This methodology takes inspiration from the Nobel Prize-winning work of Elinor Ostrom and her collaborators.[9] Ostrom's work tackled a problem of similar complexity (water resource management) to understand the governance of finite, common-pool resources.[10] Ostrom successfully used hundreds of case studies to map a broad and complex system. This methodology similarly draws from diverse case studies to map the life sciences innovation ecosystem.

Analyzing diverse case studies spanning a wide range of the life sciences ecosystem (pharmaceuticals including small molecule and biologic compounds, platform technologies, diagnostics, etc.) will reveal patterns in

9. Ostrom was awarded the Nobel Prize in Economic Sciences in 2009 "for her analysis of economic governance, especially the commons." *Elinor Ostrom*, NOBEL PRIZE, https://www.nobelprize.org/prizes/economic-sciences/2009/ostrom/facts/ (last visited Jan. 13, 2024).

10. ELINOR OSTROM, GOVERNING THE COMMONS: THE EVOLUTION OF INSTITUTIONS FOR COLLECTIVE ACTION xi, xiv-xvi (1990).

breakthrough technology discovery, development, and commercialization. The case study method will generate data as to where and how scarce resources (IP, regulatory exclusivity and resources, funding, scientific talent and labor, etc.) flow for successful inventions.[11] This data should facilitate evidence-driven policy recommendations to strike the proper balance for use of IP, regulatory exclusivity, and funding sources in incentivizing breakthrough life sciences innovations.

The pilot case study project introduced in this Issue tested the proposed methodology to determine whether a broader project including more case studies would be feasible and produce useful data. Sections II.B and II.C *infra* further describe the methodology, and Section II.D *infra* describes the pilot project implementation through an innovative course at Berkeley Law.

B. FRAMING THE PILOT CASE STUDIES IN HISTORY

A key threshold question for the pilot study involved the proper historical timeframe for case study inventions. To provide the most useful data for current policymakers considering life sciences issues, this project examines case studies falling within the "modern" era of biomedical research and innovation, starting roughly in the late 1970s. This Section briefly describes several key factors and historical developments defining the "modern" era.

1. Rise of "Big Pharma": Historical Development of Modern Pharmaceutical Companies

In the mid- to late-nineteenth centuries, dyestuff and chemical companies established research laboratories to engage in chemical synthesis of potential drug products.[12] At the same time, many apothecaries began converting into wholesale drug companies.[13] These two changes corresponded to improvements in chemical and laboratory sciences, which permitted isolation of active ingredients,[14] study of the processes by which the human body

11. Eventually, we also contemplate that this methodology could be used to trace failed development projects in the life sciences space, and to better understand the impediments that prevented those inventions from reaching the market (and thus benefitting society).

12. *See, e.g.*, *Emergence of Pharmaceutical Science and Industry: 1870-1930*, CHEMICAL & ENG'G NEWS (June 20, 2005), https://cen.acs.org/articles/83/i25/EMERGENCE-PHARMACEUTICAL-SCIENCE-INDUSTRY-1870.html#:~:text=The%20modern%20pharmaceutical%20industry%20traces,medical%20applications%20for%20their%20products.

13. *See id.*

14. *See, e.g.*, Søren Brøgger Christensen, *Natural Products That Changed Society*, 9 BIOMEDICINES 472, 1, 7 (2021) (detailing isolation of quinine for malaria treatment in nineteenth century, and noting that from the nineteenth century to the modern era, complex

metabolizes drugs,[15] and chemical analysis of the isolated and synthesized products.[16]

After World War II, pharmaceutical companies in the United States, Europe, and Japan expanded rapidly, with major investments in research, development, and marketing.[17] These companies expanded their in-house R&D capacities significantly, while continuing to collaborate with academic researchers.[18] In the early to mid-twentieth century, scientists developed improved analytical techniques and instrumentation (for example, x-ray crystallography for structural determinations, and ultraviolet (UV) and infrared (IR) spectroscopy techniques for identification and purification). These improvements, along with improved synthetic techniques, allowed pharmaceutical companies to shift focus from isolation of natural products to modification of those products and, eventually, to purely synthetic manufacturing processes—the development of new molecules.[19]

American inventors patented very few active pharmaceutical ingredients in the eighteenth and nineteenth centuries.[20] Instead, the pharmaceutical industry

naturally occurring compounds such as taxol, codeine, vincristine, vinblastine, and quinine are typically isolated from biological material).

15. *See generally* A. Conti & M.H. Bickel, *History of Drug Metabolism: Discoveries of the Major Pathways in the 19th Century*, 6 DRUG METABOLISM REV. 1 (1977) (detailing the significant scientific work of 19th century scientists in understanding the human body's metabolic pathways).

16. *See, e.g.*, Curt Wentrup, *Origins of Organic Chemistry and Organic Synthesis*, 2022 EUR. J. ORG. CHEM. e202101492, 4–5, 8–9 (2022) (detailing progress on chemical analysis in the eighteenth and nineteenth centuries).

17. *See, e.g.*, *The Pharmaceutical Golden Era: 1930-60*, CHEMICAL & ENG'G NEWS (June 20, 2005), https://cen.acs.org/articles/83/i25/PHARMACEUTICAL-GOLDEN-ERA-193060.html.

18. *Id.*

19. *Id.*

20. Albert Wertheimer & Thomas Santella, *The History and Economics of Pharmaceutical Patents*, *in* 16 THE VALUE OF INNOVATION: IMPACT ON HEALTH, LIFE QUALITY, SAFETY, AND REGULATORY RESEARCH IN HUMAN CAPITAL AND DEVELOPMENT 101, 104 (2008) ("In fact, very few medicines between 1790 and 1906 were patented products (at least not as active ingredients).").

sold unregulated "patent medicines"[21] with dubious therapeutic properties.[22] Starting in the 1880s, however, some American drug manufacturers began to seek patents covering their pharmaceutical products. By the early 1950s, both pharmaceutical companies and the medical community supported the use of patents.[23] Pharmaceutical companies now routinely rely on patents to protect compositions (active ingredient and drug product), formulations, and methods of treatment for their therapeutic products.[24]

2. The Bayh-Dole Act and Privatization of University Research

To foster commercialization of federally-funded inventions developed by universities, small businesses, and other non-profits, Congress enacted the Bayh-Dole Act in 1980. Prior to the Bayh-Dole Act, the federal government typically required contractors (including inventors working at universities) to assign inventions made using government funding to the federal government. For the first time, the Bayh-Dole Act allowed inventors to receive patents for inventions developed with federal funds.[25] The government retains certain rights in these patents, including: (1) a non-exclusive, non-transferable, irrevocable, paid-up license; and (2) the potential for march-in rights, wherein the government can grant licenses to the technology in certain limited circumstances.[26]

The Bayh-Dole Act (in conjunction with similar regimes in other jurisdictions) has facilitated a robust process for the transfer of technology from universities, through university technology transfer offices, to private

21. The term "patent medicines" refers to non-prescription medicines marketed primarily based on a trade name, where the contents (oftentimes made of commonly available ingredients like vegetables extracts or alcohol) are not disclosed to the consumer. Patent medicines did not, in fact, rely on filing or issuance of U.S. patents (or patents from other jurisdictions). Instead, these medicaments relied on secrecy to maintain exclusivity—manufacturers carefully guarded the recipes and formulations for their patent medicines, and instead use patents, copyrights, and trademarks to protect product names, packaging, and slogans. *See id.* at 104–05; *see also* Jeffrey K. Aronson, *When I Use a Word . . . Medicines Regulation—Patent Medicines*, 383 BMJ 1, 2 (2023).

22. *See* Wertheimer & Santella, *supra* note 20, at 104–07.

23. Joseph M. Gabriel, *The US Drug Industry Used to Oppose Patents – What Changed?*, CONVERSATION (June 19, 2021), https://theconversation.com/the-us-drug-industry-used-to-oppose-patents-what-changed-161319.

24. An additional objective of the Life Sciences & Innovation case study project is to further explore the history of patenting in the pharmaceutical and biotechnology industries. Case studies will add rich detail to the current understanding of patenting in these spaces, and we also anticipate developing additional publications specifically focused on the rise of patenting and its current uses in these industries.

25. 35 U.S.C. § 202.

26. *Id.* § 202(c)(4).

companies for further research.[27] Today, U.S. biomedical innovations often originate in a university, supported by NIH or NSF funding, and then move towards commercialization through a startup company that has in-licensed university technology through a technology transfer office.

3. Rise of the Biotechnology Industry

Generally, historians consider the biotechnology industry to have emerged around the time of the Cohen-Boyer patents (which cover significant advances in technology for manipulating DNA (recombinant DNA technology)), in the late 1970s.[28] Other developments directly influenced the rise of the biotechnology industry. In the 1980 *Diamond v. Chakrabarty* decision, the U.S. Supreme Court permitted inventors to patent genetically manipulated organisms.[29] Also, Genentech, the first publicly traded biotechnology company—established, in part, based on in-licensing of the Cohen-Boyer technology—smashed previous records for stock price increases during its 1980 IPO.[30] And, Congress' 1980 enactment of the Bayh-Dole Act allowed recipients of federal research funding (largely universities) to file for and own patents from federally-funded inventions.[31]

---

27. *See, e.g.*, Gabrielle Athanasia, *The Legacy of Bayh-Dole's Success on U.S. Global Competitiveness Today*, at 4, CTR. FOR STRATEGIC & INT'L STUDIES (Jan. 12, 2022), https://www.csis.org/blogs/perspectives-innovation/legacy-bayh-doles-success-us-global-competitiveness-today#:~:text=The%20Implications%20of%20the%20Bayh%2DDole%20Act&text=In%20essence%2C%20it%20allows%20institutions,who%20can%20then%20commercialize%20them (noting that the Bayh-Dole Act has had a "significant and lasting impact on U.S. innovation and industry," including $1.3 trillion in growth of the U.S. economy, 4.2 million new jobs, and more than 11,000 new startup companies from American universities); Bhaven N. Sampat, *Lessons from Bayh-Dole*, 468 NATURE 755, 755 (2010) (claiming that U.S. universities earn almost $2 billion annually from licensing post-Bayh-Dole Act).

28. In the 1970s, Stanley Cohen (Stanford University) and Herbert Boyer (University of California, San Francisco) developed the technology claimed in U.S. Patent No. 4,237,224 (titled "Process for producing biologically functional molecular chimeras) and subsequent patents. These patents cover technology for generating recombinant proteins—proteins containing two or more genes—fundamental to the modern biotechnology industry. *See, e.g.*, U.S. Patent No. 4,237,224; Maryann P. Feldman, Alessandra Colaianni & Connie Kang Liu, *Lessons from the Commercialization of the Cohen-Boyer Patents: The Stanford University Licensing Program*, *in* 17.22 HANDBOOK OF BEST PRACTICES (2007); Rajendra K. Bera, *The Story of the Cohen-Boyer Patents*, 96 CURRENT SCI. 760, 761 (2009).

29. Diamond v. Chakrabarty, 447 U.S. 303 (1980).

30. Laura Fraser, *Genentech Goes Public*, GENENTECH (Apr. 28, 2016), https://www.gene.com/stories/genentech-goes-public (documenting the impressive IPO of Genentech, including a rise from $35 a share to $88 a share within an hour of the IPO on Oct. 14, 1980).

31. *See supra* Section II.C.2 for a brief description of the Bayh-Dole Act.

4. Modernization of the FDA, Regulatory Regimes, and Clinical Trials

FDA regulation, marketing exclusivity, and clinical trials all play critical roles in pharmaceutical and medical device development.

Congress passed the Federal Food, Drug, and Cosmetic Act in 1938,[32] requiring pharmaceutical manufacturers for the first time to demonstrate proof of safety to the FDA before marketing a drug in the United States. Only in 1962, under the Kefauver-Harris Amendments,[33] did Congress first require manufacturers to demonstrate proof of efficacy to the FDA before marketing a drug. In 1970, the FDA began requiring manufacturers to provide patient package inserts outlining the risks and benefits of the drug.[34] And, in 1984, Congress overhauled the regulatory and litigation regimes related to approval of small molecule drugs in the United States through the Drug Price Competition and Patent Restoration Act (commonly known as the "Hatch-Waxman Act").[35] The Hatch-Waxman Act provides both innovator and generic drug manufacturers with regulatory exclusivities based on FDA regulatory approval of their proposed drug product.

The modern clinical trial framework arose during and after World War II. Multiple advances came to fruition during this time, including: the development of double blind controlled trials;[36] random curative trials;[37] requirements for voluntary informed consent in clinical trials in the 1947 Nuremberg Code;[38] and formal statements of ethical principles guiding human

32. Federal Food, Drug, and Cosmetic Act, 21 U.S.C. § 301, Pub. L. 75-717, 52 Stat. 1040 (1938).

33. Drug Amendments of 1962, 21 U.S.C. § 301, Pub. L. 87-781, 76 Stat. 780 (1962).

34. *Milestones in U.S. Food and Drug Law*, FDA, https://www.fda.gov/about-fda/fda-history/milestones-us-food-and-drug-law (last visited Jan. 21, 2024).

35. Drug Price Competition and Patent Term Restoration Act of 1984, 21 U.S.C. § 301, 35 U.S.C. § 271, Pub. L. 98-417, 98 Stat. 1585 (1984).

36. Arun Bhatt, *Evolution of Clinical Research: A History Before and Beyond James Lind*, *in* 1 PERSPECTIVES IN CLINICAL RESEARCH 6, 7–8 (2010) (discussing the first double blind controlled trial (extract from *Penicillium patulinum* to treat common cold in 1943), in which physicians and patients were blinded).

37. *Id.* at 8–9; *see also* SUZANNE WHITE JUNOD, FDA AND CLINICAL DRUG TRIALS: A SHORT HISTORY 7 (2008), https://www.fda.gov/media/110437/download (both discussing the first random curative trial in 1946, using randomized allocation-controlled trial for streptomycin in tuberculosis).

38. Bhatt, *supra* note 36, at 8; *see also Nuremberg Code*, WIKIPEDIA, https://en.wikipedia.org/wiki/Nuremberg_Code (last visited Jan. 21, 2024).

trials in the 1948 Geneva Declaration,[39] the 1964 Helsinki Declaration,[40] and the 1966 International Covenant on Civil and Political Rights.[41] In 1991, the U.S. Department of Health and Human Services published a Federal Policy for the Protection of Human Subjects (widely known as the "Common Rule"); twenty U.S. federal departments and agencies have committed to follow this rule.[42] The Common Rule outlines protections for children, women, and prisoners; requires documentation of informed consent; and outlines modern practices for institutional review boards and compliance.[43] Finally, in 1996, the International Conference on Harmonization published Good Clinical Practice guidelines, which provide a universal standard for ethical conduct in clinical trials.[44]

5. Improvements in Life Sciences Technologies and Methods

Finally, significant advances in analytical technologies and methods in the 1960s and 1970s (modern nuclear magnetic resonance and high-pressure liquid chromatography techniques; complex calculation techniques using computers; database technology; etc.) allowed scientists to develop mechanistic and structural understandings of targets and pathways.[45] Scientists took advantage

39. WORLD MED. ASS'N, DECLARATION OF GENEVA – VERSION 1948, https://www.wma.net/wp-content/uploads/2018/07/Decl-of-Geneva-v1948-1.pdf (outlining every physician's ethical duties, which included pledges to focus on the health of the patient and not to use medical knowledge to violate human rights); *see also* WORLD MED. ASS'N, DECLARATION OF GENEVA – THE "MODERN HIPPOCRATIC OATH," https://www.wma.net/what-we-do/medical-ethics/declaration-of-geneva/ (last visited Jan. 21, 2024) (including revised, later versions of the Geneva Declaration).

40. WORLD MED. ASS'N, *WMA Declaration of Helsinki – Ethical Principles for Medical Research Involving Human Subjects*, https://www.wma.net/policies-post/wma-declaration-of-helsinki-ethical-principles-for-medical-research-involving-human-subjects/ (last visited Jan. 21, 2024) (formal statement of ethical principles by the World Medical Association).

41. International Covenant on Civil and Political Rights, G.A. Res. 2200A (XXI) (1966), Art. 7 ("No one shall be subjected to torture or to cruel, inhuman or degrading treatment or punishment. In particular, no one shall be subjected without his consent to medical or scientific treatment.").

42. *Federal Policy for the Protection of Human Subjects ('Common Rule')*, U.S. DEP'T HEALTH & HUM. SERVS., https://www.hhs.gov/ohrp/regulations-and-policy/regulations/common-rule/index.html#:~:text=For%20all%20participating%20departments%20and,regulations%20of%20that%20department%2Fagency (last visited Jan. 21, 2024).

43. *Id.*

44. International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use, *ICH Harmonised Guideline: Good Clinical Practice (GCP)* (rev. 2023) https://database.ich.org/sites/default/files/ICH_E6%28R3%29_DraftGuideline_2023_0519.pdf.

45. Edwin D. Becker, *A Brief History of Nuclear Magnetic Resonance*, 65 ANALYTICAL CHEM. 295, 297–300 (1993); Celia Henry Arnaud, *50 Years of HPLC*, 94 CHEM. & ENG'G NEWS 28 (2016).

of these improved analytical technologies to develop complex molecular structure-activity relationships that tie the molecular structure of a compound or molecule to its function.[46] Further, the rise of rational design techniques in the 1950s and beyond (based on structure-activity relationships) permitted scientists to design pharmaceutical compounds to fit a disease-associated biological target.[47] These rationally designed molecules formed the basis of potential therapeutics designed to alter the function of the target. The rational design model initially performed somewhat poorly in identifying viable pharmaceutical candidates, so the pharmaceutical industry transitioned to more brute force "empirical" methods, such as high-throughput screening techniques, to search vast libraries of small molecules for therapeutically effective compounds.[48]

C. DEVELOPING A NEW METHODOLOGY FOR EXAMINING LIFE SCIENCES BREAKTHROUGHS

Sections II.A and II.B *supra* highlight the rationale for a comparative case study-based approach to investigating the complex and fragmented "modern" life sciences ecosystem. To better standardize the case study approach, case study authors followed a framework for examining stages of development, various institutions, funding mechanisms, and the roles of IP, regulatory approval, and clinical trials. This Section outlines this framework, developed to probe potential innovation drivers and impediments. The drivers, impediments, and other considerations *supra* are exemplary—future case studies will likely reveal additional innovation drivers and impediments.

1. Lifecycle and Framing Considerations

Case study authors first considered the type or nature of innovation, as well as the major features and transitions in the development history, for their chosen invention. The following sets of questions in these areas guided the authors' initial inquiries.

- **Type or Nature of Innovation:**

46. John C. Dearden, *The History and Development of Quantitative Structure-Activity Relationships (QSARs)*, 1 INT'L J. QUANTITATIVE STRUCTURE-PROP. RELATIONSHIPS 1, 5–13 (2016).

47. Matthias Adam, *Integrating Research and Development: The Emergence of Rational Drug Design in the Pharmaceutical Industry*, 36 STUD. IN HIST. & PHILOSOPHY SCIS. PART C: STUD. IN HIST. & PHILOSOPHY BIOLOGICAL & BIOMEDICAL SCIS. 513 (2005).

48. *A Short History of Drug Discovery*, UCI SCHOOL PHARMACY & PHARMACEUTICAL SCIS., https://pharmsci.uci.edu/programs/a-short-history-of-drug-discovery/ (last visited Jan. 21, 2024).

- Is the innovation underlying the invention collateral (based on already-existing technology), or is it unique or groundbreaking in nature? How did the nature of the innovation affect the development process?
- Was development of the innovation driven by serendipity,[49] genius, and/or brute force on the part of the inventors? If any of these factors were present, how influential were they in the invention process?

- **Major Features of Development History:**
  - **Unmet Medical Need or Scientific Development:** What unmet medical need, or scientific development or advance, drove the invention process? What uncertainty existed at the time that the invention process began? How did uncertainty evolve over the development of the invention?
  - **Location:** In what location(s) did each stage of innovation occur (university vs. startup company vs. large pharmaceutical or biotech company)? Did the location of innovation evolve over the development history? If so, how?
- **Transitions in Development Process:** Where are the transitions between various phases of the development process? What defines these transitions?
  - **Early-Stage:** What incentives existed in the early-stage (pre-clinical) development phase? The Motivations for Human Behavior in Innovation outline in Section II.C.2 *infra* provides exemplary potential drivers and impediments.
  - **Transition Across the "Valley of Death":**[50]
    - What factors motivated funders to help inventors and companies through early-stage development?

---

49. "Serendipity" in this context refers to accidental discovery, unexpected opportunities, or insights that arose by chance. Numerous instances of serendipity in drug discovery have been catalogued in academic literature. *See, e.g.*, David C. Thompson & Samantha M. Copeland, *Serendipity in Research and Development: The Promise of Putting Into Place Patterns for Paying Attention*, 28 DRUG DISCOVERY TODAY 1–5 (2023); Thomas A. Ban, *The Role of Serendipity in Drug Discovery*, 8 DIALOGUES CLIN. NEUROSCI. 335–42 (2006).

50. The "valley of death" phrase is commonly used to describe the challenging development stage for therapeutics between early-stage academic research (proof of concept) and later-stage clinical testing and commercialization. *See, e.g.*, Declan Butler, *Translational Research: Crossing the Valley of Death*, 453 NATURE 840, 840 (2008); Marcus C. Parrish, Yuan Jin Tan, Kevin V. Grimes & Daria Mochly-Rosen, *Surviving in the Valley of Death: Opportunities and Challenges in Translating Academic Drug Discoveries*, 59 ANN. REV. PHARM. & TOXICOLOGY 405, 406 (2019).

- What factors made the invention and potential product(s) a good bet for funders?

- **Moving Towards Commercialization:**
  - **Entities:** Which entity or entities drove commercialization? Why?
  - **Selection of Invention:** Why did the commercializing entity select this invention and potential product(s) for commercialization (potential profits, ability to protect or create exclusivity, compatibility with remainder of portfolio, etc.)?
  - **Clinical Trial Strategy:** How did the commercializing entity approach clinical trial strategy? Did this entity combine clinical trials? Did this entity pursue multiple indications at once or separately?
  - **Adverse Events Uncertainty:** Did issues with adverse events arise during clinical trials? If so, how did the commercializing entity handle these events?
  - **Manufacturing Uncertainty:** What uncertainty existed about scaling up for manufacturing processes and commercialization?
  - **Routes of Administration Uncertainty:** What uncertainty existed about potential routes of administration (if a therapeutic)?

2. Motivations for Human Behavior in Innovation

Next, case study authors considered the professional and personal motivations of scientists and research groups. Often, these considerations arise in the early stages of life sciences innovation, but occasionally the motivations of a participant in later-stage, commercialization-focused innovation may have impacted the overall development story. As examples, authors considered the following non-exhaustive list of motivations.

- **Scientific drivers, including:**
  - General scientific curiosity;
  - Frustration with available scientific methods to solve a problem or achieve a goal;
  - Lack of access to needed resources to use currently available methods; and
  - Scientific drivers based on specific features of the disease or unmet medical need, unique patient population, etc.
- **Personal characteristics, including:**

  - Altruism, whether in general or specific to the disease or unmet medical need underlying the innovation; and
  - Tenacity beyond that expected generally in scientific research, especially considering the nature of impediments faced and what factors drove the tenacity.
- **Professional recognition, including:**
  - Tenure and/or permanent employment;
  - Publication(s);
  - Esteem, praise, and/or respect from peers, research colleagues and others in the field; and
  - Awards and/or prizes.
- **Financial considerations, including:**
  - Grants or continued research support;
  - Royalties from IP generated from research; and
  - Stability in employment based on positive research results (e.g., tenure).

3. Role of Institutions

Each case study author also identified the key institutions (government entities, universities, funders, etc.) involved in development of the invention, from conception to final commercialization. The following questions guided the case study authors on these issues.

- To identify the pertinent institutions:
  - Which institutions were involved in discovery of the invention and scientific principles underlying the invention?
  - Which institutions were involved in development of the invention and the product(s), including in later stages of development (such as translational research and the commercialization phase)?
- For each institution identified:
  - How did the institution's policies or rules affect the development of the invention?
  - If the institution was a funding agency, did the funder have specific rules or guidelines that affected development of the invention?

4. Roles of Public and Private Funding in Development and Commercialization

Next, case study authors examined the markets in which their innovations arose, sources and amounts of funding for each stage of innovation, and plans

for monetization. The following sets of questions guided the authors' inquiry with respect to each of these factors.

- **Market Analysis:**
  - At the beginning of the development process, which market(s) did the inventors anticipate entering with the invention and its product(s)? At this time, what financial expectations existed for products entering this market?
    - Did a market exist for the product(s) at the beginning of the development process?
    - Where did the inventors and/or manufacturers plan to market the final product(s)? Did this goal change throughout development?
    - What factors affected any market uncertainty? Put another way, what was the size and robustness of the market for the invention?
  - What unmet medical need or scientific problem did the invention and its product(s) seek to solve? Did the market for this need or problem change over time?
  - What did the market look like for similar products? Were there potential competitors in the pipeline?
  - How did the market mature during development?
- **Financing Each Stage of Invention and Product Development:**
  - How was each stage of development funded? If publicly available, how much did each stage of development cost?
    - What types of funding contributed to development at each stage? What advantages and constraints did each type of funding have?
    - What sources of funding were used for pre-clinical research (government grants, philanthropy, university support, etc.)?
    - What sources of funding were used for clinical trial and translational research?
  - What requirements and/or restrictions did the funders place on the scientists or companies developing the invention and its product(s) at each stage?
  - Why were funders motivated to provide monetary support for development at each stage?

  - How many rounds of funding did the invention and its product(s) receive? How did ownership rights to the invention and its product(s) move between entities?
  - How did the invention and its product(s) navigate across the "valley of death" and survive early-stage funding issues?
  - At any stage of development, was the invention and its product(s) subject to a joint collaboration agreement or other requirement for joint development? If so, how did the two (or more) parties allocate funding?
  - Does any action involved in development of the invention or product(s) pose antitrust risk (e.g., mergers or patent litigation settlements in a potentially anticompetitive manner)?
- **Changes in Funding Sources:**
  - How did funding sources evolve throughout the development process, and how did funding sources change?
- **Monetizing the Invention and any Related Product**
  - How did the developers plan to monetize the invention and any related product(s) (direct sales, insurance coverage, reimbursements, licensing and litigation, etc.)?

5. IP Strategy in Development

One of the key goals of this project was to examine the various roles that IP can play in the development of life sciences inventions. Each case study examined the IP strategy surrounding its invention through a careful review of the following considerations.

- **IP Portfolio and Strategy:** What types of IP protection (or other forms of relevant exclusivity) exist for the product(s) or invention (e.g., patent, trade secret, exclusivity related to data)?
  - Which IP is the "key" IP, and why?
  - Was the IP protection in effect during marketing of the product(s)? As of now, has the IP protection expired?
  - What is the size of the IP portfolio covering the invention? Is there evidence that the inventors sought to use the size of the portfolio as a deterrent for competition?
  - For patents: what types of patents did the inventors seek and obtain (composition, method of treatment, formulation, manufacturing, etc.)?

        - Was there uncertainty as to the availability of the type of patent, either at filing or later in the life of the patent? If so, how did this change the IP holder's strategy?
    - For trade secrets: what is the nature of the trade secret (e.g., manufacturing, key algorithm, data set, etc.)?
    - For other forms of IP: what is the nature of the IP right held? Why was this form of IP selected? What is the strength of this IP right?
    - If there is no IP protection on the invention or a key portion of the invention: why not?
    - Did the innovator company or manufacturer seek to extend IP protection or other exclusivity through additional patents, changing formulations, or switching patients to other, related products with remaining exclusivity?
- **Location of IP Protection:** Where did the IP holder plan to market the final product(s)? Has the market expanded or contracted? Did the marketing entity successfully seek IP rights in those jurisdictions?
- **Blocking IP from Others:** Did potentially blocking IP protection (held by others) exist when the inventors began work on the invention? If so, how did the inventors overcome the obstacle? And, if not, did the lack of IP protection in the space encourage innovation by the inventors?
- **Importance of IP Protection:**
    - Was obtaining IP protection on the future product or a key portion of it necessary for commercialization?
    - At what stage(s) of development did IP protection become important (often at transition stages, e.g., in-licensing, technology transfer, and/or funding rounds)?
    - Did structural constraints and/or standard pathways for development for the class of invention indicate IP may play a critical role in commercialization? Do those factors apply or not apply to the specific invention in the case study (e.g., recouping R&D costs, clinical trial expenses)?
- **Methods for Obtaining IP:**
    - How did the inventors obtain their IP (filing patents, protecting trade secrets, in-licensing, technology transfer from universities, acquisition of a company holding IP)?
    - How did the method(s) by which the inventors obtained IP affect development of the invention?

- **Ownership, Joint Ventures and Collaborations, and Exclusive Use Considerations:**
  - **Ownership:** Did ownership change during the development and/or commercialization of the invention and any product(s)?
  - **Joint Ventures and Collaborations**: In any joint ventures or collaborations, how did partners or collaborators determine and apportion ownership of resulting IP?
  - **Exclusive Use:** Throughout development and commercialization, which entity or entities held the right to exclusively use key aspects of the invention? Through what IP rights?
    - Did university or startup employees assign their IP rights to their companies?
    - What was the chain of sales, licensing, or acquisitions of patents by entities, if such chains existed?
- **Compulsory Licensing:** Have there been attempts to obtain a compulsory license to any IP involved in the products commercialized from the invention? If so, how? What result?
- **IP Litigation:** How did competition develop in the technology space? Summarize any relevant IP litigation.

6. Clinical Trials, Regulatory Approval, and Regulatory Exclusivity

Clinical trials, regulatory approval, and regulatory exclusivity can all drive or impede life sciences innovation, depending on the circumstances. As described *supra*, clinical trials are often the most expensive part of the R&D process in the life sciences. But regulatory rewards, such as accelerated approvals and the subsequent marketing exclusivity granted to successful products, often encourage development of eligible life sciences innovations. The case study authors considered the following clinical trial and regulatory factors in their inquiries.

- **Clinical Trial Considerations:**
  - Did the clinical trial sponsor and/or manufacturer proceed through clinical trials in a sequential fashion, on a single indication? Or did it make modifications (e.g., pursued Phase II and III trials at the same time, pursued trials on multiple indications simultaneously, etc.)? If modifications were used, why?
  - Did the FDA or another regulatory agency flag any issues with the clinical trial plans or protocols?

- Did the FDA or another regulatory agency flag any potential indications as problematic based on clinical trial data or other factors?
- Were the clinical trial(s) unique in other respects? If so, why?

- **Applicable Regulatory Regimes and the Regulatory Approval Process:**
  - What type of regulatory reviews did the product undergo in the United States? What kinds of regulatory review processes occurred in other countries? How was development outside of the United States particularly relevant to the development history and strategy of the invention, especially where it differed significantly from the regulatory review process in the United States
  - How did the regulatory review process affect the overall development process for the product?
  - Was the product eligible for Breakthrough Therapy Designation[51] or another form of accelerated review? Did the product successfully complete the accelerated review process?
  - What sources of uncertainty existed during regulatory approval?
  - Did the FDA or another regulatory agency pose challenges or hurdles during the regulatory review process?
  - Did the FDA or another regulatory agency raise any concerns about the methods of treatment and indications selected?
- **Regulatory Exclusivity:** Did the product receive regulatory exclusivity from the FDA or another agency? If so, how much exclusivity, and for what reason?
  - Was the product eligible for orphan drug exclusivity or another version of extended exclusivity?
  - Did the manufacturer seek pediatric exclusivity for the product?

7. Insurance Reimbursement Issues

For certain life sciences innovations, insurance reimbursement issues can impede the innovation lifecycle or can dictate development strategies. Case

51. The FDA grants the Breakthrough Therapy designation to a proposed therapeutic product when it "treats a serious or life-threatening condition and preliminary clinical evidence indicates that the drug may demonstrate substantial improvement on a clinically significant endpoint(s) over available therapies." *Frequently Asked Questions: Breakthrough Therapies*, U.S. FOOD & DRUG ADMIN. (Feb. 3, 2022), https://www.fda.gov/regulatory-information/food-and-drug-administration-safety-and-innovation-act-fdasia/frequently-asked-questions-breakthrough-therapies#:~:text=A%20breakthrough%20therapy%20designation%20is,(s)%20over%20available%20therapies.

study authors considered the following insurance-related factors where applicable, as well.

- For the commercialized product, did potential impediments to insurance reimbursement dictate or influence any key decisions in designing the final product?
- Did any earlier versions of the technology face impediments that changed the course of innovation?

8. Ethical, Moral, and Political Considerations

Finally, case study authors examined the ethical, moral, and political considerations that affected the innovation process. A few exemplary considerations follow that the case study authors used to analyze their impact on the subject innovation.

- **Exemplary Considerations:**
  - **Presence of a Public Health Crisis:** Did a public health crisis (or similar major issue) trigger development of the invention?
  - **Presence of Stigma:** Did stigma or public resistance exist as to research or treatment of the unmet medical need? If so, how did the inventors (or activists) overcome this stigma?
  - **Area of Scientific Innovation:** Did ethical, moral, or political considerations impact research in the particular scientific area in which the innovation arose? Did ethical, moral, or political considerations limit the scope of the research related to the innovation?
- **Impacts:**
  - **Overall Impact:** How did ethical, moral, or political considerations impact development of the invention?
  - **Funding:** At any stage of development, did ethical, moral, or political considerations restrict available funding (government or otherwise)? If so, how did the inventors or companies obtain the necessary funding to continue development of the invention?

D. IMPLEMENTING THE CASE STUDY METHODOLOGY: BERKELEY LAW'S 2022–23 LSI WORKSHOP

The previous Section described the case study methodology to highlight the importance of developing a wide range of detailed case studies on breakthrough innovations across the life sciences ecosystem. As a pilot study for this methodology, with the support of the Berkeley Center for Law & Technology's Life Sciences Law & Policy Center, Berkeley Law hosted the

two-semester LSI Workshop in the 2022–23 academic year.[52] Allison A. Schmitt and Peter S. Menell co-taught this course and led the pilot phase of the project.

Each student enrolled in the LSI Workshop engaged in an intensive writing experience resulting in a case study centered on a life sciences invention. These inventions spanned a wide range of breakthrough and iterative innovations, including small molecule therapeutics, biologic therapeutics, platform technologies, diagnostics, medical devices, and medical uses of artificial intelligence. Most successful case studies focused on commercialized innovations (primarily due to more publicly available information allowing for a full exploration of the innovation process).

Students who completed the full-year course drafted a detailed development history and identified key innovation drivers and impediments that led to success for their invention.[53] Students regularly tested their ideas and received feedback through draft edits, in-class presentations, and peer discussion groups.

Each case study author examined various key issues as part of recapping the development history of their invention. To provide necessary scientific background for the invention, each author explored the scientific landscape in which the invention developed. Additionally, authors explained the unmet medical or societal need driving development of the invention, as well as the invention's development steps (typically from early stage research efforts through commercialization). In particular, the development histories examined human inventors' stories and motivations that, in many cases, kickstarted development of the invention. Authors also explored the various institutions (universities, governmental agencies and funders, and private actors) that pushed ideas through to commercialization. Further, each author explored key themes related to the roles of IP, regulatory approval regimes, and public and private funding.

To guide the case study research, the 2022–23 LSI Workshop included a series of lectures given by Schmitt and special guests. These lectures explored key topics related to life sciences innovation, including:

- The history of innovation in the life sciences space and the development of IP protection for these inventions;

52. The course enrolled a wide range of interested students, including: (1) second- and third-year J.D. students with interest in life sciences, IP, regulatory, and corporate practices; (2) one LL.M. student with interest in life sciences patent practice; and (3) several UC Berkeley Ph.D. students from various life sciences disciplines.

53. *See infra* Section II.C for details on the methodology underlying case study development.

- The key institutions supporting life sciences breakthroughs (e.g., the U.S. Patent and Trademark Office (USPTO); the FDA; governmental and philanthropic funding agencies);
- The Bayh-Dole Act and the university technology transfer and government licensing regimes that have arisen in response to the Act's requirements;
- The funding mechanisms for life sciences innovations (government grants, philanthropic organizations, venture capital, private equity, funding rounds, etc.);
- The regulatory and IP law relevant to pharmaceutical and biological products, such as: (1) the Hatch-Waxman and Biologic Price Competition & Innovation Act regimes; (2) inventorship considerations in the life sciences; (3) continuation practice in the life sciences; (4) advanced topics in novelty and obviousness; (5) obviousness-type double patenting; and (6) induced infringement and section viii carveout practice ("skinny labels");
- The FDA's regulation of safety and efficacy of pharmaceuticals and medical devices;
- Modern clinical trials;
- Artificial intelligence's use cases in the life sciences; and
- Drug pricing and profits considerations in the United States and beyond.

To understand each invention's development, students embarked on extensive interdisciplinary research. Their research required review of many types of sources, including: scientific resources, such as treatises and journal articles; legal resources, such as treatises, textbooks, and law review articles; patent landscapes; administrative materials; publicly available licensing and collaboration information; and, in several cases, personal interviews with inventors.

III. CASE STUDY ARTICLES IN THIS ISSUE

Using the case study methodology described in Part II, authors developed a first set of case studies. Table 1 lists the five case studies published in this Issue as Articles. This Part provides a summary of each Article, focused on the key development history milestones, innovation drivers, and innovation impediments identified in the case studies.

Table 1: First Round of Case Study Articles

Author	Case Study Subject	Type of Invention	Title
Kaidi (Ted) Zhang (Ph.D. (Chemistry), 2024)	Lyrica (pregabalin)	Small molecule therapeutic	*Serendipitous Lab Discovery to Commercial Blockbuster: The Invention of Lyrica*[54]
William P. Kasper (J.D., 2024)	Truvada (emtricitabine / tenofovir)	Small molecule therapeutic	*Innovation to Contain the HIV/AIDS Crisis: A Truvada Case Study*[55]
Vincent Joralemon (J.D., 2024)	Spravato (ketamine)	Small molecule therapeutic	*How Ketamine Became an Antidepressant*[56]
Christine R. O'Brien Laramy (J.D., 2024)	Yescarta (axicabtagene ciloleucel, CAR-T cell therapy)	Biologic therapeutic	*The CAR-T Cell Therapy Innovation Drivers: A Yescarta Case Study*[57]
Caressa N. Tsai (J.D., 2024)	Next-generation DNA sequencing	Platform technology;[58] research tool	*The Invention of Next-Generation Sequencing*[59]

A. SMALL MOLECULE THERAPEUTICS

Three of the Articles in this Issue focus on small molecule therapeutics: Lyrica (pregabalin), Truvada (emtricitabine/tenofovir combination product), and Spravato (ketamine). These case studies reflect unique pathways to market. Lyrica's development illustrates a more traditional small molecule path to market. Truvada's story is more complex. As a combination product (combining two FDA-approved small molecules) to treat a disease that received significant stigma at the start of the innovative process, Truvada

54. Kaidi (Ted) Zhang, *Serendipitous Lab Discovery to Commercial Blockbuster: The Invention of Lyrica*, 39 BERKELEY TECH. L.J. 393 (2024).

55. William P. Kasper, *Innovation to Contain the HIV/AIDS Crisis: A Truvada Case Study*, 39 BERKELEY TECH. L.J. 425 (2024).

56. Vincent Joralemon, *How Ketamine Became an Antidepressant*, 39 BERKELEY TECH. L.J. 497 (2024).

57. Christine O'Brien Laramy, *The CAR-T Cell Therapy Innovation Drivers: A Yescarta Case Study*, 39 BERKELEY TECH. L.J. 553 (2024).

58. This Article uses the term "platform technology" to refer to a life sciences technology, machine, or other type of innovation that can generate multiple outputs such as data, potential therapeutic molecules, etc.

59. Caressa N. Tsai, *The Invention of Next-Generation Sequencing*, 39 BERKELEY TECH. L.J. 613 (2024).

demonstrates the important roles that activists and governmental intervention can play in commercialization. Spravato's development reflects challenges, such as challenging IP landscapes and insurance reimbursement regimes, in repurposing an already known small molecule (ketamine) for a new therapeutic purpose.

The innovation drivers and impediments identified in each case study reflect the challenges inventors and manufacturers face to develop and commercialize small molecule therapeutics, and the key roles that institutions, funders, the IP system, and regulatory regimes play in shaping product development.

1. Lyrica

In *Serendipitous Lab Discovery to Commercial Blockbuster: The Invention of Lyrica*,[60] Kaidi (Ted) Zhang describes the discovery process, development history, and innovation drivers and impediments surrounding the remarkable success of Lyrica, a small molecule therapeutic currently indicated for treatment of certain epileptic seizures, neuropathic pain, postherpetic neuralgia, and fibromyalgia.[61] Lyrica's development came at a time when significant unmet medical needs existed for new treatments for fibromyalgia,[62] neuropathic pain,[63] and epilepsy.[64] Zhang identifies the key role that U.S. and international public health organizations played in reducing stigma surrounding epilepsy and promoting epilepsy treatment research in the late twentieth century.[65]

Zhang describes the initial discovery of Lyrica's active ingredient, the small molecule pregabalin, through a collaboration between chemists Ryszard Andruszkiewicz and Richard Silverman at Northwestern University.[66] Pregabalin is one of a class of fourteen 3-alkyl GABA derivatives that Andruszkiewicz synthesized under the direction of Silverman in 1988.[67] Both

60. Zhang, *supra* note 54.

61. *Package Insert – LYRICA*, U.S. FOOD & DRUG ADMIN. 1, 3–5, 38–54, 58 (Dec. 13, 2023), https://www.accessdata.fda.gov/drugsatfda_docs/label/2024/021446s041,022488s018,209501s005lbl.pdf.

62. *Pfizer's Lyrica Receives FDA Approval for Fibromyalgia Based on Expedited Review*, PFIZER (June 21, 2007), https://www.pfizer.com/news/press-release/press-release-detail/pfizer_s_lyrica_receives_fda_approval_for_fibromyalgia_based_on_expedited_review.

63. *FDA Approves Lyrica For The Management of Neuropathic Pain Associated With Spinal Cord Injury Based on Priority Review*, PFIZER (June 20, 2012), https://www.pfizer.com/news/press-release/press-release-detail/fda_approves_lyrica_for_the_management_of_neuropathic_pain_associated_with_spinal_cord_injury_based_on_priority_review.

64. *See generally* WORLD HEALTH ORGANIZATION, ATLAS: EPILEPSY CARE IN THE WORLD (2005).

65. Zhang, *supra* note 54, at Section IV.A.

66. *Id.* at Sections III.B, IV.B.

67. *Id.* at Section III.B.

epileptic seizures and certain neuropathic pain conditions can be traced to diminished GABA levels in the brain.[68] At the time, Silverman thought that the 3-alkyl GABA derivative compounds would increase GABA neurotransmitter levels in the human brain.[69] Early-stage funding for this work primarily came from government grants—the NIH awarded over $10 million (in 2020 dollars) across thirty-seven grants to support the development of the compound.[70]

As Zhang details, pregabalin proceeded through early commercialization stages in a serendipitous fashion. Pregabalin was not, in fact, the early frontrunner compound for further development.[71] Parke-Davis's decision to test all fourteen 3-alkyl GABA derivative compounds (as opposed to the limited testing strategy of rival Upjohn, which focused only on the most promising 3-alkyl GABA derivative compound based on early *in vitro* enzymology testing) proved critical in identifying pregabalin as the final lead compound.[72] Further serendipity became clear only much later, when subsequent studies demonstrated that the mechanism of action for pregabalin and its analogs differed significantly from that initially theorized by Silverman.[73]

Zhang explains that the privatization mechanisms available under the 1980 Bayh-Dole Act (in particular, the availability of university-held patents for inventions funded by government grants) played a crucial role in commercializing Lyrica.[74] In fact, Lyrica was one of the first major pharmaceutical products to arise under the Bayh-Dole regime.[75] Northwestern's technology transfer office marketed pregabalin to pharmaceutical companies, as Northwestern (like other universities) lacked the

68. *See, e.g.*, David M. Treiman, *GABAergic Mechanisms in Epilepsy*, 42 EPILEPSIA 8, 9 (2001) (detailing GABA's role in epilepsy); Caijuan Li et al., *The Etiological Contribution of GABAergic Plasticity to the Pathogenesis of Neuropathic Pain*, 15 MOLECULAR PAIN 1, 4 (2019) ("Many neuropathic pain conditions are associated with reduced synaptic inhibition, such as occurs with a decreased GABA level.").

69. *See* Zhang, *supra* note 54, at Section II.A, for further details on the relevant scientific mechanisms.

70. *Id.* at Section IV.B (citing Rachel Barenie et al., *Discovery and Development of Pregabalin (Lyrica): The Role of Public Funding*, 97 NEUROLOGY e1653, e1653–60 (2021)).

71. *Id.* at Section III.C.

72. *Id.* at Section IV.D.

73. *Id.* at Section III.F; *see also id.* at Section IV.B (citing Justin S. Bryans & David J. Wustrow, *3-Substituted GABA Analogs with Central Nervous System Activity: A Review*, 19 MED. RSCH. REVS. 149, 168–70 (1999)).

74. *See id.* at Sections III.B, III.C, IV.B, IV.C.

75. *Id.* at Sections III.A, III.E.

capacity to conduct clinical trials or engage in large-scale manufacturing of pregabalin.[76]

Lyrica's commercialization pathway also depended on Silverman's strong belief in the value of patenting research outputs.[77] Based on his experiences with Lyrica and other early-stage research, Silverman believed patent exclusivity is critical for commercialization of university-based research: "[I]f you do basic science and you don't patent your result, but then you publish it, a company isn't going to follow up on those compounds. The company would not be able to have exclusivity."[78]

Various parties involved in Lyrica's development—including Silverman, Northwestern, and Warner-Lambert (Parke-Davis and Pfizer's parent company)—filed for patents on the small molecule compound (pregabalin molecule), synthetic methods and derivatives, methods of treatment, and large-scale synthesis methods.[79] This "moat" of patents proved effective in maintaining innovator exclusivity on the original Lyrica formulation until 2018.

In driving the later-stage Lyrica clinical and commercialization work of pharmaceutical giant Parke-Davis (and later, Pfizer), Zhang flags the important roles for strategic choices, serendipity, and the potential for significant commercial success.[80] As noted *supra*, Parke-Davis's early serendipitous decision to test all fourteen 3-alkyl GABA derivative compounds for activity led to the unexpected selection of pregabalin as the lead compound.[81] Parke-Davis also focused on effectiveness of pregabalin in a murine model, rather than in *in vitro* testing.[82] Finally, Parke-Davis's concurrent development of gabapentin, another GABA-modulating compound, provided the company with additional insight toward the development of pregabalin.[83]

Later, Parke-Davis pursued an aggressive clinical trial strategy, electing to run Phase II and Phase III trials concurrently for multiple potential pregabalin indications.[84] Although riskier than the conventional clinical trial strategy of pursuing one type of study and one indication at a time, Parke-Davis saved

76. *Id.* at Sections III.C, IV.C.

77. *Id.* at Sections III.A, IV.B.

78. *Id.* at Section IV.B (quoting Peter Kotecki, *In Focus: As Lyrica Profits Dry Up, Northwestern Seeks Another 'Blockbuster' Drug*, DAILY NORTHWESTERN DRUG MONEY (Apr. 10, 2016) https://dailynorthwestern.com/2016/04/10/featured-stories/in-focus/in-focus-as-lyrica-profits-dry-up-northwestern-seeks-another-blockbuster-drug/).

79. *Id.* at Section III.E, Table 2.

80. *Id.* at Section IV.D.

81. *Id.*

82. *Id.*

83. *Id.*

84. *Id.* at Section III.D.

significant development time and costs with concurrent trials.[85] Parke-Davis's riskier strategy paid off: the FDA approved pregabalin for multiple indications in short succession.[86]

Finally, Zhang's case study briefly details Pfizer's later development of Lyrica CR,[87] an extended-release formulation of Lyrica's pregabalin. The FDA approval for Lyrica CR granted Pfizer additional exclusivity for the pregabalin active ingredient, albeit in a new, once-daily dose formulation.

2. Truvada

In *Innovation to Contain the HIV/AIDS Crisis: A Truvada Case Study*,[88] William P. Kasper describes the complex development history and innovation drivers and impediments leading to the commercialization of Truvada, a combination therapy for treatment of, and pre-exposure prophylaxis (PrEP) for, HIV-1 infections.[89] Truvada is comprised of two small molecule active ingredients: tenofovir (formulated as the prodrug tenofovir disoproxil fumarate) and emtricitabine.[90]

Kasper describes the critical role that the HIV/AIDS public health crisis played in shaping Truvada's development path. This crisis reached lethal pandemic levels in the late twentieth century.[91] Yet in the early 1980s, the U.S. federal government hesitated to fund HIV/AIDS treatment research, despite both government appropriations for this research and grant proposals from interested scientists.[92] Significantly, AIDS activists raised awareness about the enormous human suffering from this pandemic and demanded federal support for HIV therapeutics research. Eventually, U.S. governmental agencies demonstrated leadership in their response to the AIDS crisis. Global

85. *Id.* (citing ANDREW J. THORPE & LLOYD E. KNAPP, CASE STUDY: DISCOVERY AND DEVELOPMENT OF PREGABALIN (LYRICA®) 356 (2013)).

86. FDA granted initial approval for Lyrica's use for neuropathic pain associated with diabetic peripheral neuropathy and post-herpetic neuralgic in December 2004, for adjunctive therapy for the treatment of partial-onset seizures in June 2005, and for the treatment of fibromyalgia in June 2007. *See* Zhang, *supra* note 54, at Section III.D.

87. U.S. FOOD & DRUG ADMIN., PACKAGE INSERT – LYRICA® CR 1–33 (Dec. 13, 2023), https://www.accessdata.fda.gov/drugsatfda_docs/label/2024/021446s041,022488s018,209501s005lbl.pdf.

88. Kasper, *supra* note 55.

89. U.S. FOOD & DRUG ADMIN., PACKAGE INSERT – TRUVADA® 1, 3, 29–31, 36 (Oct. 11, 2023), https://www.accessdata.fda.gov/drugsatfda_docs/label/2023/021752Orig1s063lbl.pdf.

90. *Id.* at 1, 5, 18–19, 36.

91. Kasper, *supra* note 55, at Section II.A (quoting THE EVOLUTION OF HIV/AIDS THERAPIES (Chem. Heritage Found. & Sci. Hist. Inst. 2012), https://vimeo.com/59281508).

92. *Id.* at Section III.A.1.

governmental agencies and philanthropic organizations also played instrumental roles in pushing HIV/AIDS treatments to the global South.[93]

University scientists first discovered both active ingredients in Truvada.[94] Although large pharmaceutical companies (Bristol-Myers for tenofovir, Burroughs-Wellcome for emtricitabine) initially licensed the active ingredients and began further research towards commercialization, these companies eventually abandoned development efforts.[95] Gilead Sciences, a startup company focused on antiviral therapeutics, stepped in to pursue development of both compounds to commercialization[96] (Viread for the prodrug form of tenofovir;[97] Coviracil for the single compound form of emtricitabine[98]). In conjunction with the U.S. Centers for Disease Control and Prevention (CDC), Gilead later developed the combination product Truvada to combine the therapeutic benefits from both individual compounds in a once-daily formulation.[99]

The Truvada case study highlights the importance of serendipity in the development of both tenofovir and emtricitabine. For tenofovir, Kasper points to serendipity (and genius) in Antonín Holý's identification of tenofovir's mechanism of action.[100] And, for emtricitabine, serendipity arose in the choice to modify an intermediate enantiomeric mixture by fluorination to create a racemic mixture with better metabolic properties.[101]

As with many synthetic chemistry endeavors, brute force also played a role in development efforts for tenofovir and emtricitabine. For tenofovir, the scientific team synthesized many derivatives to find the optimal compound.[102] And, for emtricitabine, the inventors tested many synthetic methods to find the optimal synthetic route to the final compound.[103]

Efficient transfer of the tenofovir and emtricitabine small molecule inventions to private company partners also played a critical role in bringing Truvada to market.[104] The development stories for both compounds followed

93. *Id.* at Section III.A.3.b.
94. *See id.* at Sections III.B, IV.B.
95. *See id.* at Sections III.B.1–2, IV.B.1.b, IV.B.2.b.
96. *See id.* at Sections III.B, III.C, IV.B, IV.C.
97. *Id.* at Section III.B.1.b.
98. *Id.* at Section III.B.2.
99. *Id.* at Sections III.C, IV.C.
100. *Id.* at Section IV.B.1.a.i.
101. *Id.* at Section IV.B.2.a.i.
102. *Id.* at Section IV.B.1.a.i.
103. *Id.* at Section IV.B.2.a.1.
104. *See id.* at Section III.A.3.d.

similar paths.[105] First, university teams developed the compounds (for tenofovir, Antonín Holý (Czechoslovak Academy of Sciences) and Erik De Clercq (Catholic University of Leuven, Belgium)); for emtricitabine, Dennis Liotta and team (Emory University).[106] Second, universities transferred the compound technology through licensing patents obtained under the auspices of the Bayh-Dole Act (or a similar mechanism) to a private pharmaceutical company.[107] Third, the private company abandoned the compound due to a deprioritization in various merger & acquisition (M&A) deals.[108] Fourth, Gilead eventually licensed or acquired patents covering both active ingredients[109] and received FDA approval to market each compound as a separate therapeutic product.[110] Later, motivated by a desire to create a therapeutic that would require fewer doses per day, Gilead and the CDC developed the combination Truvada therapy.[111]

The Truvada story is intertwined inextricably with Gilead's development into the dominant pharmaceutical company in the antiviral space.[112] In the 1980s, while at the startup stage, Gilead competed with other companies of various sizes beginning work on HIV/AIDS therapeutics.[113] Gilead elected to focus on compounds like tenofovir in the early 1990s[114] and later acquired Triangle Pharmaceuticals and purchased IP from Emory to obtain the undisputed rights to emtricitabine.[115]

Gilead pursued PrEP to significantly expand its patient base (and its potential profit margin) with a HIV-preventative treatment.[116] Public health agencies including the CDC strongly encouraged Gilead to develop a PrEP product.[117] Based on their collaboration with Gilead to develop Truvada for PrEP, the CDC filed method of use patents related to use of Truvada as PrEP against HIV infection. Later, to encourage distribution of more free products and services to those in need of PrEP treatments, the CDC unsuccessfully attempted to assert its patents against Gilead.[118]

105. *Id.* at Sections III.B.1, III.B.2.
106. *Id.* at Sections III.B.1, III.B.2.a, IV.B.1.a.
107. *Id.* at Sections III.B.1, III.B.2, IV.B.1, IV.B.2.
108. *Id.* at Sections III.B.1.ii, III.B.2.ii, IV.A.3, IV.B.
109. *Id.* at Section III.B.1.a.
110. *Id.* at Sections III.B.1.b, III.B.2
111. *Id.* at Section IV.A.3
112. *Id.* at Section IV.C.1.a
113. *Id.* at Section III.A.3.e
114. *Id.* at Section III.B.1.b.
115. *Id.* at Section IV.B.2.b.
116. *Id.* at Section IV.C.2.b.
117. *Id.*
118. *Id.* at Sections III.C, IV.C.1.a.

Gilead built its comprehensive Truvada patent portfolio through filing its own patents and a strategic licensing and acquisition strategy. Gilead licensed tenofovir from the Czech Academy of Sciences,[119] patented tenofovir prodrugs,[120] and acquired the patent rights to emtricitabine from Emory University.[121] Finally, Gilead received several patents directed to methods of treatment for HIV using Truvada.[122]

Gilead faced two significant patent-related challenges during development of Truvada. First, due to the risk of compulsory patent licensing from the Doha Declaration, Gilead voluntarily licensed its tenofovir prodrug patents.[123] Second, as noted *supra*, the CDC unsuccessfully attempted to assert its PrEP patent claims against Gilead.[124]

Multiple regulatory factors also impacted Truvada's development. Both tenofovir and emtricitabine separately benefitted from FDA fast-track approval processes and received new chemical entity exclusivity upon approval.[125] Gilead later obtained accelerated approval for the Truvada combination product through an abbreviated approval process requiring only bioequivalence studies comparing Truvada to the already approved tenofovir and emtricitabine products.[126]

Finally, this case study highlights the ethical, moral, and political considerations that drove Truvada's development. In particular, activism in the face of HIV/AIDS stigma created the political environment necessary for governmental support of HIV therapeutic development.[127] Later, for development of a combination PrEP product, public health agencies, activists, and scientists sought to protect vulnerable communities (especially in the global South) from potential transmission of HIV.[128]

3. Spravato

In *How Ketamine Became an Antidepressant*,[129] Vincent Joralemon describes the recent development of ketamine as a therapeutic for treatment-resistant depression in adults and depressive symptoms in adults with major depressive

119. *Id.* at Sections III.B.1.b, III.B.1.ii, IV.B.1.a.i, IV.C.1.a.
120. *Id.* at Section III.B.1.b.
121. *Id.*
122. *Id.* at Section III.C.1.b.
123. *Id.* at Section III.B.1.b.
124. *Id.* at Sections III.C, IV.C.1.a.
125. *Id.* at Section IV.C.1.a.
126. *Id.* at Sections III.C.1.b, IV.C.1.a.
127. *Id.* at Section III.A.3.b.
128. *Id.* at Section IV.C.2.a.
129. Joralemon, *supra* note 56.

disorder with acute suicidal ideation and/or behavior.[130] Many clinicians now believe that use of ketamine in depression treatment is "one of the most significant advances in the field of depression" in recent years.[131]

Compared to the development pathway of many other small molecules (including the Lyrica and Truvada examples described *supra*), the path to ketamine's repurposing differed in several important ways. First, clinicians originally used ketamine as an anesthetic (with significant dissociative side effects making the drug problematic for anesthetic use).[132] The repurposing of ketamine for antidepressant use began in the 1990s. At the time, clinicians knew that a large number of patients with major depressive disorder did not respond to available antidepressants.[133] To tackle this problem, scientists at Yale School of Medicine identified glutamate-modulating compounds as a class of promising new depression therapeutics.[134] With increased scientific understanding of the science underlying development of glutamate-modulating antidepressants,[135] government scientists at the National Institute of Mental Health (NIMH) began collaborations with the Yale scientists and teams from other institutions.[136] NIMH funded most early-stage glutamate-targeted antidepressant investigations.[137]

After promising early-stage clinical results,[138] Husseini Manji, the director of the Mood and Anxiety Disorders program at NIMH, moved to Janssen's Neuroscience Research & Development program in 2008.[139] Manji's personal understanding of the ongoing NIMH research (particularly the challenges) proved invaluable to Janssen's development of ketamine as an antidepressant. Manji drove commercialization-focused research, including development of an intranasal form of delivery.[140] But, because testing showed that intranasal administration delivered much less ketamine to the brain than intravenous administration, Janssen sought a more potent form of ketamine for its proposed product. To solve this problem, Janssen developed a solely S-

130. U.S. FOOD & DRUG ADMIN., PACKAGE INSERT – SPRAVATO® 1, 4, 33–40, 44 (Oct. 18, 2023), https://www.accessdata.fda.gov/drugsatfda_docs/label/2023/211243s012lbl.pdf.

131. Joralemon, *supra* note 56, at Section III.C.1.e (quoting Ronald S. Duman & George K. Aghajanian, *Neurobiology of Rapid Acting Antidepressants: Role of BDNF and GSK-3β*, 39 NEUROPSYCHOPHARMACOLOGY 233, 233 (2014)).

132. *Id.* at Section I.

133. *Id.* at Sections II.B, II.C.

134. *Id.* at Section III.C.1.

135. *Id.* at Section II.B.7.

136. *Id.* at Sections III.C.1, III.C.1.b.

137. *Id.* at Section III.C.1.b.

138. *Id.* at Section III.C.1.b-d.

139. *Id.* at Section III.C.3.a.

140. *Id.* at Sections III.C.3.a-c.

enantiomer formulation of ketamine (often referred to as "esketamine"). In patent filings, Janssen presented data showing the esketamine formulation has three to four times higher potency than racemic ketamine.[141]

But, Janssen's need for a ketamine compound with increased potency was not the whole story: the lack of available IP exclusivity for certain ketamine products likely also influenced Janssen's commercialization path.[142] Patents on racemic ketamine (filed in 1966) and intranasal administration of ketamine for pain management (filed in 1996) had already been granted by the USPTO well before Janssen began its commercialization efforts towards Spravato.[143] Joralemon hypothesizes that Janssen may have lacked incentives to pay for clinical trials on racemic ketamine formulations, given the blocking effects of these earlier-granted patents.[144] Instead, Janssen elected to pursue commercialization and patenting of the esketamine enantiomer—a common, though controversial, strategy to obtain patent exclusivity in the United States.[145] Janssen offered some evidence for increased potency of esketamine (as compared to racemic ketamine) in its patents, but many question this data (and the clinical trial evidence on safety and efficacy using esketamine).[146]

How Ketamine Became an Antidepressant suggests several instances of serendipity in the discovery and development process of Spravato. For example, at a time when available antidepressants failed to satisfy the medical need, scientists turned their attention to glutamate signaling as a potential target for new antidepressants, and unexpectedly discovered antagonistic activity of ketamine against NMDA, a downstream target of glutamate.[147] And, when scientists struggled with the limited bioavailability of intranasal ketamine formulations, the S-enantiomer of ketamine provided the necessary potency boost.[148]

Accelerated regulatory approval and marketing exclusivity also incentivized Spravato development. The FDA had previously approved racemic ketamine formulations for anesthetic indications.[149] But, the FDA

141. *Id.*

142. Joralemon also notes a significant profit motive for Janssen, as after initial "lackluster" margins, sales of Spravato® have grown substantially in 2023. *See id.* at Section III.C.3.f.

143. *Id.* at Section IV.A.

144. *Id.* at Sections III.C.3.a, IV.D.

145. *See id.* at Sections III.C.3.a-b.

146. *Id.* at Sections III.C.3.c, III.C.3.f. Janssen's strategy for seeking patent protection on an enantiomeric formulation could not be executed worldwide, as many non-U.S. jurisdictions do not allow for the patenting of enantiomers. *See id.* at Section IV.A.

147. *Id.* at Section II.B.7, III.C.1.

148. *Id.* at Section III.C.3.a.

149. *Id.* at Section III.C.3.b.

approved Spravato as the first (and currently only) ketamine product approved for use in treating depression (in conjunction with one or more traditional antidepressants).[150] Because of the need for new depression treatments, the FDA approved Spravato under the Breakthrough Therapy Designation, allowing Janssen to fast track its Phase III trials based on success of previous Phase II trials.[151] The FDA also granted Janssen five years of new chemical entity marketing exclusivity for use of an enantiomer of a previously approved racemic mixture.[152] However, Joralemon hypothesizes that these regulatory fast tracking and exclusivity incentives may have been insufficient to encourage clinical trials on racemic ketamine formulations when patent protection was likely unavailable.[153] Although there is some evidence that clinicians have used ketamine formulations for depression off-label since the early 2000s,[154] regulators have attempted to deter this practice—for example, the United Kingdom has issued recommendations encouraging off-label use of ketamine for depression treatment only as a last resort, and the FDA recently issued explicit warnings to deter this off-label use.[155]

The need for insurance coverage and reimbursement played a major role in motivating Janssen to seek FDA approval for a repurposed esketamine product. Insurers typically require FDA approval for products as a prerequisite for providing coverage.[156] Conversely, insurance companies typically decline to reimburse off-label ketamine usage. Insurance coverage (and the reimbursement that flows from such coverage) thus motivates clinicians and patients to favor Spravato over other, much cheaper off-label racemic ketamine formulations.[157]

150. *Id.* at Sections III.C.3, Section IV.B.

151. *Id.* at Section III.C.3.d.

152. *Patent and Exclusivity For: N211243 (Esketamine Hydrochloride (Spravato) Spray EQ 28 mg Base)*, FDA ORANGE BOOK, https://www.accessdata.fda.gov/scripts/cder/ob/patent_info.cfm?Product_No=001&Appl_No=211243&Appl_type=N.

153. Joralemon, *supra* note 56, at Section IV.D.1.

154. *Id.* at Section III.C.3.b.

155. *Id.* at Sections III.C.3.b., IV.B (citing *FDA Alerts Health Care Professionals of Potential Risks Associated with Compounded Ketamine Nasal Spray*, U.S. FOOD & DRUG ADMIN. (Feb. 16, 2022), https://www.fda.gov/drugs/human-drug-compounding/fda-alerts-health-care-professionals-potential-risks-associated-compounded-ketamine-nasal-spray#:~:text=Ketamine%20hydrochloride%5Ba%5D%20(tradename,and%20maintenance%20of%20general%20anesthesia).

156. *Id.* at Section IV.D.2.

157. *Id.*

B. BIOLOGIC THERAPEUTICS: YESCARTA (CAR-T CELL THERAPY)

The pilot project also included one case study of a biologic therapeutic product. In *The CAR-T Cell Therapy Innovation Drivers: A Yescarta Case Study*,[158] Christine R. O'Brien Laramy describes Yescarta's development history and innovation drivers. Yescarta is an immunotherapy treatment comprising T cells genetically modified to target the CD19 protein associated with various large B-cell lymphomas.[159] Yescarta and other chimeric antigen receptor T cell ("CAR-T cell") therapies rely on genetically modified versions of a patient's own immune cells to target and kill cancer cells.[160]

Thus far, the FDA has approved six CAR-T cell therapy treatments for blood cancers.[161] These therapies have several potential advantages over standard chemotherapy treatment, including: (1) reduced treatment time; (2) fewer side effects, of lessened duration; and (3) longer-lasting efficacy.[162]

Yescarta's development story features substantial competition and manufacturing challenges. This story begins with basic scientific research conducted in parallel at several university and governmental research institutions.[163] These universities and research institutions transferred their technologies to multiple pharmaceutical companies and startups competing to market the first CAR-T cell therapy. This competition fostered rapid technological development but also led to ongoing litigation over IP ownership and freedom-to-operate issues.[164] In addition, the CAR-T cell therapy manufacturing process is significantly more complex and expensive than that for small molecule therapeutics: manufacturers must tailor each dose to the recipient, so a single formulation cannot be copied for later large-scale

158. O'Brien Laramy, *supra* note 57.

159. The FDA has approved Yescarta for use in "[a]dult patients with large B-cell lymphoma that is refractory to first-line chemoimmunotherapy or that relapses within 12 months of first-line chemoimmunotherapy," and "[a]dult patients with relapsed or refractory large B-cell lymphoma after two or more lines of systemic therapy, including diffuse large B-cell lymphoma (DLBCL) not otherwise specified, primary mediastinal large B-cell lymphoma, high grade B-cell lymphoma, and DLBCL arising from follicular lymphoma." Recently, under an accelerated approval regime, the FDA approved Yescarta for "[a[dult patients with relapsed or refractory follicular lymphoma (FL) after two or more lines of systemic therapy." U.S. FOOD & DRUG ADMIN., PACKAGE INSERT - YESCARTA® 1 (Mar. 1, 2024), https://www.fda.gov/media/108377/download?attachment.

160. O'Brien Laramy, *supra* note 57, at Sections II.D–F.

161. *Id.* at Table 3, Table 5, Table 6.

162. *Id.* at Section I (citing Zoom Interview with Dario Campana, Professor, Nat'l Univ. of Sing., Dep't of Paediatrics (Apr. 11, 2023)).

163. *Id.* at Sections III.A, III.B, IV.B.

164. *See, e.g.*, *id.* at Section IV.B.1

production.[165] This manufacturing expense required significant funding even for early-stage, small clinical trials (and compounded the costs of later-stage, larger trials).[166]

This case study identifies multiple instances of serendipity in the early stage development process, including the convergence of several key interdisciplinary collaborations between T cell, hematology, and oncology experts from various universities and government agencies, and funding for a research landscape conducive to an immunotherapy-based approach to cancer therapy.[167] A "flash of genius" also arose with one scientist's key insight to engineer T cells to act like other successful biologic therapeutics (antibodies); an insight critical to CAR-T cell therapy invention.[168]

Funding also played a critical role in shaping Yescarta's development story. In the early foundational stages of CAR-T cell therapy development, government grants, philanthropy, and private investment fueled research.[169] Multiple startups arose in the CAR-T cell therapy space to access private sector funding throughout the development process.[170] In transitioning to the clinical phase, manufacturers required substantial funding to scale CAR-T cell therapy manufacturing.[171] Grants and charitable donations funded early-stage smaller clinical trials; in some cases, research institutions with hospital arms had manufacturing capabilities sufficient to perform early-stage clinical trials (with only a few patients).[172] Private sector funding from large pharmaceutical and biotech companies funded larger, later-stage clinical trials necessary for FDA approval.[173]

The Yescarta case study also highlights the importance of various human drivers. At least one scientist demonstrated tenacity in pursuing CAR-T cell therapy research with limited grant funding, by seeking out key collaborations to learn background techniques underlying the CAR-T cell therapy breakthrough.[174] The case study also identifies the key role of scientific curiosity as a driver for early-stage university and government inventors.[175] For some early-stage scientists in the CAR-T cell therapy space, the possibility of

165. *Id.* at Sections II.F, III.B, IV.B.
166. *Id.* at Section III.B, III.C.
167. *Id.* at Sections IV.A.2–5.
168. *Id.* at Section IV.A.1.
169. *Id.* at Section III.A, Table 1.
170. *Id.* at Sections III, IV.A.2.
171. *See id.* at Sections III. B.
172. *Id.* at Section III.B, Table 2.
173. *Id.* at Section III.C, Table 3, Figure 8.
174. *Id.* at Section IV.A.1.
175. *Id.* at Sections IV.A.1–5.

financial rewards through patenting, royalties, and potential commercialization served as a major driver;[176] for others, potential financial incentives did not play a role[177] (and, in some cases, these financial benefits only became evident in hindsight[178]). O'Brien Laramy also notes the importance of altruism for many early-stage scientists—research clinicians often hoped to offer their patients more treatment options for cancer.[179]

The CAR-T cell therapy IP landscape is complex, as reflected in the various licensing schemes between university, government, and private innovators.[180] This case study highlights the effect of IP considerations on commercialization of Yescarta and other CAR-T cell therapy products. These considerations included: (1) uncertainty surrounding the patentability of composition claims directed to certain features of the CAR constructs;[181] (2) expiration of key composition claims near the date of regulatory approval; and (3) use of trade secrets to protect the complex manufacturing processes for CAR-T cell therapies.[182] CAR-T cell therapy companies often engaged in a collaborative licensing model, where a startup company in-licensed university CAR-T cell therapy technology and involved the academic innovators in ongoing research activities as co-founders and collaborators.[183]

Finally, the Yescarta case study identifies key FDA regulatory incentives for CAR-T cell therapies arising both during the FDA's review process and later once marketing commenced. First, the FDA granted Yescarta the Breakthrough Therapy designation in July 2015,[184] allowing for expedited review. In fact, all CAR-T cell therapies approved by the FDA to date have received the Breakthrough Therapy designation for at least one indication.[185] Second, regulatory exclusivities motivated CAR-T cell therapy development. New biological therapeutics like Yescarta receive twelve years of marketing exclusivity upon approval.[186] And, all FDA-approved CAR-T cell therapies have received at least one orphan drug exclusivity designation, granting seven additional years of marketing exclusivity.[187] The purpose of orphan drug exclusivity is to incentivize development of therapeutics for diseases affecting

176. *Id.* at Sections IV.A.1, IV.A.5.
177. *Id.* at Section IV.A.3.
178. *Id.* at Section IV.A.4.
179. *Id.* at Sections IV.A.1–5.
180. *Id.* at Section IV.B.1.
181. *Id.* at Section IV.B.1, Table 4.
182. *Id.* at Sections IV.B.1–2.
183. *Id.* at Section IV.B.1.
184. *Id.* at Section IV.C.1.
185. *Id.* at Section IV.C.1, Table 5.
186. *Id.* at Section IV.C.
187. *Id.* at Section IV.C.2, Table 6.

small patient populations (where a pharmaceutical company may not expect to recoup its R&D investment without extended exclusivity).[188]

C. PLATFORM TECHNOLOGY: NEXT-GENERATION SEQUENCING

Finally, one case study in this Issue reviews the development of a breakthrough platform technology. In *The Invention of Next-Generation Sequencing*,[189] Caressa N. Tsai explains the development story of Illumina's "next-generation sequencing" (NGS) technology.[190] The NGS technology encompasses faster and cheaper DNA sequencing methods as compared to "first generation" sequencing techniques developed in the 1970s (including Maxam-Gilbert and Sanger sequencing).[191] In the early 2000s, scientists developed NGS platforms, which allowed for "massively parallel" DNA sequencing.[192] Tsai notes that, "[w]ith NGS [technology], it is now possible to sequence the entire human genome in one day, for approximately $1,000."[193] And, Tsai outlines the significant improvements that commercial NGS technology has provided to three important life sciences applications: (1) diagnostic testing for genetic variants that may indicate disease;[194] (2) personalized medicine applications to guide physician treatment strategies;[195] and (3) direct-to-consumer genomics applications such as personalized genetic testing kits.[196]

The Invention of Next-Generation Sequencing tells the story of how Illumina came to dominate the NGS market.[197] Tsai describes two major phases of development: (1) a foundational phase, driven by university research and

188. *Orphan Drug Act – Relevant Excerpts*, U.S. FOOD & DRUG ADMIN. (Mar. 9, 2018), https://www.fda.gov/industry/designating-orphan-product-drugs-and-biological-products/orphan-drug-act-relevant-excerpts ("[B]ecause so few individuals are affected by any one rare disease or condition, a pharmaceutical company which develops an orphan drug may reasonably expect the drug to generate relatively small sales in comparison to the cost of developing the drug and consequently to incur a financial loss.").

189. Tsai, *supra* note 59.

190. *Id.* at Part I ("Today, DNA sequencing is among the most important techniques driving life sciences research, with DNA aptly perceived as the key to unlocking new diagnostic and therapeutic strategies." (citing Marcos Morey et al., *A Glimpse into Past, Present, and Future DNA Sequencing*, 110 MOLECULAR GENETICS & METABOLISM 3, 3–4 (2013)).

191. *See id.* at Part I.

192. *Id.* at Section II.B.

193. *Id.* (citing Dale Muzzey et al., *Understanding the Basics of NGS: From Mechanism to Variant Calling*, 3 CURRENT GENETIC MED. REPS. 158, 158–59 (2015)).

194. *Id.* at Section II.C.1.

195. *Id.* at Section II.C.2.

196. *Id.* at Section II.C.3.

197. *Id.* at Section II.B (citing Complaint ¶¶ 1, 34, 35, Illumina, Inc. & Pacific Biosciences California, Inc., F.T.C. Docket No. 9387 (Dec. 17, 2019)).

public funding sources and focused on scientific curiosity and altruistic goals; and (2) a later commercialization phase, driven by private funding sources and Solexa's (and later, Illumina's) pursuit of IP protection.[198]

Tsai highlights serendipity in the development of NGS platform technology. The Solexa (now Illumina) idea emerged from a collaboration between Shankar Balasubramanian and David Klenerman—yet these scientists did not begin collaborating for the purpose of creating a commercialized NGS platform.[199] Instead, the scientists sought to understand the enzyme kinetics of DNA polymerase and were struggling to capture the exact timing of nucleotide incorporation.[200] The key scientific serendipity occurred when Balasubramanian, Klenerman, and their two postdoctoral fellows met at the Panton Arms in Cambridge to discuss their enzyme kinetics research.[201] There, the team developed the idea of using a parallelized approach to overcome the nucleotide incorporation visualization issue.[202] But, the scientists also realized that parallelization might also dramatically improve DNA sequencing applications.[203] This meeting resulted in the first conceptualization of the Illumina NGS platform.

A series of human factors (scientific curiosity, altruism, and academic recognition) drove early-stage development of DNA sequencing approaches. For first-generation sequencing technologies, researchers initially pursued research questions driven by scientific curiosity, rather than commercialization or IP acquisition goals.[204] For example, the scientists participating in the Human Genome Project focused on altruistic aims, facilitated by non-commercial public funding (typically from governmental sources such as the U.K. Medical Research Council and the NIH) and open-source distribution of sequencing data.[205] This open-source vision conflicted with the competing private effort at Celera Genomics, led by Craig Venter, which focused on the commercial potential of sequencing technology and marketing sequencing data.[206] Eventually, the altruistic view won out. After a short monetization effort by Celera, the genomic data generated by both efforts ended up in the public domain.[207] Tsai notes that academic recognition likely drove many

198. *Id.* at Sections IV (Introduction), IV.B.1.
199. *Id.* at Sections III.D, IV.A.5.
200. *Id.* at Section III.D.
201. *Id.*
202. *Id.*
203. *Id.*
204. *Id.*; Section IV.A.5.
205. *Id.* at Section IV.A.2, IV.A.4.
206. *Id.* at Section IV.A.2.
207. *Id.*

researchers as DNA sequencing publications consistently received publication offers from high-impact journals.[208]

In later-stage development of the Illumina NGS platform, other innovation drivers rose to dominance, including private funding, broad IP protection, and a focus on commercialization. As NGS technology is significantly more expensive compared to earlier sequencing techniques, funding played a critical role in pushing the technology towards commercialization.[209] Most key innovators in the Illumina NGS story worked at universities or in other academic settings and spun their work out into startups.[210] For example, Solexa's success occurred, at least in part, due to early funding from the Abingworth investment firm, a firm focused on funding life sciences research including DNA sequencing applications.[211]

The history surrounding the IP landscape of NGS illustrates several interesting milestones relevant to Illumina's success. First, as the progenitors of the first-generation foundational sequencing methods (Maxam-Gilbert and Sanger) declined to seek patent protection, NGS companies could exploit available IP space (from a lack of blocking patents).[212] Scientists developed the first-generation sequencing technologies in the 1970s, before Congress enacted the Bayh-Dole Act. Patenting was also not within the "ethos" for scientists at this time. Moreover, the U.K. Medical Research Council expressly barred Sanger from patenting his work as a condition of his funding. Second, as discussed *supra*, Human Genome Project era researchers had differing views on using patent protection and mandating public distribution of DNA sequencing data. Researchers affiliated with the Human Genome Project generally declined to patent their work or seek data exclusivity, fearing preemption of future research. In particular, the Human Genome Project required participants to disclose sequence data in public databases within approximately twenty-four hours of generation.[213] Conversely, researchers affiliated with Celera sought patents on various research outputs, including expressed sequence tags (fragments of cDNA), and sought to monetize data generated from sequencing efforts.[214] The altruistic perspective of the Human Genome Project scientists eventually won out. Coincidentally, later case law restricted patent eligibility for biological inventions, including genes.[215] Third,

208. *Id.* at Section IV.A.3.
209. *Id.* at Section IV.B.1.
210. *Id.* at Section IV.A.4.
211. *Id.* at Sections III.D, III.E, IV.B.1.
212. *Id.* at Sections III.A, III.B, IV.A.1.
213. *Id.* at Sections III.B, IV.A.2.
214. *Id.* at Section IV.A.2.
215. *Id.*

during the Solexa (now Illumina) era, companies focused on obtaining a broad patent portfolio to support commercialization efforts.[216] Tsai notes that Illumina now holds patents on "virtually every eligible aspect of their [NGS] technology."[217] Tsai traces the development of the patented technology for the three key elements of NGS (the use of a solid support array,[218] bridge PCR clustering for read amplification,[219] and sequencing-by-synthesis[220]), including strategic in-licensing deals (most notably for the bridge PCR clustering technology).[221]

Solexa and other startup companies competed to reach the market first with an NGS machine.[222] In effect, Solexa "won" because it reached the market first.[223] Later, Illumina essentially sought a monopoly on all macromolecule sequencing markets by acquiring Solexa.[224] Illumina's willingness to aggressively enforce its patent portfolio through litigation remains a significant deterrent to potential competitors in the NGS space; this enforcement strategy began as early as the Solexa merger in 2007.[225] And, Illumina has continued a merger and acquisition campaign in the sequencing space, encountering scrutiny from the Federal Trade Commission for potentially anticompetitive practices.[226]

IV. NEXT STEPS: DRAWING INITIAL LESSONS AND EXPANDING THE CASE STUDY UNIVERSE

The five Articles published in this Issue reflect the successful completion of the pilot case study project, in which authors implemented the case study framework described in Section II.C *supra* to identify the innovation drivers and impediments for each invention. Section IV.A explores initial lessons learned through comparison across the case studies, and Section IV.B describes the planned next steps for the project.

216. *Id.* at Section IV.B.2.

217. *Id.* (citing *Illumina Virtual Patent Marking*, ILLUMINA, https://www.illumina.com/company/legal/patents.html (last visited Oct. 22, 2022)).

218. *Id.* at Sections III.C.1, IV.B.2.a.

219. *Id.* at Sections III.C.2, IV.B.2.b.

220. *Id.* at Sections III.C.3, IV.B.2.c.

221. *Id.* at Sections III.D, IV.B.2.b, IV.B.3.

222. *Id.* at Section IV.B.4.

223. *Id.*

224. *See id.* at Sections III.E, IV.B.4.

225. *Id.* at Section IV.B.5.

226. *Id.*

A. INITIAL LESSONS

These five Articles span a wide range of industries and development pathways within the life sciences ecosystem. Although drawing wide-reaching comparative conclusions at this early stage of the project is somewhat challenging (and additional case studies will certainly allow for more comprehensive comparisons and insights), comparison across these five case studies reveals several key lessons and observations about innovation drivers and impediments. These lessons address factors important to innovation across a wide range of technological areas.

First, interestingly, all five case studies in this Issue illustrate a key role for serendipity, usually in the identification or combination of principles underlying scientific breakthroughs in early-stage development.[227] Although further study will be needed to confirm this principle, these results indicate that the process for optimizing innovative life sciences inventions should include cultivating environments in which serendipitous discoveries can arise. This observation favors enhancing the volume of basic, foundational scientific research conducted at universities and research institutions through increased governmental and philanthropic funding for basic scientific research.

Second, the chronology of invention for each case study begins with fundamental academic research. In all five case studies, early-stage university research (typically funded by a governmental entity) produced a proof of concept for the invention, which then could be translated into the commercialization process.[228] This finding reflects the key role of technology transfer via the Bayh-Dole Act or similar mechanisms in other jurisdictions (as reflected in the Truvada case study) in facilitating the privatization of university research for commercialization. Planned future research will further probe the details of these privatization mechanisms and their impacts on the life sciences ecosystem as a whole.

Third, in several of the case studies (Truvada, CAR-T cell therapy, and next-generation sequencing), startup companies played critical roles in commercializing technology transferred from universities.[229] These startup

227. *See* Zhang, *supra* note 54, at Sections II.A, III.F, IV.D; Kasper, *supra* note 55, at Sections IV.B.1.a.i, IV.B.2.a.i; Joralemon, *supra* note 56, at Sections II.B.7, III.C.1, III.C.3.a; O'Brien Laramy, *supra* note 57, at Sections IV.A.1–5; Tsai, *supra* note 59, at Sections III.D, IV.A.5.

228. *See* Zhang, *supra* note 54, at Sections III.A–C, IV.B–C; Kasper, *supra* note 55, at Sections III.B, IV.B; Joralemon, *supra* note 56, at Section III.C; O'Brien Laramy, *supra* note 57, at Sections III.A–B, IV.A–B; Tsai, *supra* note 59, at Sections III.C–D, IV.A.

229. *See* Kasper, *supra* note 55, at Sections III.B.1, III.B.2, III.C, IV.B.1.b, IV.B.2.b; O'Brien Laramy, *supra* note 57, at Section III.C; Tsai, *supra* note 59; at Sections III.D–E, IV.B.

companies succeeded in commercialization efforts for several reasons, including: specialized scientific expertise in the relevant technological area(s); focused and intensive efforts on a single objective or therapeutic target; and successful pursuit of funding to support a focused research agenda. These examples, along with many others in the life sciences ecosystem, highlight that startups can serve as highly successful vehicles for riskier, breakthrough innovations in the life sciences space. Additional policy incentives and funding are likely to boost the effectiveness of the startup model in fostering early-stage, risky innovation projects.

This discussion is not intended to suggest that large pharmaceutical companies do not play a critical role in bringing many inventions to commercialization. Certainly, not all successful life sciences innovation requires startup companies, and large pharmaceutical companies also face significant risk in the commercialization process. As reflected even in this small set of case studies, large pharmaceutical companies brought Lyrica and Spravato through the commercialization process successfully, facing uncertainty and risk throughout development.[230] But large pre-existing companies face competing priorities and may lack focused scientific expertise in particular areas. The key presence of startup companies in multiple case studies suggests that, at least for some inventions, focused efforts and expertise can play an integral role in successful commercialization, and that the benefits of the startup model should be further studied and incentivized. Future case studies will further examine the key role that startups play in the life sciences ecosystem.

Fourth, in each case study, IP rights fostered commercialization efforts. Whether via patent or trade secret, each commercializing entity prioritized the development of a robust IP portfolio.[231] These entities also engaged in vigorous exploitation and protection of the IP landscape surrounding the commercialized product through: (1) strategic in-licensing of valuable assets;[232] (2) avoidance of compulsory licensing through voluntary licensing procedures;[233] (3) strategic patent filing to exploit available IP space but avoid

230. *See* Zhang, *supra* note 54, at Sections III.C–D; Joralemon, *supra* note 56, at Section III.C.3.

231. *See* Zhang, *supra* note 54, at Sections III.E, IV.C, IV.D; Kasper, *supra* note 55, at Sections III.B, III.C, IV.B, IV.C; Joralemon, *supra* note 56, at Sections III.C.3, IV.A, V.C.2; O'Brien Laramy, *supra* note 57, at Section IV.B; Tsai, *supra* note 59, at Sections III.E, IV.B.2, IV.B.3.

232. *See* Zhang, *supra* note 54, at Sections III.E, IV.C, IV.D; Kasper, *supra* note 55, at Sections III.B, III.C, IV.B, IV.C; Joralemon, *supra* note 56, at Section III.C.3; O'Brien Laramy, *supra* note 57, at Section IV.B; Tsai, *supra* note 59, at Sections III.E, IV.B.2, IV.B.3.

233. *See* Kasper, *supra* note 55, at Section III.B.1.b.

prior art and potential subject matter patentability issues;[234] and/or (4) defense of their IP rights through litigation.[235] These often resource-intensive efforts indicate that the commercializing entities viewed IP protection as essential to recoup their significant R&D investments. Additional case studies will further elucidate IP's role in facilitating the entry of much-needed funding into the life sciences development ecosystem, particularly in the earlier stages of development.

Fifth, several case studies (including Lyrica, Truvada, Spravato, and Yescarta) describe innovation drivers related to regulatory mechanisms designed to accelerate marketing approval, allow for more efficient clinical trials, and provide additional exclusivity upon approval.[236] The availability of accelerated regulatory mechanisms and abbreviated clinical trial designs provides important incentives for innovators to select certain pharmaceutical products and indications. Further, manufacturers appear to view these incentives, along with mechanisms for additional exclusivity (such as the orphan drug designation), as important tools to augment IP exclusivity and incentivize eligible projects.

Sixth, as shown by the Spravato case study, insurance reimbursement incentives may heavily influence development strategy for certain therapeutic cases.[237] In that example, insurers required FDA approval for esketamine as a treatment-resistant depression therapeutic to obtain insurance coverage and reimbursement.[238] Off-label use of cheaper racemic ketamine alternatives would likely be ineligible for reimbursement under current rules, forcing clinicians and patients to favor Spravato—a more expensive but reimbursable product.[239] For repurposed drugs, policymakers could consider further regulation of insurance reimbursement practices or development of new mechanisms to incentivize clinical testing for repurposed drugs to expand patient access to effective treatments and lower drug costs.

Seventh and finally, ethical, moral, and political considerations may significantly impact life sciences innovation, as demonstrated by at least

234. *See* Joralemon, *supra* note 56, at Sections III.C.3, IV.D, V.C.2; O'Brien Laramy, *supra* note 57, at Section IV.B; Tsai, *supra* note 59, at Sections III.E, IV.B.2.

235. *See* Zhang, *supra* note 54, at Section III.E; Kasper, *supra* note 55, at Sections III.C, IV.C.1.a; O'Brien Laramy, *supra* note 57, at Section IV.B.1; Tsai, *supra* note 59, at Section IV.B.5.

236. *See* Kasper, *supra* note 55, at Sections III.C.1.b, IV.C.1.a; Joralemon, *supra* note 56, at Sections III.C.3.d, IV.B, IV.D.1; O'Brien Laramy, *supra* note 57, at Section IV.C.1 & Table 5.

237. *See* Joralemon, *supra* note 56, at Section IV.D.2.

238. *See id.*

239. *See id.*

Truvada (for HIV treatment and prevention)[240] and Lyrica (for, among other indications, epilepsy).[241] Both case studies highlight the importance of advocacy in the face of stigma to develop the political environments needed to fund scientific research to develop therapeutics for stigmatized diseases.

B. EXPANDING THE CASE STUDY UNIVERSE

The ultimate goal of the comparative case study approach outlined in this Article is to draw evidence-based comparative insights and actionable conclusions across a wide range of case studies. This approach provides a robust understanding of the many factors that drive and impede innovation in this fragmented and diverse space. This Article and Issue present a model to identify additional policy solutions to maximize life-changing and life-saving innovations.

Section IV.A highlights a number of policy-oriented insights based on the pilot study; further development of the policies proposed here—and identification of additional policies to advance life science innovation—will require a larger pool of case studies. Ideally, this project would include a broad range of life science inventions arising from diverse development and commercialization strategies, which engaged with key institutions and funding sources in unique ways. Future case studies should diversify the types of breakthrough life sciences inventions studied, including additional small molecule therapeutics, biologic therapeutics, platform technologies, and diagnostic methods. With this broad pool of case studies, researchers will be able to draw data-driven insights and formulate policy solutions to effectively promote biomedical advances, particularly in light of the new technological challenges such as the emergence of big data and artificial intelligence.

240. *See* Kasper, *supra* note 55, at Sections III.A.I, III.A.3.a–c, IV.A.1–2, IV.C.2.a.
241. *See* Zhang, *supra* note 54, at Section IV.A.

SERENDIPITOUS LAB DISCOVERY TO COMMERCIAL BLOCKBUSTER: THE INVENTION OF LYRICA

Kaidi (Ted) Zhang[†]

TABLE OF CONTENTS

I. INTRODUCTION

The development and successful commercialization of new pharmaceutical drugs are intricate processes that require a delicate balance of scientific innovation, strategic decision-making, and serendipitous discovery.

DOI: https://doi.org/10.15779/Z38959C86N

† Ph.D. Candidate, University of California, Berkeley, College of Chemistry. For valuable advice and feedback thanks to Professor Allison Schmitt, Professor Peter Menell, Will Kasper, Caressa Tsai, Yuhan Wu and Karissa Lin. Special thanks to Professor Richard Silverman for the interview.

The discovery and development story of Lyrica is a fascinating representation of such a balance: a drug initially developed for treating epilepsy became the first-line treatment for neuropathic pain; a proposed mechanism that was confirmed in the lab turned out to be false in animal testing; a basic science discovery in a university developed into one of the most profitable blockbuster drugs. This Article delves into the story behind the creation of Lyrica, highlighting the key players, pivotal moments, and factors that contributed to this innovative therapeutic. From the collaborative efforts of academic researchers to the involvement of pharmaceutical giants, this Article examines the multifaceted nature of innovation in life sciences.

Part II provides a technical summary of pregabalin, the active pharmaceutical ingredient of Lyrica, and explores the historical context of drugs designed to address epilepsy and neuropathic pain—key therapeutic targets for Lyrica. Part III discusses the evolution of Lyrica's development, shedding light on the pivotal contributions of scientists, academic institutions, and pharmaceutical firms. Finally, Part IV examines several factors that either catalyzed or impeded the invention of Lyrica. This section delves into the specific driving forces that spurred the creation of Lyrica.

II. TECHNICAL PRIMER

Pregabalin, sold under the brand name Lyrica exclusively until 2019, is an anticonvulsant, analgesic, and anxiolytic medication for treating epilepsy, neuropathic pain, fibromyalgia, opioid withdrawal, and generalized anxiety disorder.[1] To provide context for the unique discovery and development story of Lyrica, this Part will explain the molecular structure and mechanism of action of pregabalin, as well as the history of epilepsy and neuropathic pain treatment—two of the main indications for treatment with Lyrica.

A. STRUCTURE AND MECHANISM OF PREGABALIN

γ-aminobutyric acid (GABA) is an important endogenous neurotransmitter in the human brain that helps to regulate neuronal activity by inhibiting the firing of neurons (Figure 1A).[2] Diminished levels of GABA in the brain have been shown to contribute to epileptic seizures. Epilepsy is a

1. *Pregabalin Monograph for Professionals*, DRUGS.COM (Nov. 23, 2022), www.drugs.com/monograph/pregabalin.html; Rainer Freynhagen et al., *Pregabalin for the Treatment of Drug and Alcohol Withdrawal Symptoms: A Comprehensive Review*, 30 CNS DRUGS 1191, 1192–93 (2016); James E. Frampton, *Pregabalin: A Review of Its Use in Adults with Generalized Anxiety Disorder*, 28 CNS DRUGS 835, 835 (2014).

2. Richard B. Silverman, *From Basic Science to Blockbuster Drug: The Discovery of Lyrica*, 47 ANGEWANDTE CHEMIE INT'L EDITION 3500, 3500 (2008).

neurological disorder characterized by abnormal electrical activity in the brain, which leads to repeated seizures.[3] Direct injection of GABA into the brain can alleviate epileptic symptoms, but the lipophobic nature of GABA limits its use as an anticonvulsant drug.[4]

Gabapentin (Figure 1B) and pregabalin (Figure 1C) are synthetic derivatives of GABA with similar biological activity but enhanced lipophobicity—which makes both more effective as anticonvulsant drugs. The enhanced lipophobicity is derived from additional alkyl groups on gabapentin and pregabalin, compared to endogenous GABA.[5] Gabapentin is the active pharmaceutical ingredient in Neurontin.[6] Pregabalin, or 3-alkyl γ-aminobutyric acid, is the main ingredient of Lyrica.

The development of both gabapentin and pregabalin stemmed from researchers probing into the fundamental mechanisms underlying epileptogenesis.[7] The initial discovery of new mechanisms informed new potential targets for anti-epileptic drug therapies.[8] Both gabapentin and pregabalin were developed due to their association with the glutamate-GABA cycle. Glutamate and GABA interconvert in the brain to balance the excitatory neurotransmitter glutamate and the inhibitory neurotransmitter GABA (Figure 2).[9] The conversion of glutamate into GABA is catalyzed by the enzyme L-glutamic acid decarboxylase (GAD). GABA is then released into the synaptic cleft and binds to GABA receptors on the postsynaptic neuron, inhibiting its firing.[10]

3. *Epilepsy and Seizures*, NAT'L INST. NEUROLOGICAL DISORDERS & STROKE, https://www.ninds.nih.gov/health-information/disorders/epilepsy-and-seizures (last visited Sept. 9, 2023) [hereinafter NIH Epilepsy Information].

4. ELKA TOUITOU & BRIAN W. BARRY, ENHANCEMENT IN DRUG DELIVERY 575–89 (2006).

5. *Id.*

6. *Neurontin*, DRUGS.COM (Feb. 21, 2022), https://www.drugs.com/neurontin.html.

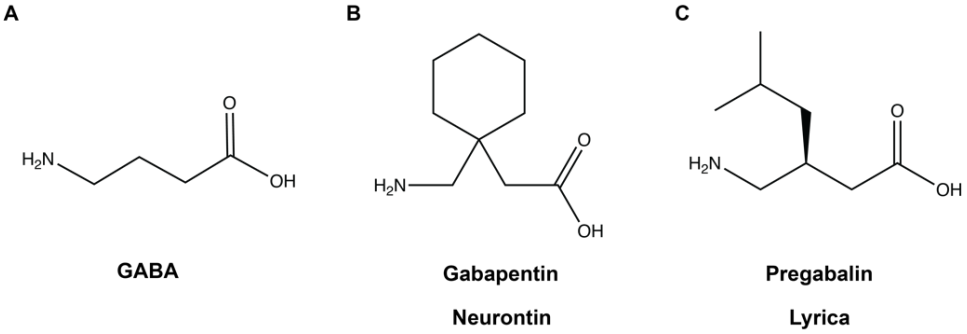
7. NIH Epilepsy Information, *supra* note 3.

8. *Id.*

9. Anne B. Walls et al., *The Glutamine–glutamate/GABA Cycle: Function, Regional Differences in Glutamate and GABA Production and Effects of Interference with GABA Metabolism*, 40 NEUROCHEMICAL RSCH. 402, 402–03 (2015).

10. *Id.*

Figure 1: Chemical Structures of (A) γ-Aminobutyric Acid (GABA), (B) Gabapentin, and (C) Pregabalin.



GABA aminotransferase (GABA-AT) is the enzyme responsible for the degradation of GABA in the brain. Increased concentration of GABA-AT leads to a decrease in GABA accumulation, which can contribute to epileptic seizures. Therefore, one ideal compound for treating epilepsy might work by decreasing GABA-AT concentration while maintaining the level of GAD to ensure the production of sufficient GABA.[11]

Initially, scientists hypothesized that GABA derivatives could be regulated by the enzymes that control the concentration of GABA in the brain and thereby modulate the glutamate-GABA cycle.[12] However, it was later discovered that gabapentin and pregabalin do not directly affect the enzymes involved in GABA metabolism.[13] Instead, they bind to a specific type of voltage-gated calcium channel in the brain, thereby reducing the release of certain neurotransmitters, including glutamate, which can contribute to the development of seizures.[14]

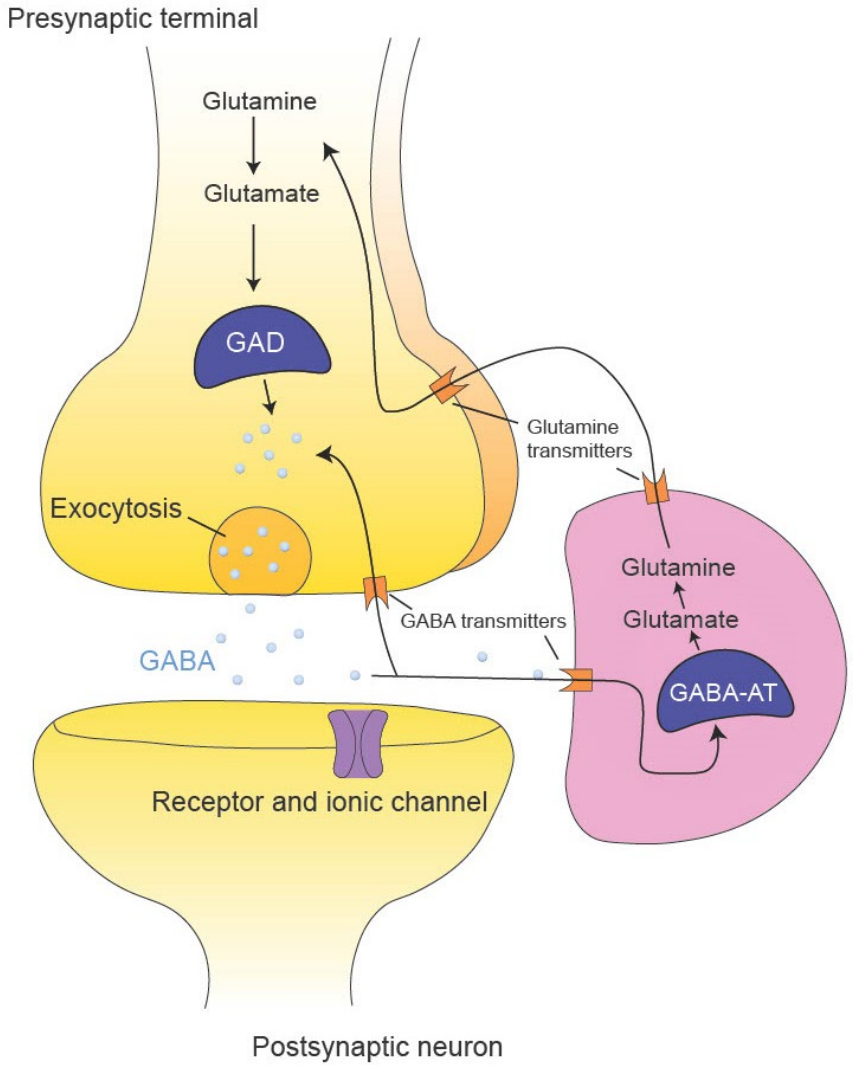
11. Silverman, *supra* note 2, at 3500.

12. Charles P. Taylor et al., *3-Alkyl GABA and 3-Alkylglutamic Acid Analogues: Two New Classes of Anticonvulsant Agents*, 11 EPILEPSY RSCH. 103, 104–05 (1992).

13. Silverman, *supra* note 2, at 3502.

14. David McClelland et al., *A Study Comparing the Actions of Gabapentin and Pregabalin on the Electrophysiological Properties of Cultured DRG Neurones from Neonatal Rats*, 4 BMC PHARMACOLOGY 1, 2 (2004).

Figure 2: A Simplified Schematic of the GABA-Glutamine Cycle in a GABAergic Synapse; GABA-AT Converts GABA into Glutamate While GAD Does the Reverse.



B. EPILEPSY AND ITS TREATMENT

Epilepsy is defined by the International League Against Epilepsy (ILAE) as a disease of the brain that results in at least two unprovoked seizures at least twenty-four hours apart.[15] It affects over fifty million people worldwide, with

15. Christian M. Kaculini et al., *The History of Epilepsy: From Ancient Mystery to Modern Misconception*, 13 CUREUS 1, 1 (2021).

over 80% of the burden in developing countries.[16] Shockingly, based on a survey in 2005, 80–90% of those affected were left untreated.[17] The development of treatments for epilepsy will be discussed below, and major milestone medications are listed in Table 1.

Table 1: Selected Milestone Treatments Developed for Epilepsy and Their Effectiveness Against Standard Screening Processes.

Drug	Time Developed	Maximal Electroshock Seizure test	Subcutaneous Pentylenetetrazol	Intravenous Pentylenetetrazol
Potassium bromide	1850s	N/A	N/A	N/A
Phenobarbital	1910s	Yes	Yes	Yes
Phenytoin	1930s	Yes	Weak effect	Yes
Diazepam	1960s	No effect	Yes	Yes
Gabapentin	Early 1990s	Yes	Yes	Yes
Levetiracetam	1990s	No effect	No effect	Yes
Pregabalin	Late 1990s	Yes	Weak effect	Yes

The search for anti-epileptic drugs (AEDs) began in the 19th century, but only after epilepsy was no longer mystified as a "sacred disease" for which only divine intervention can be the cure and discrimination against those afflicted had subsided.[18] The first drug therapy for epilepsy, potassium bromide, was serendipitously discovered by Sir Charles Locock in 1857.[19] He initially associated epilepsy with excessive masturbation and menstrual periods.[20] After realizing potassium bromide caused impotency on himself, he tested it and found it to effectively treat seizure in all but one of fourteen or fifteen women.[21] Another early medication phenobarbital (5-ethyl-5-phenylbarbituric acid), marketed under the name Luminal, was manufactured in 1912 by Bayer

16. WORLD HEALTH ORGANIZATION, ATLAS: EPILEPSY CARE IN THE WORLD 3 (2005) [hereinafter WHO, EPILEPSY CARE].

17. *Id.*

18. MERVYN J. EADIE & PETER F. BLADIN, A DISEASE ONCE SACRED: A HISTORY OF THE MEDICAL UNDERSTANDING OF EPILEPSY 165–69, 226–30 (2001).

19. Mervyn J. Eadie, *Sir Charles Locock and Potassium Bromide*, 42 J. ROYAL COLL. PHYSICIANS EDINBURGH 274, 275 (2012).

20. *Id.*

21. *Id.*

initially to treat insomnia since it had sedative effects on dogs.[22] Alfred Hauptmann later discovered its superior anti-seizure efficacy over potassium bromide.[23] These examples illustrate that most of the early treatments for epilepsy resulted from fortuitous discoveries.

On the back of these accidental discoveries, researchers began to explore systematic screening methods to identify additional AEDs, which lead to the development of two important animal models to be used for preliminary testing. In the early 1930s, Tracy J. Merritt and H. Houston Putam established an electroshock threshold model in cats. They discovered and showed the clinical efficacy of phenytoin (sold under the brand name Dilantin) provided by the pharmaceutical company Parke-Davis, in addition to the efficacy of a few other chemicals. Parke-Davis also sponsored this research.[24] The electroshock test was later adapted for use in mice and rats, and the maximal electroshock seizure (MES) test was created.[25] Essentially, the MES test involves passing an electrical stimulus of sufficient intensity to induce maximal seizures of the rats' hind limbs.[26] In this model, researchers looking to assay the activity of possible AEDs can easily evaluate the augmentation of the threshold current, with or without AED administration.[27] The MES test is easily conducted, requires a minimal investment in equipment and technical expertise, and is well-standardized.[28]

In the 1940s, Guy M. Everett and Richard K. Richards developed another animal model that used subcutaneous (s.c.) administration of pentylenetetrazol (PTZ)—later shown to be a GABA-AT antagonist[29]—to induce seizures in mice.[30] This model can be used to test the antagonistic activity of possible

22. Zeid Yasiry & Simon D. Shorvon, *How Phenobarbital Revolutionized Epilepsy Therapy: The Story of Phenobarbital Therapy in Epilepsy in the Last 100 Years*, 53 EPILEPSIA 26, 27 (2012).

23. *Id.*

24. Roger J. Porter & Harvey J. Kupferberg, *The Anticonvulsant Screening Program of the National Institute of Neurological Disorders and Stroke, NIH: History and Contributions to Clinical Care in the Twentieth Century and Beyond*, 42 NEUROCHEMICAL RSCH. 1889, 1889 (2017).

25. James EP Toman et al., *Properties of Maximal Seizures, and Their Alteration by Anticonvulsant Drugs and Other Agents*, 9 J. NEUROPHYSIOLOGY 231, 232 (1946).

26. Margarida M. Castel-Branco et al., *The Maximal Electroshock Seizure (MES) Model in the Preclinical Assessment of Potential New Antiepileptic Drugs*, 31 METHODS & FINDINGS EXPERIMENTAL & CLINICAL PHARMACOLOGY 101, 102 (2009).

27. *Id.*

28. *Id.*

29. Guy M. Everett & Richard K. Richards, *Comparative Anticonvulsive Action of 3, 5, 5-trimethyloxazolidine-2, 4-dione (Tridione), Dilantin and Phenobarbital*, 81 J. PHARMACOLOGY & EXPERIMENTAL THERAPEUTICS 402, 402 (1944).

30. *Pentylenetetrazol Seizure Threshold Test (mouse, rat)*, NAT'L INST. NEUROLOGICAL DISORDERS & STROKE, https://panache.ninds.nih.gov/TestDescription/TestPST (last visited May 23, 2023).

AEDs against PTZ, to alleviate seizure induction.[31] PTZ can also be administered intravenously (i.v.).[32]

The MES test is a model of generalized tonic-clonic seizures that involve both stiffening and twitching or jerking of a person's muscles. On the other hand, the s.c. PTZ-induced seizures are thought to mimic the myoclonic epilepsy that causes sharp, uncontrollable muscle movements in humans.[33] Administering i.v. PTZ allows for a test based on threshold doses of PTZ instead of threshold time typically used in s.c. PTZ, thanks to i.v. PTZ's higher reliability and reproducibility.[34] This test can bring insight into seizure susceptibility and different phases of seizures in individual animals.[35]

The MES and PTZ seizure tests in rodents paved the way for the discovery of succinimides, trimethadione, and many other AEDs in the 1950s and 1960s.[36] These animal models also laid the foundation for the U.S. National Institutes of Health (NIH)/National Institute of Neurological Disorders and Stroke (NINDS)-sponsored Anticonvulsant Screening Program (ASP) in the 1970s. The ASP, led by Edwart Swinyard, Dixon Woodbury, and their colleagues at the University of Utah, played a crucial role in the development of new AEDs by offering pharmaceutical companies a standardized screening process.[37] With the ASP, companies were able to evaluate a large number of chemicals (over 20,000 compounds in total) in a consistent manner.[38] The program also provided guidance for clinical trials, including information for pharmacokinetic and safety studies.[39] Several of the drugs brought forward by this program, such as felbamate, topiramate, rufinamide, lacosamide, and retigabine, later became standard treatment options for epilepsy. Notably, ASP contributed to the discovery of gabapentin, but not pregabalin.[40]

With increasing knowledge of epilepsy, new screening methods were developed and greater attention was directed towards preventative and

31. *Id.*

32. *Id.*

33. KATARZYNA SOCAŁA & PIOTR WLAŹ, EXPERIMENTAL AND TRANSLATIONAL METHODS TO SCREEN DRUGS EFFECTIVE AGAINST SEIZURES AND EPILEPSY 79 (2021).

34. Sanjay N. Mandhane et al., *Timed Pentylenetetrazol Infusion Test: A Comparative Analysis with sc PTZ and MES Models of Anticonvulsant Screening in Mice*, 16 SEIZURE 636, 640 (2007).

35. *Id.* at 637.

36. Wolfgang Löscher, *Animal Models of Seizures and Epilepsy: Past, Present, and Future Role for the Discovery of Antiseizure Drugs*, 42 NEUROCHEMICAL RSCH. 1873, 1877 (2017).

37. Porter & Kupferberg, *supra* note 24, at 1890.

38. *Id.* at 1891.

39. *Id.*

40. Wolfgang Löscher & Dieter Schmidt, *Modern Antiepileptic Drug Development Has Failed to Deliver: Ways out of the Current Dilemma,* 52 EPILEPSIA 657, 657–58 (2011).

curative efforts.[41] Unfortunately, none of the currently available clinical AEDs can alter epileptogenesis in the human brain.[42] In 2015, the ASP became the Epilepsy Therapy Screening Program (ETSP), ushering in a new multi-step screening process that targets various types of epilepsies[43] as well as epileptogenesis.[44] This new comprehensive approach led to the discovery of Levetiracetam—one of the most prescribed AEDs in history—despite this drug initially failing both the MES and s.c. PTZ tests.[45]

Thanks to the rapid development of epilepsy treatment, most first-line treatment options of AEDs have become available around the world. However, the cost of the drugs still varies significantly across regions. For instance, the cost for treatment is three and a half times higher for phenytoin in low-income countries than high-income countries.[46] Accessibility of new AEDs will continue to be a major challenge for patients in the future.

C. NEUROPATHIC PAIN AND ITS TREATMENT

Neuropathic pain is defined by the International Association for the Study of Pain (IASP) as pain resulting from a lesion or disease affecting the somatosensory nervous system.[47] Chronic pain with neuropathic characteristics is estimated to affect 7–10% of the general population.[48] Though the discussion of neuropathic pain can be traced back to medieval Persia,[49] Silas Weir Mitchell was accredited with starting the systematic scientific investigation of neuropathic pain following his detailed accounts of causalgia, a severe burning pain in a limb caused by injury to a peripheral nerve,

41. Jong M. Rho & H. Steve White, *Brief History of Anti-Seizure Drug Development*, 3 EPILEPSIA OPEN 114, 117–18 (2018).

42. *Id.* at 117.

43. Anne T. Berg et al., *Revised Terminology and Concepts for Organization of Seizures and Epilepsies: Report of the ILAE Commission on Classification and Terminology, 2005–2009*, 51 EPILEPSIA 675 (2010). According to the International League Against Epilepsy (ILAE), there are over thirty epilepsy syndromes.

44. John H. Kehne et al., *The National Institute of Neurological Disorders and Stroke (NINDS) Epilepsy Therapy Screening Program (ETSP)*, 42 NEUROCHEMICAL RSCH. 1894, 1897–900 (2017).

45. Henrik Klitgaard & Peter Verdru, *Levetiracetam: The First SV2A Ligand for the Treatment of Epilepsy*, 2 EXPERT OPINION ON DRUG DISCOVERY 1537, 1537–38 (2007).

46. WHO, EPILEPSY CARE, *supra* note 16.

47. Bridin P. Murnion, *Neuropathic Pain: Current Definition and Review of Drug Treatment*, 41 AUS. PRESCRIBER 60, 60 (2018).

48. Oliver van Hecke et al., *Neuropathic Pain in the General Population: A Systematic Review of Epidemiological Studies*, 155 PAIN 654, 660 (2014); Didier Bouhassira et al., *Prevalence of Chronic Pain with Neuropathic Characteristics in the General Population*, 136 PAIN 380, 384 (2008).

49. Mojtaba Heydari et al., *The Origin of the Concept of Neuropathic Pain in Early Medieval Persia (9th-12th Century Ce)*, 13 ACTA MEDICO-HISTORICA ADRIATICA 9, 10 (2015).

in American Civil War casualties.[50] However, the exact definition of neuropathic pain is still a matter of debate.[51]

As neuropathic pain may not respond well to primary analgesics, it is often treated with adjuvant analgesics, i.e., drugs that do not have analgesia as a primary indication (e.g., antidepressants and AEDs).[52] Tricyclic antidepressant (TCA) drugs were reported to have analgesic effects over sixty years ago, but were approved for neuropathic pain only in the early 1990s.[53] AEDs have been used to treat trigeminal neuralgia, a type of neuropathic pain, since the 1960s.[54] The first published attempt to use AEDs for neuropathic pain dates back to 1942, when phenytoin was used to treat patients with trigeminal neuralgia.[55] Other possible treatment options include antipsychotics, anxiolytics, antiarrhythmics, and opioids.[56]

As awareness of the burden of neuropathic pain on patients increased in the early 2000s, many randomized controlled trials (RCTs) were conducted, and evidence-based guidelines were established for the search of new treatments under the auspices of IASP.[57] Gabapentin and pregabalin were shown to bind to voltage-gated calcium channels (at the α_2-δ subunit), producing changes in neurotransmitter release.[58] Both have proven efficacious compared to placebo treatments administered to individuals with multiple neuropathic pain conditions.[59] Nowadays, TCAs and AEDs such as gabapentin and pregabalin are used as first-line treatment options for neuropathic pain, with opioids and tramadol as secondary options.[60] Overall,

50. SILAS WEIR MITCHELL ET AL., GUNSHOT WOUNDS AND OTHER INJURIES OF NERVES 35–36 (1989).

51. John W. Scadding, *Treatment of Neuropathic Pain: Historical Aspects*, 5 PAIN MED. 1, 6 (2004).

52. *Id.* at 4–6; M. Sam Chong & Zahid H. Bajwa, *Diagnosis and Treatment of Neuropathic Pain*, 25 J. PAIN & SYMPTOM MGMT. 4, 5–6 (2003).

53. F. Paoli et al., *Preliminary Note on the Action of Imipramine in Painful States*, 102 REVUE NEUROLOGIQUE 503, 503 (1960); Søren H. Sindrup & Troels S. Jensen, *Pharmacologic Treatment of Pain in Polyneuropathy*, 55 NEUROLOGY 915, 919 (2000).

54. Ahmad Beydoun, *Symptomatic Treatment of Neuropathic Pain: A Focus on the Role of Anticonvulsants*, MEDSCAPE CME CIRCLE LECTURE (2001).

55. M. Bergouignan, *Cures Heureuses De Nevralgies Faciales Essentielles Par Le Diphenylhydantoinate De Soude*, 63 REV LARYNGOL OTOL RHINOL (1942); Risheng Xu et al., *Trigeminal Neuralgia: Current Approaches and Emerging Interventions*, J. PAIN RSCH. 3437, 3439 (2021).

56. Scadding, *supra* note 51, at 4–6.

57. Alec B. O'Connor & Robert H. Dworkin, *Treatment of Neuropathic Pain: An Overview of Recent Guidelines*, 122 AM. J. MED. 22, 22–23 (2009).

58. *Id.* at 25.

59. *Id.*

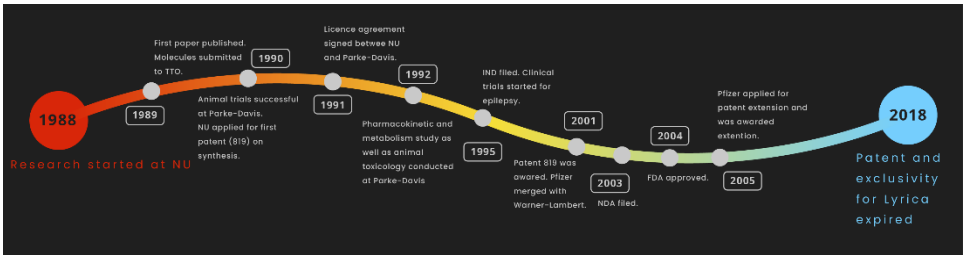
60. LI XU ET AL., TRANSLATIONAL RESEARCH IN PAIN AND ITCH 118–25 (2016).

surprisingly few safe and effective treatments for neuropathic pain have been developed.[61] And the mechanism of action of these treatment options is likely non-specific, i.e., many act by generally modulating pain and neuronal depressant activity, rather than specifically targeting the underlying neurological mechanism of pain.[62] Unfortunately, recent drugs developed through a bottom-up translational approach have failed subsequent RCTs.[63]

III. CHRONOLOGY OF THE DEVELOPMENT OF LYRICA

The discovery and development of Lyrica took place over three distinct stages. The first stage involved the synthesis and investigation of pregabalin at Northwestern University from 1988 to 1989. In 1990, the Northwestern Technology Transfer Office then licensed the chemical composition to Parke-Davis, which conducted animal pharmacokinetic and metabolism experiments for six months and then animal toxicology studies for two years. The second stage involved clinical trials, which began in 1995 after filing an Investigational New Drug Application (IND) and lasted for over eight years. The final stage was the approval by the FDA in late 2004, which led to the introduction of Lyrica into the market. Overall, the development of Lyrica was a lengthy and complex process that required multiple stages of testing and refinement.[64]

Figure 3: Timeline of the Development of Lyrica.



61. Nanna Brix Finnerup et al., *Neuropathic Pain: From Mechanisms to Treatment*, PHYSIOLOGICAL REVS. 258, 283 (2020).

62. Nadine Attal & Didier Bouhassira, *Translational Neuropathic Pain Research*, 160 PAIN 23, 24 (2019); Per T. Hansson & Anthony H. Dickenson, *Pharmacological Treatment of Peripheral Neuropathic Pain Conditions Based on Shared Commonalities Despite Multiple Etiologies*, 113 PAIN 251, 251–53 (2005).

63. *Id.* at 252.

64. Silverman, *supra* note 2, at 3500–02.

A. BACKGROUND OF THE SCIENTISTS

The initial development of Lyrica began with a collaboration between Ryszard Andruszkiewicz and Richard Silverman. Andruszkiewicz was a well-trained chemist from the Gdańsk University of Technology. He was experienced in the synthesis of enzyme inhibitors, as evidenced by his publications on inhibitors of glucosamine synthetase[65] before he joined Silverman at Northwestern University in 1988 as a visiting professor.

Silverman realized that he wanted to become a chemist at the early age of eight.[66] He has always been interested in drug design and applied science, and went to graduate school with the intention of eventually working in the pharmaceutical industry.[67] Silverman worked for the renowned organic chemist David Dolphin at Harvard for his Ph.D.[68] During his degree, he was drafted to the United States Army as a physical sciences assistant for two years. Silverman has since explained that Dolphin gave students a lot of freedom to work on different projects and develop their own ideas.[69] Though Silverman's main project—focused on the synthesis of a natural product—was not going smoothly, he found his passion in biology in a side project.[70] After essentially teaching himself biology and hearing an enzymology talk by Robert Abeles, Silverman decided to join the Abeles lab at Brandeis as a postdoctoral fellow.[71] Silverman started his independent career as a professor at Northwestern in 1976, and in 1978 began working on the design and mechanism of chemicals that inhibit GABA-AT.[72] Silverman's focus at the time was epilepsy treatment, though these chemicals have also exhibited activity against Alzheimer's, Huntington's, and Parkinson's disease.[73] Overall, one of Silverman's main research interests became the development of new, mechanism-based inactivators to treat neurological diseases.[74]

---

65. Ryszard Andruszkiewicz et al., *Synthesis of N3-Fumaramoyl-L-2, 3-Diaminopropanoic Acid Analogues, The Irreversible Inhibitors of Glucosamine Synthetase*, 27 INT'L J. PEPTIDE & PROTEIN RSCH. 449 (1986).

66. Zoom interview with Richard B. Silverman, Professor, Northwestern Univ. Dep't. of Chemistry (May 8, 2023) [hereinafter Silverman Interview].

67. *Id.*

68. *Id.*

69. *Id.*

70. *Id.*

71. *Id.*

72. Richard B. Silverman & Mark A. Levy, *Syntheses of (S)-5-Substituted 4-Aminopentanoic Acids: A New Class of γ-Aminobutyric Acid Transaminase Inactivators*, 45 J. ORGANIC CHEMISTRY 815, 815 (1980).

73. Silverman, *supra* note 2.

74. Silverman Interview, *supra* note 66.

Silverman had a keen interest in patenting his research after he was tenured in 1986.[75] He started his career just as the Bayh-Dole Act was passed in 1980,[76] which injected a profit motive into government-funded university research.[77] Prior to passage of this legislation, universities and their researchers were not permitted to patent discoveries supported by federal funding. Lyrica became one of the first major patented drugs resulting from federally funded university research. Prior to the discovery of Lyrica, Silverman had already patented several of his works.[78] He continued patenting significant portions of his research and is an inventor on over 130 patents.[79]

B. SCIENCE BREAKTHROUGH

The discovery of Lyrica resulted from Silverman's keen scientific insight in conjunction with Andruszkiewicz's dogged laboratory research. Pregabalin, the active pharmaceutical ingredient of Lyrica, was among the 3-alkyl GABA derivatives Silverman tasked Andruszkiewicz with synthesizing in 1988. He developed interest in these compounds' capacity to treat epilepsy based on two hypotheses. First, that the blood-brain barrier penetrance of chemical compounds might be improved by the addition of carbon atoms, which often improve lipophilicity.[80] Second, that the generation of different alkyl analogs might produce a chemical compound that selectively inhibits GABA-AT without affecting GAD.[81] Silverman reasoned that a compound with both of these features (i.e., blood-brain barrier penetrance and selective inhibition of GABA-AT) would be an excellent candidate for enhancing GABA levels in the brain, and therefore possibly for treating epilepsy. Andruszkiewicz completed the synthesis of this set of GABA derivatives and published the results in the German journal Synthesis in 1989, with funding from the NIH.[82] Andruszkiewicz then tested the activity of the synthesized molecules on enzymes extracted from pig brains, and found that all fourteen compounds

75. *Id*; *Patents*, NORTHWESTERN U. SILVERMAN GRP. https://silverman.northwestern.edu/news-events/ (last visited Sept. 11, 2023) [hereinafter Silverman Group Patents].

76. 35 U.S.C. § 200-12 (2012) (the Bayh-Dole Act of 1980).

77. Samuel Loewenberg, *The Bayh-Dole Act: A Model for Promoting Research Translation?*, 3 MOLECULAR ONCOLOGY 91, 91 (2009).

78. Silverman Group Patents, *supra* note 75; *see, e.g.*, U.S. Patent No. 4,528,028 (issued July 9, 1985) (patenting chemicals that thwart growth of unwanted plants); U.S. Patent No. 4,582,529 (issued Apr. 15, 1986) (same).

79. *See* Silverman Group Patents, *supra* note 75.

80. Silverman, *supra* note 2, at 3500–02.

81. *Id.*

82. Ryszard Andruszkiewicz & Richard B. Silverman, *A Convenient Synthesis of 3-Alkyl-4-aminobutanoic Acids*, 1989 SYNTHESIS (GERMANY) 953, 953 (1989).

inhibited GABA-AT and activated GAD, leading to a potential enhancement of GABA formation in the brain.[83] Thus, the 3-alkyl GABA derivatives indeed were candidates for increasing rates of GABA formation in the brain, as per Silverman's initial hypothesis. The results were too good to believe, and Silverman asked Andruszkiewicz to test them again.[84] These remarkable results were published in the Journal of Biological Chemistry, and Silverman sent the drugs to pharmaceutical companies for further testing with the help of the technology transfer office.[85]

C. TECHNOLOGY TRANSFER

The development and commercialization of Lyrica were made possible by Northwestern University's technology transfer office (TTO). The TTO was established in 1981, thanks to the passage of the Bayh-Dole Act that allowed U.S. universities to patent their research results.[86] As a result, the number of patents granted to universities increased significantly, from 1% among all patents in 1975 to over 2.5% in 1990.[87] Biotechnology patents issued to universities, in particular, saw a growth of 123% in the ten years from 1969 to 1979.[88] The establishment of over 3,000 TTOs since the passage of Bayh-Dole further contributed to this growth.[89] TTOs employ specialized attorneys to handle licensing, patenting, contract drafting, and commercialization efforts.[90] Northwestern University's TTO,[91] one of the 200 TTOs established immediately after the Bayh-Dole Act was passed, grew from an office with only a director and an assistant director in 1989[92] to the most financially

83. Ryszard Andruszkiewicz & Richard B Silverman, *4-Amino-3-Alkylbutanoic Acids as Substrates for γ-aminobutyric Acid Aminotransferase*, 265 J. BIOLOGICAL CHEMISTRY 22288, 22289–91 (1990).

84. Silverman, *supra* note 2, at 3500–02.

85. *Id.*; Andruszkiewicz & Silverman, *supra* note 83.

86. 35 U.S.C. § 200-12 (2012) (the Bayh-Dole Act of 1980).

87. David C. Mowery et al., *The Growth of Patenting and Licensing by US Universities: An Assessment of the Effects of the Bayh–Dole Act of 1980*, 30 RSCH. POL'Y 99, 104 (2001).

88. *Id.*

89. Kristen Osenga, *Rembrandts in the Research Lab: Why Universities Should Take a Lesson from Big Business to Increase Innovation*, 59 ME. L. REV. 407, 419 (2007).

90. David Orozco, *Assessing the Efficacy of the Bayh-Dole Act Through the Lens of University Technology Transfer Offices (TTOS)*, 21 N.C.J.L. & TECH. 115, 121 (2019).

91. Northwestern University later renamed the TTO the "Innovation and New Ventures" (INVO) office. It has processed between 124 and 219 invention disclosures per year between 2002 and 2022. *See* INVO, INVENTIVE ACTIVITY FY 2022 (2022), https://www.invo.northwestern.edu/documents/invo_inventive_activity_fy_2022.pdf. In 2022, INVO disclosed 219 inventions, filed 584 patent applications, executed 260 licensing agreements, and generated $14.1 million in licensing revenue.

92. Silverman Interview, *supra* note 66.

successful TTO by 2009, despite the university ranking only 30th in research expenditure.[93]

In 1989, Professor Silverman disclosed his invention of the fourteen GABA analogs (synthesized by Andruszkiewicz) to Northwestern's TTO, which then contacted multiple companies through mail about their interest in launching animal testing of these compounds as putative AEDs.[94] Only Upjohn Pharmaceutical and Parke-Davis Pharmaceuticals responded positively to the TTO.[95] Upjohn showed interest in testing the most effective chemical among the fourteen synthesized (the 3-methyl GABA analog) based on Andruszkiewz's laboratory testing on enzymes, which was a reasonable request as most of the lab chemicals would not be effective in animal tests.[96] However, the Upjohn team found only a weak anticonvulsant effect from the 3-methyl analog, which ended their interest in this series of compounds.[97]

On the other hand, the potential impact of this class of compounds as AEDs incentivized Parke-Davis' investment in *all*, not just one, of the Silverman-Andruskiewicz analogs. Thus, Parke-Davis conducted MES mice tests on all the alkyl-substituted GABA analogs made by Silverman and Andruskiewicz.[98] They had already conducted tests on alkyl-substituted GABA analogs before, such as gabapentin, discussed *supra* (Figure 1B).[99] Gabapentin was later approved by the U.S. Food and Drug Administration (FDA) in 1993 and has been commercialized as Neurontin since 2004.[100] A similar compound, one of the Silverman-Andruskiewicz analogs, was pregabalin, introduced *supra* (Figure 1C).

In 1990, Parke-Davis informed Silverman that pregabalin (3-isobutyl GABA) was the most potent anticonvulsant agent they had tested.[101] Notably, pregabalin also did not cause ataxia, the unsteady motion of limbs and torso commonly seen in anticonvulsant drugs.[102] Based on these promising findings,

93. RONDA BRITT, ACADEMIC RESEARCH AND DEVELOPMENT EXPENDITURES: FISCAL YEAR 2009 67 (2011).

94. Silverman, *supra* note 2, at 3501.

95. *Id.*

96. Chi Heem Wong et al., *Estimation of Clinical Trial Success Rates and Related Parameters*, 20 BIOSTATISTICS 273, 273 (2019).

97. Silverman, *supra* note 2, at 3501.

98. Richard B. Silverman et al., *3-Alkyl-4-Aminobutyric Acids: The First Class of Anticonvulsant Agents that Activates L-Glutamic Acid Decarboxylase*, 34 J. MEDICINAL CHEMISTRY 2295, 2297 (1991); Justin S. Bryans & David J. Wustrow, *3-Substituted GABA Analogs with Central Nervous System Activity: A Review*, 19 MED. RSCH. REVS. 149, 168–70 (1999).

99. DOUGLAS S. JOHNSON & JIE JACK LI, THE ART OF DRUG SYNTHESIS 226–27 (2013).

100. Rama Yasaei et al., *Gabapentin*, *in* STATPEARLS (2022).

101. Silverman et al., *supra* note 98, at 2297.

102. *Id.* at 2298.

Northwestern and Warner-Lambert, the parent company of Parke-Davis, signed a license agreement at the end of 1990.[103] The agreement provided Northwestern University with a 4.5% royalty based on global sales, while Silverman received an additional 1.5% royalty, 10% of which he shared with Andruszkiewicz.[104] Though Silverman himself was interested in continuing to research this molecule—and a postdoctoral researcher in his lab was working to elucidate the activation mechanism—these experiments were ultimately unsuccessful.[105] Nonetheless, he maintained communication with the Warner-Lambert scientists, receiving updates on the drug every six months.[106] After the merger between Warner-Lambert with Pfizer, Pfizer scientists were instructed not to discuss the drug with anyone, including Silverman.[107]

D. CLINICAL TRIALS AND COMMERCIALIZATION

The clinical development of pregabalin (later, to become Lyrica) followed an atypical path. After a standard Phase I study, the Phase II and III trials for pregabalin were often combined, with multiple indications pursued simultaneously.[108] After entering into the licensing agreement with Northwestern, Parke-Davis conducted all of the pharmacological and clinical studies. The pharmacokinetic and metabolism study lasted for six months in 1992 and the animal toxicology took another two years.[109] By the end of 1995, the Investigational New Drug Application (IND) was filed.[110] In 1996, Phase I clinical trials began and lasted for two and a half years. In three separate studies, the pharmacokinetics of single and multiple doses were characterized in healthy volunteers, with two additional studies conducted to assess the effect of food on pregabalin pharmacokinetics.[111] These studies revealed that pregabalin has a linear and predictable plasma concentration profile across different doses, which makes it easier to dose compared to gabapentin.[112] Therefore, most clinical studies on pregabalin thereafter utilized twice-daily

103. Silverman, *supra* note 2, at 3502.

104. Peter Kotecki, *In Focus: As Lyrica profits dry up, Northwestern seeks another 'blockbuster' drug*, DAILY NORTHWESTERN DRUG MONEY (Apr. 10, 2016) https://dailynorthwestern.com/2016/04/10/featured-stories/in-focus/in-focus-as-lyrica-profits-dry-up-northwestern-seeks-another-blockbuster-drug/.

105. Silverman Interview, *supra* note 66.

106. *Id.*

107. *Id.*

108. ANDREW J. THORPE & LLOYD E. KNAPP, CASE STUDY: DISCOVERY AND DEVELOPMENT OF PREGABALIN (LYRICA®) 356–59 (2013).

109. Silverman, *supra* note 2, at 3501.

110. *Id.*

111. Howard N. Bockbrader et al., *Clinical Pharmacokinetics of Pregabalin in Healthy Volunteers*, 50 J. CLINICAL PHARMACOLOGY 941, 945–47 (2010).

112. *Id.* at 946.

dosing.[113] These promising results accelerated the later trials and provided a basis for combining Phase II and III trials.

Early Phase II trials started with pain (acute dental pain)[114] and epilepsy[115] indications in 1997, and anxiety[116] as an indication in 1998. Positive results from the shorter studies provided a robust basis for launching larger scale studies for all three indications.[117] While traditional clinical trials would typically progress from a dose-response study in a small sample to larger samples with targeted doses to prove clinical efficacy,[118] pregabalin's clinical trials often combined Phases II and III, a practice with higher inherent risk but significant reductions in development time and cost.[119] More than 100 clinical trials involving over 10,000 patients with epilepsy, neuropathic pain, and general anxiety disorder were conducted.[120] This deluge of studies happened within five years, despite a short delay introduced by a temporary pause due to murine toxicology results.[121]

Pfizer bought Warner-Lambert, including Parke-Davis, in 2000.[122] Ironically, Upjohn (already merged with Pharmacia),[123] which passed on the chance to license pregabalin, was also acquired by Pfizer in 2002, and filed a New Drug Application (NDA) for pregabalin (under the brand name Lyrica)

113. *Id.* at 941.

114. C. M. Hill et al., *Pregabalin in Patients with Postoperative Dental Pain*, 5 EUR. J. PAIN 119, 119–21 (2001).

115. Santiago Arroyo et al., *Pregabalin Add-on Treatment: A Randomized, Double-Blind, Placebo-Controlled, Dose-Response Study in Adults with Partial Seizures*, 45 EPILEPSIA 20, 20–23 (2004).

116. Douglas E. Feltner et al., *A Randomized, Double-Blind, Placebo-Controlled, Fixed-Dose, Multicenter Study of Pregabalin in Patients with Generalized Anxiety Disorder*, 23 J. CLINICAL PSYCHOPHARMACOLOGY 240, 240–43 (2003).

117. THORPE & KNAPP, *supra* note 108, at 356.

118. *Id.* at 358.

119. *Id.*

120. Silverman, *supra* note 2, at 3501.

121. Kay A. Criswell et al., *Mode of Action Associated with Development of Hemangiosarcoma in Mice Given Pregabalin and Assessment of Human Relevance*, 128 TOXICOLOGICAL SCIS. 57, 57–59 (2012). Research suggests pregabalin increases incidence of hemangiosarcomas in carcinogenicity studies in 2-year mice but not in rats. This, therefore, delayed the clinical trials for pregabalin. The International Programme on Chemical Safety and International Life Sciences Institute developed a Human Relevance Framework (HRF) analysis whereby presence or absence of key events can be used to assess human relevance. They found evidence that supports a species-specific process and demonstrates the tumor findings in mice are not relevant to humans at the clinical dose of pregabalin.

122. Melody Petersen, *Pfizer Gets Its Deal to Buy Warner-Lambert for $90.2 Billion*, N.Y. TIMES (Feb. 8, 2000), https://www.nytimes.com/2000/02/08/business/pfizer-gets-its-deal-to-buy-warner-lambert-for-90.2-billion.html.

123. Claire McKenna, *Pfizer buys Pharmacia for $60 bn*, 325 BRIT. MED. J. 123, 123 (2002).

in October 2003.[124] Lyrica was approved for medical use in Europe in July 2004 for the treatment of peripheral neuropathic pain and as an adjunctive therapy for partial seizures in patients with epilepsy.[125] Then, it was approved by the FDA for the management of neuropathic pain associated with diabetic peripheral neuropathy and post-herpetic neuralgia in December 2004[126] and for adjunctive therapy for the treatment of partial-onset seizures in June 2005.[127] Finally, in June 2007, Lyrica was approved for the treatment of fibromyalgia.[128] With numerous indications, Lyrica became Pfizer's flagship blockbuster drug. It generated over $3.1 billion in revenue for Pfizer in 2010 alone.[129]

E. PATENTS AND EXCLUSIVITY OF LYRICA

In parallel to the clinical development and FDA approval of Lyrica for several indications, discussed *supra*, a complex story of patents, exclusivity, and litigation unfolded. Warner-Lambert, the mother company of Parke-Davis, and Pfizer built a systematic patent network around the use of GABA derivatives, while Silverman and Northwestern held key patents that were licensed to Warner-Lambert. Silverman and the Northwestern TTO began applying for patents associated as early as 1990, when their compounds were being tested on animals.[130] U.S. Patent No. 6,197,819 (issued in 2001), held by Silverman and Andruszkiewicz, described the general methodology of synthesizing alkyl-substituted GABA within laboratory settings.[131] U.S. Patent No. 5,563,175 (issued in 1996), held by Northwestern and Warner-Lambert, described GABA derivatives' capability for treating epilepsy.[132] Both patents were eventually licensed exclusively to Warner-Lambert.[133] U.S. Patent No.

124. Letter from Robert J. Meyer, to Jonathan M. Parker (Dec. 30, 2004), https://www.accessdata.fda.gov/drugsatfda_docs/appletter/2004/21446ltr.pdf (approving the Lyrica® NDA) hereinafter Lyrica® FDA Approval Letter].

125. *COMPANY NEWS; EUROPEAN UNION APPROVES LYRICA FROM PFIZER*, N.Y. TIMES (July 7, 2004), https://www.nytimes.com/2004/07/07/business/company-news-european-union-approves-lyrica-from-pfizer.html.

126. Lyrica® FDA Approval Letter, *supra* note 124.

127. *Lyrica (pregabalin) - 4 indications*, CENTERWATCH, https://www.centerwatch.com/directories/1067-fda-approved-drugs/listing/3803-lyrica-pregabalin (last visited Sept. 14, 2023).

128. *Id.*

129. PFIZER, PFIZER REPORTS FOURTH-QUARTER AND FULL-YEAR 2010 RESULTS; PROVIDES 2011 FINANCIAL GUIDANCE AND UPDATES 2012 FINANCIAL TARGETS, https://s28.q4cdn.com/781576035/files/doc_financials/2010/q4/q4performance_020111.pdf.

130. U.S. Patent No. 6,197,819 (issued Mar. 6, 2001) [hereinafter "the '819 patent"].

131. *Id.*

132. U.S. Patent No. 5,563,175 (issued Oct. 8, 1996) [hereinafter "the '175 patent"].

133. Silverman, *supra* note 2, at 3501.

6,046,353, held by Warner-Lambert, described a way to produce pregabalin in large quantities.[134] In the following years, Warner-Lambert patented the use of pregabalin and other GABA derivates to treat more and more indications, based on the ongoing collection of clinical trial data. For example, Warner-Lambert held: a patent[135] for treating pain with an extensive collection of 3-alkyl substituted GABA molecules; a patent[136] for pain prevention using a GABA analog combined with a non-steroid anti-inflammatory drug; a patent[137] for treating gastronomical damage with a GABA analog; and a patent claiming a large array of 3-alkyl substituted GABA analogs[138] for treating physiological conditions caused by psychostimulants with GABA derivatives.

In February 2005, Pfizer applied for patent term extensions for the '819 and '876 patents, following the FDA approval of two of its NDAs related to Lyrica.[139] The U.S. Patent and Trademark Office (PTO) agreed and extended the term of both patents through December 30, 2018.[140] In the late 2000s, a collective of generic manufacturer companies including Teva Pharmaceuticals USA and Mylan Pharmaceuticals filed Abbreviated New Drug Applications (ANDAs) for generic versions of Lyrica, albeit of different enantiomers.[141] Pfizer sued the generic companies in 2009 for patent infringement.[142] The district court upheld Pfizer's asserted claims against enablement, written description, and obviousness challenges, and the Federal Circuit affirmed this decision in 2014.[143]

In 2017, Pfizer obtained FDA approval for an extended-release, once-daily dose form of the originally patented pregabalin formulation ("Lyrica CR")[144] and settled with Sun Pharmaceutical Industries Ltd. for alleged patent infringement of Sun's '205 patent on a gastroretentive tablet comprising

134. U.S. Patent No. 5,637,767 (issued June 10, 1997) [hereinafter "the '767 patent"].

135. U.S. Patent No. 6,001,876 (issued Dec. 14, 1999) (later reissued as U.S. RE41,920) [hereinafter "the '876 patent"].

136. U.S. Patent No. 6,242,488 (issued June 5, 2001) [hereinafter "the '488 patent"].

137. U.S. Patent No. 6,127,418 (issued Oct. 3, 2000) [hereinafter "the '418 patent"].

138. U.S. Patent No. 6,194,459 (issued Feb. 27, 2001) [hereinafter "the '459 patent"].

139. Pfizer Inc. v. Teva Pharms. U.S.A., Inc., 882 F. Supp. 2d 643 (D. Del. 2012).

140. *Id.* at 730.

141. *Id.* Enantiomers are molecules that are mirror images of each other.

142. *Id.*

143. *Federal Circuit Upholds Lyrica Patents*, FOLEY & LARDNER LLP (Feb. 11, 2014), https://www.foley.com/en/insights/publications/2014/02/federal-circuit-upholds-lyrica-patents; *Pfizer v. Teva*, 882 F. Supp. 2d; Pfizer Inc. v. Teva Pharms. USA, Inc., 555 F. App'x 961 (Fed. Cir. 2014).

144. *U.S. FDA Approves LYRICA® CR (Pregabalin) Extended-Release Tablets CV*, PFIZER (Oct. 12, 2017), https://www.pfizer.com/news/press-release/press-release-detail/u_s_fda_approves_lyrica_cr_pregabalin_extended_release_tablets_cv.

pregabalin.[145] In 2018, Pfizer obtained approval for an additional six months of pediatric exclusivity for Lyrica in response to the FDA's direct request to Pfizer to evaluate the drug for pediatric efficacy.[146] This approval was based on the positive data from the Phase III trial conducted at the Pediatric Epilepsy Program at Pfizer.[147]

145. Suzanne Monyak, *Pfizer's Lyrica Update Infringes Patent, Sun Pharma Says*, LAW360 (Apr. 5, 2019), https://www.law360.com/articles/1147190/pfizer-s-lyrica-update-infringes-patent-sun-pharma-says; U.S. Patent No. 9,393,205 (issued July 19, 2016).

146. *Pfizer Receives Six Months Pediatric Exclusivity for Lyrica® (Pregabalin)*, BUSINESSWIRE (Nov. 27, 2018), https://www.businesswire.com/news/home/20181127005811/en/Pfizer-Receives-Months-Pediatric-Exclusivity-LYRICA%C2%AE-pregabalin.

147. *LYRICA® (Pregabalin) Oral Solution CV Phase 3 Trial in Pediatric Epilepsy Meets Primary Endpoint*, PFIZER (May 17, 2018), https://www.pfizer.com/news/press-release/press-release-detail/lyrica_pregabalin_oral_solution_cv_phase_3_trial_in_pediatric_epilepsy_meets_primary_endpoint-0.

Table 2: Major U.S. Patents for Lyrica.

Patent Number	Owner	Assignee	Filing Date	Issue Date	Key Claims
6,197,819	Silverman and Andruszkiewicz	Northwestern University	Apr. 11, 1995	Mar. 6, 2001	Synthesis of pregabalin
5,563,175	Silverman, Andruszkiewicz and scientists at Warner-Lambert	Northwestern University and Warner-Lambert	Apr. 12, 1995	Oct. 8, 1996	GABA analogue for epilepsy treatment
6,001,876	Lakhbir Singh	Warner-Lambert	Jul. 16, 1997	Dec. 19, 1999 Reissued Nov. 9, 2010	Pregabalin for pain treatment
6,194,459	Scientists at Warner-Lambert	Warner-Lambert	Aug. 13, 1998	Feb. 27, 2001	Physiological condition treatment after pyschostimulus
6,046,353	Scientists at Warner-Lambert	Warner-Lambert	Aug. 26, 1998	Apr. 4, 2000	Large scale production for GABA analogues
6,127,418	Scientists at Warner-Lambert	Warner-Lambert	Apr. 19, 1999	Oct. 3, 2000	Gastronomical damage treatment
6,242,488	Scientists at Warner-Lambert	Warner-Lambert	May 9, 2000	Jun. 5, 2001	Pain treatment and prevention

Warner-Lambert and Pfizer also obtained global exclusivity for Lyrica. For example, they secured European Patent No. 0641330, owned by Silverman and Andruszkiewicz, for seizure treatment and EP(UK) No. 0934061 for neuropathic pain treatment.[148] The former patent expired in 2014 while the latter expired in 2017.[149] Several companies (e.g., Mylan and Actavis) launched Lyrica generics with a "skinny labeling" strategy, seeking approval for only epilepsy and not neuropathic pain treatment. Pfizer sued the generic manufacturers for patent infringement, despite the companies and National

148. Warner-Lambert Co. v. Generics (UK) Ltd. (trading as Mylan) [2018] UKSC 56.

149. Eric Sagonowsky, *Pfizer Falls Short in U.K. Patent Appeal for Blockbuster Lyrica*, FIERCE PHARMA (Nov. 14, 2018), https://www.fiercepharma.com/pharma/pfizer-falls-short-u-k-patent-appeal-for-blockbuster-lyrica.

Health Services warning against off-label uses as the generics went on the market.[150] After a lower court invalidated Pfizer's patent for pain treatment in 2015, the U.K. Supreme Court upheld the lower court's decision in 2018 and went further to hold that even if the patents were valid, they would not have been infringed.[151] However, while Pfizer was not successful in ligation in the United Kingdom, Pfizer made staggering profits from the global exclusivity of Lyrica. Based on the terms of the licensing agreement, the scientists at Northwestern University received some of this revenue.

F. EPILOGUE

Lyrica generated a significant amount of profit for Northwestern University and created financial support for future students. Approximately $1.4 billion has gone into the university endowment because of Lyrica.[152] In 2007, Northwestern sold its worldwide royalty interest in Lyrica to Royalty Pharma for $700 million in cash, parts of which went to Silverman and Andruszkiewicz.[153] It also partially supported a $100 million integrated biology building for molecular therapeutics and diagnostics, named after Silverman and his wife, to facilitate future drug discovery research.[154] Andruszkiewicz also used part of the Lyrica money to fund a new building in the Gdańsk University of Technology for biological research.[155]

Interestingly, the mechanism of pregabalin turned out to be completely different from what was originally proposed. Silverman and Andruskiewicz initially aimed to inhibit GABA-AT and activate GAD to enhance levels of GABA. However, further studies done by Parke-Davis revealed that pregabalin's anticonvulsant effects do not relate to any significant activation of GAD or the inhibition of GABA-AT.[156] Later research found that both gabapentin and pregabalin bind to calcium channels and attenuate calcium flux

150. *Id.*

151. *Warner-Lambert*, UKSC 56.

152. Janet Lorin, *The Pill That Made Northwestern Rich*, BLOOMBERG (Aug. 18, 2016), https://www.bloomberg.com/news/articles/2016-08-18/the-pill-that-made-northwestern-rich#xj4y7vzkg.

153. Alan K. Cubbage, *Royalty Pharma Acquires a Portion of Northwestern University's Royalty Interest in Lyrica for $700 Million*, NORTHWESTERN U. NEWS (Dec. 18, 2007), https://www.northwestern.edu/newscenter/stories/2007/12/lyrica.html.

154. Stephen Anzaldi, *Chemist Helps Fund New Research Center*, CHEM. & ENG'G NEWS (Mar. 12, 2007), https://cen.acs.org/articles/85/i11/Chemist-Helps-Fund-New-Research.html.

155. *WSPÓŁTWÓRCA Innowacyjnego Leku, Prof. Ryszard Andruszkiewicz, Wspiera Talenty Naukowe*, INFOWIRE.PL (May 30, 2019), infowire.pl/generic/release/442168/wspoltworca-innowacyjnego-leku-prof-ryszard-andruszkiewicz-wspiera-tal.

156. Bryans & Wustrow, *supra* note 98.

into the neuron.[157] This leads to the inhibition of the excitatory neurotransmitter L-glutamate and might be the reason behind the anticonvulsant effect of Lyrica.[158]

IV. INNOVATION DRIVER ANALYSIS

Lyrica owes its success to a group of key contributors, including Silverman, Andruskiewicz, Northwestern University's TTO, Parke-Davis, and Pfizer. Each of these entities was driven by different motivations, which may be canonically characterized as positive or negative drivers of innovation. It is also essential to consider the public policies and societal attitudes that persisted in the background of the Lyrica saga, which can also either foster or hinder innovation. This analysis aims to examine the factors that facilitated or obstructed the development of Lyrica and how they may impact the advancement of life sciences research more broadly.

A. PUBLIC AWARENESS OF EPILEPSY

The innovation of new treatments for epilepsy was initially hindered by the stigma associated with the disease. The earliest recorded cases of epilepsy date back to multiple ancient civilizations,[159] yet throughout history, people believed that epilepsy was caused by evil spirits entering the human body, leading to exorcism or other religious and spiritual remedies.[160] This misunderstanding not only deterred the search for medicinal remedies but also led to discrimination against people with epilepsy. Until the mid-20th century, many U.S. states prohibited people with epilepsy from getting married, and some even encouraged eugenic sterilization.[161] Public facilities had the right to deny access for epileptic patients until the 1970s.[162] This stigma persists to this day, especially in developing countries where the belief that evil spirits cause epilepsy carries on. Consequently, some patients in these countries can exhibit symptoms without receiving treatment for six to fourteen years.[163] It was not until the late 20th century that efforts from organizations such as the World Health Organization, the International League Against Epilepsy, and the

157. Yannick P. Maneuf et al., *Gabapentin Inhibits The Substance P-Facilitated K-Evoked Release of [³H] Glutamate from Rat Caudal Trigeminal Nucleus Slices*, 93 PAIN (2001) 191, 195; Bryans & Wustrow, *supra* note 98, at 172.

158. Yannick P. Maneuf et al, *supra* note 157.

159. Emmanouil Magiorkinis et al., *Hallmarks in the History of Epilepsy: Epilepsy in Antiquity*, 17 EPILEPSY & BEHAV. 103, 103–07 (2010).

160. WHO, EPILEPSY CARE, *supra* note 16, at 16.

161. Kaculini et al., *supra* note 15, at 4.

162. *Id.*

163. *Id.*

International Bureau of Epilepsy aimed at reducing stigma began to create an environment conducive to developing modern medicinal treatments for epilepsy.[164] In the United States, NIH and NINDS created ASP for systematic screening for antiepileptic drugs in the 1970s.[165] These efforts eventually led to the development of new treatments for epilepsy. Therefore, the stigma surrounding epilepsy hindered progress, while the work of public health organizations helped to boost innovation in epilepsy treatment.

B. EARLY STAGES

Andruszkiewicz and Silverman played a pivotal role in the development of Lyrica, with their work on the molecular synthesis of pregabalin. Andruszkiewicz, who was already a lecturer at Gdańsk University of Technology,[166] came to the United States to further his career. During his visiting scholar opportunity at Northwestern, he teamed up with Silverman, and together, they worked on the synthesis of the drug. Visiting professors, like Andruszkiewicz, are often distinguished scholars who are invited to collaborate with host institutions. They are usually funded by their original institution and may conduct hands-on research, much like postdoctoral fellows.[167] Although Andruszkiewicz was already an accomplished professor in his field, he lacked publications where he was the corresponding author, a role typically reserved for the professor who funds the research and generates the idea. This made him eager to collaborate with a more established professor like Silverman.

Andruszkiewicz's expertise in enzymology and organic chemistry proved instrumental in the successful synthesis of all fourteen analogs of GABA. His knowledge of enzymes allowed him to quickly verify the effect of the molecules on GABA-AT and GAD, which contributed significantly to the innovation. Andruszkiewicz's passion for scientific discovery and his virtuosity in the field eventually led to his acquisition of highly profitable Lyrica patents and new publications as the corresponding author after returning to Poland.[168]

---

164. *Id.*

165. Porter & Kupferberg, *supra* note 24, at 1890.

166. *Emeritus Professor*, GDAŃSK FAC. CHEM., https://chem.pg.edu.pl/en/dptb/employees-and-phd-students/emeritus-professor (last visited Sept. 14, 2023) (listing faculty members).

167. *Description: Visiting Faculty*, HARV. U., https://academic-appointments.fas.harvard.edu/description-visiting-faculty (last visited Sept. 14, 2023) (listing faculty members).

168. Dorota Pawla et al., *Synthesis and Biological Activity of Novel Ester Derivatives of N3-(4-Metoxyfumaroyl)-(S)-2, 3-Diaminopropanoic Acid Containing Amide and Keto Function as Inhibitors of Glucosamine-6-Phosphate Synthase*, 26 BIOORGANIC & MED. CHEMISTRY LETTERS 3586, 3586 (2016).

It is also important to recognize the pivotal role played by Silverman, Andruszkiewicz's mentor, in the development of pregabalin. Silverman's tireless pursuit of scientific understanding, combined with a stroke of luck, led to the discovery of pregabalin. With his extensive knowledge of neurological diseases, Silverman understood that a molecule's lipophilicity was crucial for crossing the blood-brain barrier. He instructed Andruszkiewicz to synthesize alkyl-substituted GABA analogs, which would be more lipophilic. Silverman also realized that molecules that could both activate GABA-AT and inhibit GAD simultaneously would be more effective at increasing GABA levels in the brain. However, even though these ideas were confirmed by *in vitro* enzymatic assays, subsequent studies showed that the mechanism of action of these analogs in the animal brain was completely different.[169]

The early-stage development of pregabalin was mainly financed by public funding from governmental grants, with over thirty-seven NIH awards estimated to have contributed over $10 million in 2020 dollars to the pre-approval phase.[170] Though the synthesis conducted by Andruszkiewicz was not on any of the proposals Silverman had written,[171] the NIH still played a crucial role in supporting the lab. The financial support from the NIH, combined with contributions from Parke-Davis, enabled smooth development while the patent system provided further financial incentives.

One unique aspect of the development of pregabalin is Silverman's personal interest in patenting his research. The impact of the patent system on innovation is a subject of ongoing and robust debate. Patenting research can be considered adverse to scientific progress because it hinders the accessibility for collaboration. Excessive patenting can lead to a phenomenon referred to as the "tragedy of anticommons" by Michael Heller and Rebecca Eisenberg, where researchers underuse limited resources because too many owners can block each other.[172] In other words, scientists may be deterred from developing a field in which several patents are already present, meaning that new players are potentially excluded from entering areas of innovation. In line with this view, many scientists are content with conducting research without pursuing patent protection because they prioritize the dissemination of their knowledge in an "open science" framework—which they may also rely on

169. Bryans & Wustrow, *supra* note 98.

170. Rachel Barenie et al., *Discovery and Development of Pregabalin (Lyrica): The Role of Public Funding*, 97 NEUROLOGY, e1653, e1653–60 (2021).

171. Silverman Interview, *supra* note 66.

172. Michael A. Heller & Rebecca S. Eisenberg, *Can Patents Deter Innovation? The Anticommons in Biomedical Research*, 280 SCI. 698, 698–69 (1998).

themselves to further their own studies.[173] Academics also place high value in their reputation among peers based on their contribution to basic science in the form of publications.[174] They are often more driven by getting tenure and academic awards.[175]

Nevertheless, the profits from patent exclusivity can help incentivize faster turnout from basic science to commercial success. As Silverman commented, "The fallacy in that thinking is that if you do basic science and you don't patent your result, but then you publish it, a company isn't going to follow up on those compounds. The company would not be able to have exclusivity."[176] Pharmaceutical companies rely heavily on the patent system to secure a return on their investments, particularly the large investments they make in clinical trials.[177] For drugs entering human clinical trials for the first time between 1990 and 2001, it is estimated that the cost per new drug developed was $802 million.[178] Consequently, one of the first screening criteria for companies seeking to invest resources in pharmaceutical drug development is the patentability of the target molecule, given the possibility for market exclusivity to recoup considerable investment costs.[179] Indeed, pharmaceutical companies often abandon target compounds that are already available in the public domain.[180] Without the patent, it is possible that pregabalin would never have been developed into Lyrica. An analogous drug, gabapentin, was developed by Parke-Davis at the same time.[181] Gabapentin is foreseeably going to overshadow pregabalin if Pfizer only possesses exclusivity on the former. Silverman's desire to patent his work bridged the gap between basic science innovation and commercialization, boosting pregabalin's chances of success. The patent system also considerably altered the landscape of university innovations after the Bayh-Dole Act.[182] Overall, Andruszkiewicz's desire to

173. Cristina Weschler, *The Informal Experimental Use Exception: University Research After* Madey v. Duke University, 79 N.Y.U. L. REV. 1536, 1548 (2004).

174. Kira R. Fabrizio & Alberto Di Minin, *Commercializing the Laboratory: Faculty Patenting and the Open Science Environment*, 37 RSCH. POL'Y, 914, 915–16 (2008).

175. Mark A. Lemley, *Are Universities Patent Trolls*, 18 FORDHAM INTELL. PROP. MEDIA & ENT. L.J. 611, 621–22 (2007).

176. Kotecki, *supra* note 104.

177. Benjamin N. Roin, *Unpatentable Drugs and the Standards of Patentability*, 87 TEX. L. REV. 503, 504–09 (2008).

178. Joseph A. DiMasi et al., *The Price of Innovation: New Estimates of Drug Development Costs*, 22 J. HEALTH ECON. 151, 166–68 (2003); Christopher P. Adams & Van V. Brantner, *Estimating the Cost of New Drug Development: Is It Really $802 Million?*, 25 HEALTH AFFAIRS 420, 420 (2006).

179. Roin, *supra* note 177.

180. *Id.*

181. Yasaei et al., *supra* note 100.

182. David C. Mowery & Arvids A. Ziedonis, *Academic Patent Quality and Quantity Before and After the Bayh–Dole Act in the United States*, 31 RSCH. POL'Y 399, 399–401 (2002).

advance his career, his collaboration with Silverman, funding from the NIH, the serendipitous discovery of the efficacy of pregabalin, and Silverman's strong inclination for patenting his research all built the foundation for the innovation of Lyrica.

C. THE BAYH-DOLE ACT AND TECHNOLOGY TRANSFER OFFICES

Northwestern University's TTO played a significant role in the development of pregabalin by streamlining the process of transferring basic university science to commercial clinical studies. Prior to the passage of the Bayh-Dole Act, only a few universities experimented with technology transfer, including Stanford, MIT, and the University of Wisconsin.[183] The Wisconsin Alumni Research Foundation (WARF) was one of the pioneers in commercializing university research, founded to fund research and protect inventions of colleagues of Harry Steenbock.[184] Simultaneously, the aversion of academics towards monetizing their research was illustrated by Steenbock's refusal to transfer his patent on adding vitamin D to milk to commercial companies for years.[185] WARF eventually became a major player in technology transfer, with notable achievements such as being awarded the initial patents related to human embryonic stem cells.[186]

The passage of the Bayh-Dole Act encouraged the establishment of new TTOs, including the one at Northwestern University. This significantly reduced the friction of technology transfer in schools that did not have a TTO. For Silverman, the newly established TTO at Northwestern helped him reach out to pharmaceutical companies with his promising molecule, as the university did not have the capacity to conduct clinical trials.[187] The active outreach of TTOs accelerated the development of drugs. Despite the benefits of the Bayh-Dole Act and the establishment of TTOs in this case, their overall impact on technology transfer and commercialization in universities has been debated.[188]

---

183. DAVID C. MOWERY ET AL., IVORY TOWER AND INDUSTRIAL INNOVATION: UNIVERSITY-INDUSTRY TECHNOLOGY TRANSFER BEFORE AND AFTER THE BAYH-DOLE ACT 38–42 (2015).

184. Rima D. Apple, *Patenting University Research: Harry Steenbock and the Wisconsin Alumni Research Foundation*, 80 ISIS 374, 375–82 (1989).

185. Orozco, *supra* note 90, at 128.

186. *WARF DECADE BY DECADE*, WISC. ALUMNI RSCH. FOUND., https://www.warf.org/about-warf/history/warf-decade-by-decade/ (last visited Sept. 15, 2023); John M. Golden, *WARF's Stem Cell Patents and Tensions between Public and Private Sector Approaches to Research*, 38 J.L., MED. & ETHICS 314, 314–15 (2010).

187. Silverman Interview, *supra* note 66.

188. MOWERY ET AL., *supra* note 183.

Technology transfer and commercialization were already on the rise before the Bayh-Dole Act.[189] Even before the Act, Congress had investigated ways to commercialize federal funded research. The Technology Transfer Act was passed in 1986, which mandated federal agencies with research programs to transfer their technology for commercialization.[190] On the other hand, universities' interest in commercialization of basic research has been on the rise as well. In fact, several major research universities such as Harvard University, Stanford University, the University of California (UC), and the Massachusetts Institute of Technology (MIT), all lobbied for the passage of the Bayh-Dole Act.[191] They remained major players in university patenting after passage of the act.[192] Thus, the passage of the Bayh-Dole Act and the rise of technology transfer happened concomitantly. But the Act still prompted lots of universities to establish TTOs and get into technology transfer. Notably, two of the universities that had not been active in patenting research, Northwestern and Columbia, became the best performing TTOs, followed by UC Berkeley and MIT.[193]

One of the primary critiques leveled against TTOs is that their aggressive strategies may impede and hinder research within universities, which could lead to a lack of innovation. However, this argument is not entirely supported by evidence. While one might expect universities to focus only on research that yields patentable results, a study of the effects of the Bayh-Dole Act on academic research and patenting at Stanford and the University of California found that this was not the case.[194] The enactment of the Bayh-Dole Act did coincide with an increase in biomedical research, but it had little to do with this growth.[195] Additionally, although research results may sometimes be withheld from publication for patent applications, this is not a widespread practice in the life sciences.[196] However, it is more common among the most productive and entrepreneurial faculty.[197] Finally, universities' extensive

189. Jay P. Kesan, *Transferring Innovation*, 77 FORDHAM L. REV. 2169, 2177 (2008).

190. FRED E. GRISSOM JR & RICHARD L. CHAPMAN, MINING THE NATION'S BRAIN TRUST: HOW TO PUT FEDERALLY-FUNDED RESEARCH TO WORK FOR YOU 10 (1992).

191. David C. Mowery, *The Bayh-Dole Act and High-Technology Entrepreneurship in US Universities: Chicken, Egg, or Something Else?*, *in* UNIVERSITY ENTREPRENEURSHIP AND TECHNOLOGY TRANSFER (2005).

192. Ampere A. Tseng & Miroslav Raudensky, *Performance Evaluations of Technology Transfer Offices of Major US Research Universities*, 9 J. TECH. MGMT. & INNOVATION 93, 96 (2014).

193. *Id.*

194. Mowery & Ziedonis, *supra* note 182.

195. *Id.* at 400.

196. David Blumenthal et al., *Withholding Research Results in Academic Life Science: Evidence from a National Survey of Faculty*, 277 JAMA 1224, 1224–26 (1997).

197. *Id.*

patenting can lead to significant social costs, as they restrict the general use of new technologies and create additional financial burdens for universities when they spend a significant portion of research budgets on licensing. This has led to some universities being labeled as "patent trolls" due to their efforts in patent litigation,[198] even going as far as purchasing patents from companies and granting exclusive licenses back to those companies to protect their own patents.[199] In response, the Association of American Universities (AAU) has recommended several best practices, such as restraint, cooperation, and using patents to promote public welfare.[200]

Furthermore, despite the success story of Northwestern and Lyrica, there are only a few universities that earn a persistent profit on technology transfer.[201] According to one survey by the Association of University Technology Managers (AUTM), U.S. universities spent $335 million on legal patenting fees in 2014 alone, with most patents not generating monetary benefits.[202] Therefore, the efficacy of the strategies employed by TTOs is questionable, and there is a need for universities to consider more balanced approaches to technology transfer that prioritize public welfare and collaboration over aggressive patenting strategies. While the Bayh-Dole Act and the Northwestern TTO were instrumental in the development of Lyrica by facilitating the transfer of scientific knowledge to commercial companies, it is still unclear whether there is overarching positive impact of these factors on life science innovation in academic settings.

D. STRATEGY OF PARKE-DAVIS AND PFIZER

Pharmaceutical companies such as Parke-Davis and Pfizer are predominantly driven by commercial success, but it was a combination of serendipity and strategic choices that allowed them to fully exploit the innovation of Lyrica.

198. Lemley, *supra* note 175; Christopher M. Holman, *State Universities Push the Limits of Eleventh Amendment Sovereign Immunity at the Federal Circuit*, 39 BIOTECHNOLOGY L. REP. 347, 347–48 (2020).

199. Jeffrey S. Whittle, *State Sovereignty 101: State Universities not Immune to IPR Proceedings*, NAT'L L. REV. (June 17, 2019), https://www.natlawreview.com/article/state-sovereignty-101-state-universities-not-immune-to-ipr-proceedings; Dennis Crouch, *Sovereign Immunity Excuses University of Florida from IPR Challenge*, PATENTLYO (Feb. 1, 2017), https://patentlyo.com/patent/2017/02/sovereign-university-challenge.html.

200. AUTM, STATEMENT TO THE AAU MEMBERSHIP ON UNIVERSITY TECHNOLOGY TRANSFER AND MANAGING INTELLECTUAL PROPERTY IN THE PUBLIC INTEREST (2015).

201. Margo A. Bagley, *Academic Discourse and Proprietary Rights: Putting Patents in Their Proper Place*, 47 B.C. L. REV. 217, 234 (2005).

202. Dave Merrill et al., *Billions at State in University Patent Rights*, BLOOMBERG (May 24, 2016), https://www.bloomberg.com/graphics/2016-university-patents/.

Parke-Davis stumbled upon the development of Lyrica because they were willing to explore a wide range of molecules by investing more time and resources in assessing the entire array of analogs provided by Silverman and Andruszkiewicz. In contrast, Upjohn only tested the most promising molecule based on Silverman and Andruszkiewicz's earlier publications, missing the opportunity to discover pregabalin. Serendipity also played a role, as the molecule that performed exceptionally well in Andruszkiewicz's laboratory experiments initially did not demonstrate the same efficacy in mouse experiments. More importantly, Parke-Davis, using effectiveness in a murine model as a primary criterion, recognized the potential of pregabalin despite it having a different mechanism of action from that initially proposed by Silverman. Furthermore, Parke-Davis was concurrently developing a similar compound, gabapentin, which provided additional insight into the potential of the fourteen molecules sent by Silverman.

The clinical trial and patent strategy employed by Parke-Davis and Pfizer proved beneficial in maintaining exclusivity for the drug, which resulted in substantial financial gains for the companies and the inventors, Silverman and Andruszkiewicz. This also facilitated future innovation as both scientists contributed a significant portion of their royalty earnings to establish research facilities at their respective institutions. However, it can be argued that this strategy could hinder innovation, as other companies are discouraged from further research on pregabalin until the patent expires.

V. CONCLUSION

The innovation story of Lyrica serves as a compelling case study of discovery and development in the life sciences, showcasing the intricate interplay between academic research, technology transfer, and commercialization in the pharmaceutical industry.

First, this Article emphasizes the significance of collaboration and knowledge exchange between academia and industry. The involvement of Northwestern University's TTO and the support of pharmaceutical companies like Parke-Davis and Pfizer played crucial roles in bridging the gap between basic science research and commercial development. The success of Lyrica underscores the importance of fostering partnerships and leveraging resources to translate scientific discoveries into tangible solutions that benefit patients worldwide.

Furthermore, the serendipitous nature of the Lyrica saga reinforces the notion that breakthroughs often arise from unexpected discoveries and a willingness to explore diverse avenues. Silverman's scientific curiosity and the open-mindedness of Parke-Davis in assaying a wide range of molecules led to

the identification of pregabalin, a compound with remarkable therapeutic potential. This serves as a reminder to researchers and industry professionals to embrace curiosity, take calculated risks, and remain receptive to unanticipated outcomes that may lead to significant advancements.

This Article also sheds light on the strategic considerations and challenges surrounding intellectual property rights and patent protection. While effective patent strategies allowed for exclusivity and financial benefits for the inventors and pharmaceutical companies, there is a debate about the potential hindrance to further innovation and accessibility. It emphasizes the need to strike a balance between protecting intellectual property and fostering an environment that encourages continued research and development in the field of life sciences.

Overall, the innovation of Lyrica exemplifies the transformative power of life science research and the potential for collaboration between academia and industry to drive meaningful advancements in healthcare. It serves as an inspiration for future innovators, highlighting the importance of interdisciplinary collaboration, perseverance, and a patient-centered approach to address unmet medical needs.

As the pharmaceutical industry continues to evolve, the lessons learned from the innovation journey of Lyrica will undoubtedly shape future approaches to drug discovery, development, and commercialization. By fostering an ecosystem that nurtures collaboration, supports research translation, and balances commercial success with societal impact, we can pave the way for more groundbreaking innovations in the field of life sciences, ultimately improving the health and well-being of individuals around the world.

INNOVATION TO CONTAIN THE HIV/AIDS CRISIS: A TRUVADA CASE STUDY

William P. Kasper†

TABLE OF CONTENTS

DOI: https://doi.org/10.15779/Z38FX7402G

† J.D. Candidate, University of California, Berkeley, School of Law, Class of 2024. This case study benefitted from guidance, review, and feedback from Profs. Peter Menell and Allison Schmitt as well as other students in the 2022–23 Life Sciences & Innovation Workshop. I am grateful for this support and for the opportunity to contribute this innovation story to this issue of the *Berkeley Technology Law Journal*.

I. INTRODUCTION

> Look how far we've come . . . . This generation hasn't seen all the wasting away and dying that scared the hell out of us years ago. And most people in this generation don't know anyone who has died from the disease. People who are 25–35 don't have a clue what happened when people were dying all around us and the fear and terror of an HIV diagnosis . . . . Yes, it's no longer as bad as it once was, yet we still have over 36,000 new HIV transmissions annually here in the U.S. and it's still a major disease globally, and people are

> still dying from it. And the science and the disease don't get as much publicity as they used to.[1]
>
> —*Dr. Anthony Fauci, 2022.*

Truvada is a story of public health, fundamental research, and the pharmaceuticals industry innovating together to lift the once-deathly curse of the human immunodeficiency virus (HIV). From the early to mid-1980s, fear drove patients with the new and devastating Acquired Immunodeficiency Syndrome (AIDS) condition (and their friends) to organize among themselves, fight for government recognition, and help combat the growing AIDS pandemic. American public health authorities eventually responded to AIDS activism, such as when the U.S. Food and Drug Administration (FDA) made it easier for emergency drugs like AIDS treatments to be quickly approved.

In this period, university chemists Dr. Antonín Holý and Dr. Dennis Liotta were interested in making a mark on antiviral chemistry. Dr. Holý found a powerful anti-HIV medication called tenofovir by stroke of genius and brute force, which would go on to become its own commercialized product and one active ingredient in the combination therapy against HIV called Truvada. Separately, Dr. Liotta found another powerful anti-HIV medication called emtricitabine largely by brute force and serendipity that would become the second active ingredient of Truvada. Two different large pharmaceutical companies licensed these chemists' technologies for product development, but both companies would give up their initial licenses and make room for startup Gilead Sciences to dominate the nascent HIV treatment market. Gilead grew into a behemoth biopharmaceutical company largely because of its breakthrough HIV treatment Truvada, and recently won a unique patent litigation against the Centers for Disease Control and Prevention (CDC) to keep its intellectual property (IP) rights. The story of Truvada captures many different aspects of innovation in the life sciences sector.

II. TECHNICAL PRIMER

The purpose of Truvada is to reduce the likelihood of death (as treatment) and spread (as a preventive) in the ongoing Human Immunodeficiency Virus (HIV) pandemic.[2] The Truvada technology does this by building on earlier technologies that imitate how human biology builds DNA from RNA. To

1. John Casey, *Dr. Fauci Isn't Going Anywhere Until There's a Cure for HIV*, ADVOCATE (Mar. 24, 2022), https://www.advocate.com/health/2022/3/24/dr-fauci-isnt-going-anywhere-until-hes-found-cure-hiv.

2. *See* U.S. Patent No. 8,592,397 (filed Aug. 20, 2008) (describing in the Abstract the purpose of the claimed chemical composition) [hereinafter '397 Patent].

understand the development story and innovation drivers behind Truvada, this Article first presents technical overviews of the virus and the mechanisms of action for anti-HIV drugs like Truvada.[3] Table 1 provides a summary list of all HIV treatments and when they were first approved by the FDA. Appendix 1 summarizes the key events (that are described in detail in the next Part, Part III: Chronology of Innovation) leading to the development of Truvada.

A. HIV: THE RETROVIRUS THAT CAUSES AIDS

The core defense line of the human immune system is the helper T cell.[4] These kinds of white blood cells help the body kill all kinds of pathogens, including bacteria, viruses, fungi, and cancerous cells.[5] HIV is devastating because it gradually destroys the body's store of helper T cells, which normally reside in the lymph system. The Supreme Court summarized the mechanism of HIV infection and the resulting prognosis of AIDS in order to weigh whether HIV infection is a disability in *Bragdon v. Abbott*:[6]

> Once a person is infected with HIV, the virus invades different cells in the blood and in body tissues . . . . T-lymphocytes or CD4+ cells are particularly vulnerable to HIV. The virus attaches to the CD4 receptor site of the target cell and fuses its membrane to the cell's membrane. HIV is a retrovirus, which means it uses an enzyme to convert its own genetic material into a form indistinguishable from the genetic material of the target cell. The virus' genetic material migrates to the cell's nucleus and becomes integrated with the cell's chromosomes. Once integrated, the virus can use the cell's own genetic machinery to replicate itself. Additional copies of the virus are released into the body and infect other cells in turn . . . . The virus eventually kills the infected host cell . . . . The initial stage of HIV infection is known as acute or primary HIV infection. In a typical case, this stage lasts three months. The virus concentrates in the blood. The assault on the immune system is immediate. The victim suffers from a sudden and serious decline in the number of white blood cells. There is no latency period. Mononucleosis-like symptoms often emerge between six days and six weeks after infection, at times accompanied by fever, headache, enlargement of the lymph nodes (lymphadenopathy), muscle pain (myalgia), rash, lethargy, gastrointestinal disorders, and neurological disorders.

3. *See id.*

4. *See* Bruce Alberts et al., *Helper T Cells and Lymphocyte Activation*, *in* MOLECULAR BIOLOGY OF THE CELL (4th ed. 2002).

5. *See id.*

6. Bragdon v. Abbott, 524 U.S. 624, 633–37 (1998) (citations omitted) (defining HIV infection as a disability); *see also* Hassan M. Naif, *Pathogenesis of HIV Infection*, 5 INFECTIOUS DISEASE REPORTS SUPPL. 26, 26, 28 (2013) (describing, in depth, the HIV infection mechanism and progression of disease into AIDS if left untreated).

> Usually these symptoms abate within 14 to 21 days. HIV antibodies appear in the bloodstream within 3 weeks; circulating HIV can be detected within 10 weeks . . . . A person is regarded as having AIDS when his or her CD4+ count drops below 200 cells/mm^3 of blood or when CD4+ cells comprise less than 14% of his or her total lymphocytes.

In the summer of 1983, French virologists Drs. Françoise Barré-Sinoussi and Luc Montagnier (hereinafter, "Barré-Sinoussi" and "Montagnier," respectively), isolated a novel retrovirus[7] inside AIDS patients' lymph nodes (where helper T cells most commonly reside).[8] Similar findings of "lymphocytopathic [lymph-cell-killing] retroviruses" in AIDS patients by American doctors and virologists followed; more than two years into the AIDS pandemic, HIV was identified as its cause.[9] This finding was consistent with many doctors' unexplained observations as the AIDS pandemic began: dying AIDS patients appeared to have *no* helper T cells.[10]

This precise knowledge of the mechanism and timeline of a typical HIV/AIDS case developed over a decade of research across the globe. Congress launched the first federal legislative action with the Health Omnibus Programs Extension (HOPE) Act of 1988 alongside Reagan's first executive order on AIDS.[11] During a 2012 panel discussion, a world leader in the AIDS pandemic response, Sir Richard Feacham (hereinafter, "Feacham"), remarked that HIV was the most well-studied and well-understood human virus ever in 2000; that year, HIV was also the largest lethal pandemic mankind had ever experienced.[12] At the time of Feacham's panel discussion in 2012,

---

7. A retrovirus is a type of virus that has genetic material in the form of RNA. A retrovirus will invade a host cell, insert its RNA genetic material into the host cell's DNA, and then use its host's DNA for further replication that is difficult for the host's immune systems to detect. *See Talking Glossary of Genomic and Genetic Terms: Retrovirus*, NAT'L HUM. GENOME RSCH INST., https://www.genome.gov/genetics-glossary/Retrovirus (last visited Mar. 11, 2023).

8. *See* Barré-Sinoussi et al., *Isolation of a T-Lymphotropic Retrovirus from a Patient at Risk for Acquired Immune Deficiency Syndrome (AIDS)*, 220 SCI. 868 (1983).

9. *See* Gallo et al., *Frequent Detection and Isolation of Cytopathic Retroviruses (HTLV-III) from Patients with AIDS and at Risk for AIDS*, 224 SCI. 500 (1984); *see also* Levy et al., *Isolation of Lymphocytopathic Retroviruses from San Francisco Patients with AIDS*, 225 SCI. 840 (1984).

10. RANDY SHILTS, AND THE BAND PLAYED ON: POLITICS, PEOPLE, AND THE AIDS EPIDEMIC 42, 72 (2013).

11. *See, e.g.*, 42 U.S.C. § 300cc (describing government programs and their statutory requirements enacted in 1988 onwards for research with respect to AIDS, including establishing the NIH's Office for AIDS Research and AIDS Research Advisory Committee).

12. *See* THE EVOLUTION OF HIV/AIDS THERAPIES (Chemical Heritage Foundation & Science History Institute 2012), https://vimeo.com/59281508 (containing clip of Sir Richard Feacham, founder of the Global Fund, sharing the contrast between sheer knowledge of HIV scientifically against the lack of action in the early years, beginning at the 27 minute mark).

approximately 25–35 million people had died of AIDS-related illnesses worldwide, and recently the UN estimated 32.9–51.3 million dead of AIDS-related illnesses as of 2021.[13]

B. ANTIRETROVIRAL TECHNOLOGY FOR HIV INHIBITION

Antiretroviral therapy (ART) technology has been at the heart of the public health response to the HIV/AIDS pandemic since the 1980s. To understand Truvada and the value it adds in this field, this Section first covers ART technologies in general and then covers the technology of Truvada.

1. Antiretroviral Therapies for HIV

The very first ART to mitigate HIV infection came on the market in 1987.[14] This class of drugs—normally taken orally—has become the staple treatment for HIV infection. More recently, several ARTs are also staple preventive therapies for at-risk populations. The goal of all ART treatments, which may be given in combination as highly active antiretroviral therapy (HAART) to match each case's severity, is to halt HIV replication and to prevent the patient from developing AIDS.[15]

The National Cancer Institute collaborated with the Burroughs-Wellcome Company to invent the first treatment to slow HIV progression—azidothymidine (AZT).[16] This collaboration to develop AZT began decades earlier in search of an anti-cancer therapeutic.[17] AZT was first FDA approved for HIV treatment in 1987,[18] while Burroughs-Wellcome filed five patents that were later granted to give them a monopoly that restricted therapy access to those who could afford expensive medication.[19]

---

13. *See Global HIV & AIDS Statistics – Fact sheet*, UNAIDS, https://www.unaids.org/en/resources/fact-sheet (last visited Feb. 16, 2024).

14. *See* National Institutes of Health, *Antiretroviral Drug Discovery and Development*, NIAID, https://www.niaid.nih.gov/diseases-conditions/antiretroviral-drug-development#:~:text=In%20March%201987%2C%20AZT%20became,reverse%20transcriptase%20inhibitors%2C%20or%20NRTIs (last visited Mar. 11, 2023).

15. *See id.*

16. *See In Their Own Words… NIH Researchers Recall the Early Years of AIDS*, NAT'L INST. HEALTH, https://history.nih.gov/display/history/In+Their+Own+Words (last visited Sept. 11, 2022).

17. *See id.*

18. *See id.*

19. *See* Malcolm Gladwell, *LAWSUIT ON AIDS-DRUG PATENT SEEKS TO END FIRM'S MONOPOLY*, WASH. POST (Mar. 19, 1991), https://www.washingtonpost.com/archive/politics/1991/03/20/lawsuit-on-aids-drug-patent-seeks-to-end-firms-monopoly/cf168a7b-b071-4af3-b445-4e1c4274b52b.

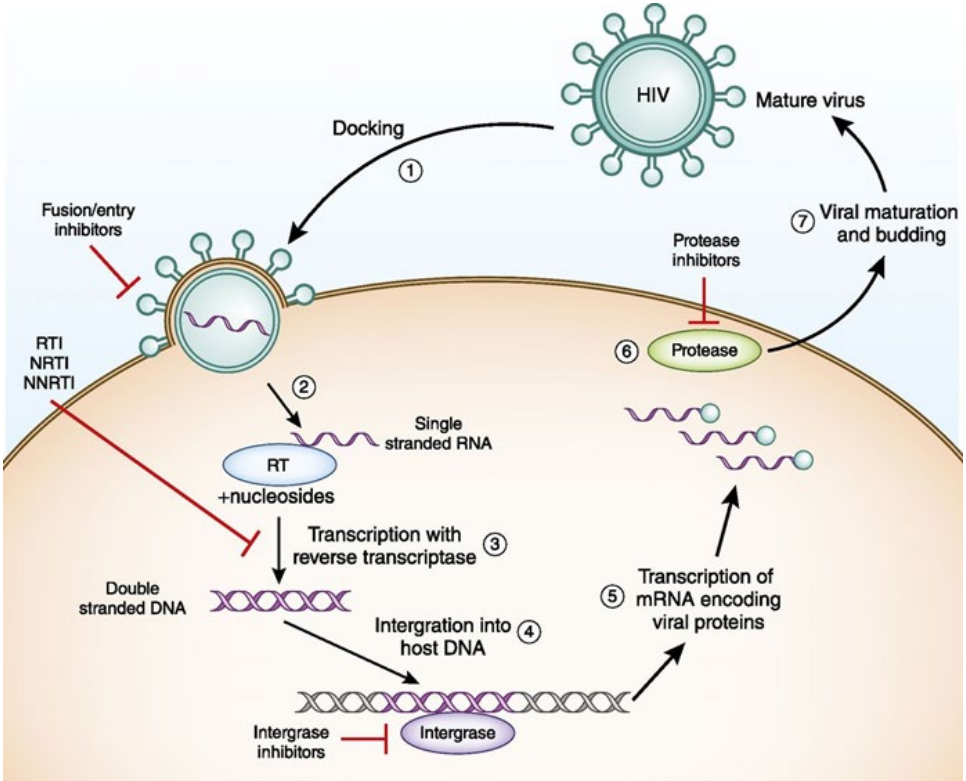
The first HIV treatment was technically successful, but it had many drawbacks. AZT was the first "nucleoside reverse transcriptase inhibitor" (NRTI) against HIV, slowing HIV's ability to infect host cells by inhibiting the virus' reverse transcriptase (RT) (an enzyme responsible for creating viral DNA from viral RNA, an essential step to permanently encode and install viral genetic material into the host cell's DNA).[20] However, in the early 1990s, researchers discovered AZT was "highly toxic to human cells" and otherwise difficult for patients to adhere to for their lifetime, so the AIDS innovation ecosystem quickly realized AZT was far from a slam-dunk cure for HIV.[21] Anger and frustration in the AIDS community (discussed *infra*, Section III.A.3) over AZT's toxicity and inequitable distribution prompted protests at federal public health authority headquarters and a race to develop better ARTs.[22]

20. *See* Parth H. Patel & Hassam Zulfiqar, *Reverse Transcriptase Inhibitors*, *in* STATPEARLS (2022), https://www.ncbi.nlm.nih.gov/books/NBK551504/#:~:text=The%20nucleoside%2Fnucleotide%20reverse%20transcriptase%20inhibitors%20(NRTIs)%20were%20the,kinases%20will%20activate%20the%20drug.

21. David T. Chiu & Peter H. Duesberg, *The Toxicity of Azidothymidine (AZT) on Human and Animal Cells in Culture at Concentrations Used for Antiviral Therapy*, 95 GENETICA 103, 103, 107–08 (1995).

22. *See* U.S. Department of Health & Human Services, *A Timeline of HIV and AIDS – 1990*, HIV.GOV, https://www.hiv.gov/hiv-basics/overview/history/hiv-and-aids-timeline/#year-1990 (last visited Sept. 11, 2022) [hereinafter *A Timeline of HIV and AIDS*].

Figure 1: Seven-step life cycle of HIV inside and outside of a human cell (orange), showing the mechanisms of HIV inhibition by different anti-retroviral technologies (red lines).[23]



The race to find a safer treatment than AZT, and ideally a cure, resulted in an explosion in the 1990s of different ART treatments against HIV coming to market; the types of ART treatment are shown with red lines in Figure 1.[24] There are now well over a dozen different ART products (shown in Table 1, *infra*), each of which typically fall into one of six novel categories.

These ART categories include: (1) NRTIs, the first being AZT, as well as nucleotide RT enzyme inhibitors (NtRTIs) that block RT transcription of viral RNA into cellular DNA (shown in step 3 of Figure 1); (2) non-nucleoside RT inhibitors (NNRTIs) that also block RT activity (shown in step 3 of Figure 1); (3) protease inhibitors (PIs) that block viral protein building blocks from

23. *See generally* Mohamed G. Atta et al., *Clinical Pharmacology in HIV Therapy*, 7 CLINICAL J. AM. SOC'Y NEPHROLOGY 435 (2018) (describing the broad set of HIV antiretroviral technologies, including the NtRTI/NRTI technology deployed by Truvada).

24. *See A Timeline of HIV and AIDS*, *supra* note 22 (explaining further in the section on 1995).

assembling into mature viral particles (shown in step 6 of Figure 1); (4) integrase inhibitors that block incorporation of viral DNA into cellular DNA (shown in step 4 of Figure 1); and (5) entry, fusion, or attachment inhibitors that change the proteins on the cell surface to prevent HIV from inserting viral RNA into the cell (shown in steps 1 and 2 in Figure 1).[25] See Figure 1 for the life cycle location upon which each HIV technologies inhibits replication, Table 1 for a list of all currently-marketed ARTs listed by life cycle location, and Table 2 for adverse effects of ARTs again grouped by life cycle location.

Table 1: Anti-retroviral compounds by class and related prodrug forms approved by the FDA.[26]

ART Class	Compound	Prodrug Forms	U.S. Trade Name	1st FDA Approval
Nucleoside RT enzyme inhibitors (NRTIs) and Nucleotide RT enzyme inhibitors (NtRTIs)	Azidothymidine (AZT) (a/k/a Zidovudine)	--	Retrovir	1987
	2',3'-dideoxy-3'-thiacytidine	Lamivudine ("3TC"): (−)-L-2',3'-dideoxy-3'-thiacytidine	Epivir	1995 (combination ART)
				2002 (once-a-day)
		Emtricitabine ("FTC"): 2',3'-dideoxy-5-fluoro-3'-thiacytidine	Emtriva (formerly Coviracil)	2003
	Abacavir (ABC)	--	Ziagen	1998
	Tenofovir	Tenofovir disoproxil fumarate (TDF)	Viread	2004
		Tenofovir alafenamide fumarate (TAF)	Vemlidy	2016
Non-nucleoside RT enzyme inhibitors (NNRTIs)	Nevirapine (NVP)	--	Viramune	1996
	Efiravenz (EFV)	--	Sustiva	1998
	Etravirine (ETR)	--	Intelence	2008
	Rilpivirine (RPV)	--	Edurant	2011 (combination ART)
	Doravirine (DOR)	--	Pifeltro	2018
Integrase inhibitors (INSTIs)	Raltegravir (RAL)	--	Isenstress	2007
	Elvitegravir (EVG)	--	One ingredient in Stribild	2012 (combination ART)
			Vitekta	2014 (once-a-day)
	Dolutegravir (DTG)	--	Tivicay	2013

25. Roger Pebody, *Types of antiretroviral medications*, NAM AIDSMAP (May 2021), https://www.aidsmap.com/about-HIV/types-antiretroviral-medications.

26. *See id.*; *see also* U.S. Food & Drug Administration, *FDA-Approved Drugs*, DRUGS@FDA, https://www.accessdata.fda.gov/scripts/cder/daf/index.cfm (providing searchable database containing FDA approval letters for each drug, containing approval dates and any toxicity concerns).

ART Class	Compound	Prodrug Forms	U.S. Trade Name	1st FDA Approval
	Bictegravir (BIC)	--	Only in a HAART called Biktarvy	2018
	Cabotegravir (CBG)	--	Apretude	2021 (injection every 2 months)
			Vocabria	2021 (once-a-day)
			One ingredient in Cabenuva	2021 (combination ART)
Entry inhibitors	Enfuvirtide (ENF)	--	Fuzeon	2003
(EIs)	Maraviroc (MVC)	--	Selzentry	2007
Protease	Lopinavir (LPV)	--	One ingredient in Kaletra	2000
inhibitors (PIs)	Atazanavir (ATV)	--	Reyataz	2003 (once-a-day)
			One ingredient in Evotaz	2015 (combination ART)
	Darunavir (DRV)	--	One ingredient in Prezista	2006 (combination ART)
			One ingredient In Prezcobix	2015 (single-tablet combination)
Attachment	Ibalizumab (IBA)	--	Trogarzo	2018 (for ART-resistant patients)
inhibitors (CIs)	Fostemsavir (FTR)	--	Rukobia	2020 (for ART-resistant patients)
PI Boosters	Ritonavir (RTV)	--	Second ingredient in Kaletra	2000
(also known as			Norvir	2004
"PK Boosters")	Cobicistat (COBI)	--	Tybost	2014

Table 2: Known risks of adverse effects of treatment by ART class and individual compound.[27]

Adverse Effect	Drug Class					
	NRTIs	NNRTIs	PIs	INSTIs	EIs	CIs
Bone Density Effects	TDF: Associated with greater loss of BMD than other NRTIs, especially when given with a PK booster. Osteomalacia may be associated with renal tubulopathy and urine phosphate wasting. TAF: Associated with smaller declines in BMD than those seen with TDF.	Decreases in bone mineral density (BMD) observed after the initiation of any ART regimen			N/A	Not evaluated

27. National Institutes of Health, *Limitations to Treatment Safety and Efficacy – Adverse Effects of Antiretroviral Agents*, HIV.GOV, https://clinicalinfo.hiv.gov/en/guidelines/hiv-clinical-guidelines-adult-and-adolescent-arv/adverse-effects-antiretroviral-agents (last visited May 20, 2023).

Adverse Effect	Drug Class					
	NRTIs	NNRTIs	PIs	INSTIs	EIs	CIs
Bone Marrow Suppression	ZDV: Anemia, neutropenia	N/A	N/A	N/A	N/A	N/A
Cardiac Conduction Effects	N/A	RPV and EFV: QTc prolongation (a potential form of heart arrythmia).	ATV/r and LPV/r: PR prolongation (a potential form of heart arrythmia). Risk factors include pre-existing heart disease and concomitant use of medications that may cause PR prolongation	N/A	FTR: QTc prolongation was seen at four times the recommended dose. Use with caution in patients with pre-existing heart disease or QTc prolongation, or concomitant use of medications that may prolong QTc interval.	N/A
Cardiovascular Disease (CVD)	ABC: Associated with an increased risk of MI in some cohort studies. Absolute risk greatest in patients with traditional CVD risk factors.	N/A	Boosted DRV and LPV/r: Associated with cardiovascular events in some cohorts	N/A	N/A	N/A
Cholelithiasis	N/A	N/A	ATV: Cholelithiasis and kidney stones may present concurrently. Median onset is 42 months after ARV initiation.	N/A	N/A	N/A
Diabetes Mellitus and Insulin Resistance	ZDV	N/A	LPV/r, but not with boosted ATV or DRV	N/A	N/A	N/A
Dyslipidemia	ZDV > ABC: ↑ Triglycerides (TG) and ↑ low-density lipoprotein cholesterol (LDL). TAF: ↑ TG, ↑ LDL, and ↑ high-density lipoprotein cholesterol	EFV: ↑ TG, ↑ LDL, ↑ HDL	All RTV- or COBI-Boosted PIs: ↑ TG, ↑ LDL, ↑ HDL LPV/r > DRV/r and ATV/r: ↑ TG	EVG/c: ↑ TG, ↑ LDL, ↑ HDL	N/A	N/A

Adverse Effect	Drug Class					
	NRTIs	NNRTIs	PIs	INSTIs	EIs	CIs
	(HDL) (no change in TC:HDL ratio) TDF has been associated with lower lipid levels than ABC or TAF.					
Gastrointestinal Effects	ZDV > Other NRTIs: Nausea and vomiting	N/A	Gastrointestinal (GI) intolerance (e.g., diarrhea, nausea, vomiting) LPV/r > DRV/r and ATV/r: Diarrhea	EVG/c: Nausea and diarrhea	N/A	LEN: Nausea and diarrhea
Hepatic Effects	When TAF, TDF, 3TC, and FTC are withdrawn in Patients with Hepatitis B (HBV) and HIV Coinfection or when HBV Resistance Develops: Patients with HBV/HIV coinfection may develop severe hepatic flares. ZDV: Steatosis	EFV: Most cases relate to an increase in transaminases. Fulminant hepatitis leading to death or hepatic failure requiring transplantation have been reported. NVP: Severe hepatotoxicity associated with skin rash or hypersensitivity. A 2-week NVP dose escalation may reduce risk. Risk is greater for women with pre-NVP CD4 counts >250 cells/mm^3 and men with pre-NVP CD4 counts >400 cells/mm^3. NVP should never be used for post-exposure prophylaxis. EFV and NVP are not recommended in patients with hepatic	All PIs: Drug-induced hepatitis and hepatic decompensation have been reported. ATV: Jaundice due to indirect hyperbilirubinemia	DTG: Persons with HBV or Hepatitis C (HCV) coinfection may be at higher risk of DTG-associated hepatotoxicity.	MVC: Hepatotoxicity with or without rash or hypersensitivity reactions (HSRs) has been reported. FTR: Transaminase elevation was seen more commonly in patients with HBV/HCV. Transient elevation of bilirubin observed in clinical trials.	N/A

Adverse Effect	Drug Class					
	NRTIs	NNRTIs	PIs	INSTIs	EIs	CIs
		insufficiency (Child-Pugh class B or C).				
Hypersensitivity Reaction Excluding rash alone or Stevens-Johnson syndrome	ABC: Contraindicated if patient is HLA-B*5701 positive. Median onset for HSR is 9 days after treatment initiation; 90% of reactions occur within six weeks. HSR Symptoms (in Order of Descending Frequency): Fever, rash, malaise, nausea, headache, myalgia, chills, diarrhea, vomiting, abdominal pain, dyspnea, arthralgia, and respiratory symptoms Symptoms worsen with continuation of ABC. Patients should not be rechallenged with ABC if HSR is suspected, regardless of their HLA-B*5701 status.	NVP: Hypersensitivity syndrome of hepatotoxicity and rash that may be accompanied by fever, general malaise, fatigue, myalgias, arthralgias, blisters, oral lesions, conjunctivitis, facial edema, eosinophilia, renal dysfunction, granulocytopenia, or lymphadenopathy Risk is greater for ARV-naive women with pre-NVP CD4 counts >250 cells/mm^3 and men with pre-NVP CD4 counts >400 cells/mm^3. Overall, risk is higher for women than men. A 2-week dose escalation of NVP reduces risk.	N/A	RAL: HSR reported when RAL is given with other drugs also known to cause HSRs. All ARVs should be stopped if HSR occurs. DTG: Reported in <1% of patients in clinical development program	MVC: HSR reported as part of a syndrome related to hepatotoxicity.	N/A
Injection Site Reaction		RPV IM Injection: Reported in >80% of patients; reactions may include localized pain/discomfort (most common), nodules, induration, swelling, erythema, hematoma.		CAB IM Injection: Reported in >80% of patients; reactions may include localized pain/discomfort (most common), nodules, induration, swelling, erythema, hematoma.	T-20 SQ Injection: Reported in almost all patients; reactions may include pain, tenderness, nodules, induration, ecchymosis, erythema.	LEN SQ injection: Reported in 47–62% of patients; reactions may include swelling, erythema, pain, nodules, inflammation, induration. Nodules and induration

Adverse Effect	Drug Class					
	NRTIs	NNRTIs	PIs	INSTIs	EIs	CIs
						may persist for months in some patients.
Lactic Acidosis	Reported with Older NRTIs, d4T, ZDV, and ddI, but not with ABC, 3TC, FTC, TAF, or TDF.	N/A	N/A	N/A	N/A	N/A
Lipodystrophy	Lipoatrophy: Associated with history of exposure to d4T or ZDV (d4T > ZDV). Not reported with ABC, 3TC or FTC, or TAF or TDF.	Lipohypertrophy: Trunk fat increase is observed with EFV-, PI-, and RAL-containing regimens; however, a causal relationship has not been established.			N/A	N/A
Myopathy / Elevated Creatine Phosphokinase	ZDV: Myopathy	N/A	N/A	RAL and DTG: ↑ creatine phosphokinase (CPK), rhabdomyolysis, and myopathy or myositis have been reported.	N/A	N/A
Nervous System / Psychiatric Effects	History of Exposure to ddI, ddC, or d4T: Peripheral neuropathy (can be irreversible)	Neuropsychiatric Events: EFV > RPV, DOR, ETR EFV: Somnolence, insomnia, abnormal dreams, dizziness, impaired concentration, depression, psychosis, suicidal ideation, ataxia, encephalopathy. Some symptoms may subside or diminish after 2–4 weeks. Bedtime dosing and taking without food may reduce symptoms. [. . .] RPV: Depression, suicidality, sleep disturbances	N/A	All INSTIs: Insomnia, depression, and suicidality have been reported with INSTI use, primarily in patients with pre-existing psychiatric conditions.	N/A	LEN: Headache

Adverse Effect	Drug Class					
	NRTIs	NNRTIs	PIs	INSTIs	EIs	CIs
		DOR: Sleep disorders and disturbances, dizziness, altered sensorium; depression and suicidality, and self-harm				
Rash	FTC: Hyperpigmentation	All NNRTIs	ATV, DRV, and LPV/r	All INSTIs	MVC, IBA, FTR	N/A
Renal Effects / Urolithiasis	TDF: ↑ Bloodserum creatinine (SCr), proteinuria, hypophosphatemia, urinary phosphate wasting, glycosuria, hypokalemia, and non-anion gap metabolic acidosis. Concurrent use of TDF with COBI- or RTV-containing regimens appears to increase risk. TAF: Less impact on renal biomarkers and lower rates of proteinuria than TDF	RPV: Inhibits creatinine (Cr) secretion without reducing renal glomerular function	ATV and LPV/r: Associated with increased risk of chronic kidney disease in a large cohort study. ATV: Stone or crystal formation; adequate hydration may reduce risk COBI (as a Boosting Agent for DRV or ATV): Inhibits Cr secretion without reducing renal glomerular function	DTG, COBI (as a Boosting Agent for EVG), and BIC: Inhibits Cr secretion without reducing renal glomerular function	IBA: SCr abnormalities ≥Grade 3 reported in 10% of trial participants. FTR: SCr > -1.8 x Upper Limit Normal (ULN) seen in 19% in a clinical trial, but primarily with underlying renal disease or other drugs known to affect creatinine.	N/A
Stevens-Johnson Syndrome / Toxic Epidermal Necrosis	N/A	NVP > EFV, ETR, RPV	Some reported cases for DRV, LPV/r, and ATV	RAL	N/A	N/A
Weight Gain	Weight gain has been associated with initiation of ART and subsequent viral suppression. The increase appears to be greater with INSTIs than with other drug classes. Greater weight increase has also been reported with TAF than with TDF and with DOR than with EFV.			INSTI > other ARV drug classes	N/A	N/A

As Figure 1 shows, each type of ART uses a different mechanism to block HIV replication. But individual active ingredients (as listed in Table 1) differ in their properties, e.g., uptake efficiency ("bioavailability") or long-term

toxicity concerns; Table 2 lists toxicity concerns by drug class. To mitigate these concerns, many of these compounds have been modified with additional chemical groups to form prodrugs.[28] A further approach combines multiple ART active ingredients to create a combined ART against HIV,[29] as is the case with Truvada ("Truvada") and Truvada for PrEP ("Truvada for PrEP").[30]

2. Truvada Technology Overview

Truvada is a combination of two antiretroviral technologies: (1) tenofovir disoproxil fumarate and (2) emtricitabine. The technology behind each is described in this Section.

a) Technical Overview of Tenofovir Disoproxil Fumarate

The first component of Truvada,[31] tenofovir, acts to inhibit HIV infection[32] like AZT: both disrupt HIV RT transcription of viral RNA to DNA in the host cell. Viral RT recognizes tenofovir as a natural nucleotide (a building block of DNA).[33] But, tenofovir differs from a natural nucleotide in a key way: it lacks the functional group (the 3'-hydroxyl group) that RT uses to chemically join one nucleotide to another in a growing DNA chain. Thus, when RT incorporates tenofovir in the growing DNA strand, instead of building a natural nucleotide, viral DNA transcription halts pre-maturely. This antiretroviral activity is an example of a NtRTI, also referred to as "nucleotide *analog*[] reverse transcriptase inhibitor" (shown in Figure 1, *supra*) (emphasis added).[34] Nucleoside reverse transcriptase inhibitors, like AZT, differ slightly in chemical structure but halt DNA transcription by the same mechanism.

28. *See generally* M. S. Palombo et al., *Prodrug and Conjugate Drug Delivery Strategies for Improving HIV/AIDS therapy*, 19 J. DRUG DELIVERY SCI. & TECH. 3, 3–14 (2009) (describing the mechanisms by which many different modifications to known antiretroviral drugs as "prodrugs" had been made to improve HIV eradication).

29. *See Antiretroviral Therapy*, PAN AM. HEALTH ORG., https://www.paho.org/en/topics/antiretroviral-therapy (last visited Nov. 5, 2022).

30. *Drug Approval Package: Truvada® (Emtricitabine and Tenofovir Disoproxil Fumarate) Tablets*, U.S. FOOD & DRUG ADMIN., https://www.accessdata.fda.gov/drugsatfda_docs/nda/2004/021752s000_TruvadaTOC.cfm (last visited Sept. 11, 2022).

31. *See id.*

32. *See* '397 Patent, *supra* note 2, at col. 2:15–19.

33. *See id.* at col. 1:20–29 (describing weaknesses of the first HIV reverse transcriptase inhibitors, including AZT, in terms of its toxicity and susceptibility to viral resistance); *see also id.* at col. 7:52–55 ("Tenofovir disoproxil fumarate (DF) is a nucleotide reverse transcriptase inhibitor."); *see also* Eric J. Arts and Daria J. Hazuda, *HIV-1 Antiretroviral Drug Therapy*, 2 COLD SPRING HARBOR PERSPS. MED. a007161, 7 (2012).

34. Parth H. Patel & Hassam Zulfiqar, *Reverse Transcriptase Inhibitors*, *in* STATPEARLS (2023) (describing the chemistry of nucleotide- and nucleoside-reverse transcriptase inhibitors

Tenofovir disoproxil fumarate (TDF) is a "prodrug" of the molecule tenofovir that is metabolized in the body into its active form.[35] Prodrugs can improve delivery of the active ingredient when the active form cannot efficiently enter target cells or metabolic processes degrade it before it can achieve sufficient therapeutic effect.[36] Since TDF helps the body get tenofovir where it needs to go and TDF shows improved efficacy over pure tenofovir when taken orally, many HIV combination therapies transitioned to include TDF.

b) Technical Overview of Emtricitabine

The second component of Truvada, emtricitabine, has a similar yet distinct mechanism of inhibiting HIV replication and infection.[37] Emtricitabine acts like AZT as a "nucleoside analog reverse transcriptase inhibitor (NRTI; see Figure 1, *supra*)," specifically imitating the nucleoside known as cytosine, another of the four fundamental building blocks of DNA and RNA.[38] As a nucleoside-impersonating inhibitor of the RT enzyme, emtricitabine works by entering into the RT enzyme's produced viral genome, "causing [early] termination" of the produced viral DNA, and ultimately rendering the viral DNA defective.[39]

Therefore, in combination, the two components of Truvada (TDF and emtricitabine) heavily inhibit the virus' RT by posing to the enzyme as defective analogs of two of the four DNA building blocks.[40] In this way, Truvada relies more heavily than other ARTs on RT inhibition (shown in Figure 1, *supra*) for the life cycle of HIV in human cells and where current medicines including NtRTIs and NRTIs like those in Truvada are used).[41]

---

in the Mechanism of Action section); *see also* Peter L. Anderson et al., *The Cellular Pharmacology of Nucleoside- and Nucleotide-Analogue Reverse-Transcriptase Inhibitors and Its Relationship to Clinical Toxicities*, 38 CLINICAL INFECTIOUS DISEASES 743, 745 (2004) (describing the TDF metabolic pathway as an adenosine nucleotide analog in the source's Figure 1).

35. *See* '397 Patent, *supra* note 2, at col. 6:64–67.

36. *See id.* at col. 4:40–51; *see also* Jarkko Rautio et al., *The Expanding Role of Prodrugs in Contemporary Drug Design and Development*, 17 NATURE REVS. DRUG DISCOVERY 559 (2018) (explaining why and how prodrugs are commonly used to develop treatments in the modern pharmaceutical industry).

37. *See* '397 Patent, *supra* note 2, at col. 9:1–39.

38. *See* E. Paintsil, Yung-Chi Cheng, *Antiviral Agents*, *in* ENCYCLOPEDIA MICROBIOLOGY 249 (3d ed. 2009).

39. *Id.*

40. *See* FDA, *Truvada® Package Insert* (rev. June 2020) at 1, https://www.gilead.com/~/media/files/pdfs/medicines/HIV/truvada/truvada_pi.pdf.

41. *See generally* Mohamed G. Atta et al., *Clinical Pharmacology in HIV Therapy*, CLINICAL J. AM. SOC'Y NEPHROLOGY (2018) (describing the broad set of HIV antiretroviral technologies, including the NtRTI/NRTI technology deployed by Truvada).

Truvada is effective: Long-term use often reduces patients' HIV load to "undetectable" levels (the first approved clinical indication for Truvada) and therefore stops progression to AIDS.[42] After a potential HIV exposure emergency, use of Truvada short-term with other ART(s) can prevent infection as a "post-exposure prophylactic" (PEP). Alternatively—and more commonly—routine or continuous "pre-exposure prophylactic" (PrEP) use of Truvada alone (the second approved clinical indication for Truvada) reduces HIV infection risk by as much as 99%.[43]

III. CHRONOLOGY OF INNOVATION

The innovations behind Truvada span more than three decades of collaboration among public and private health institutions, largely driven by the suffering and tenacity of AIDS patients. Appendix 1 at the end of this Article provides a summary table of key events in the Truvada innovation story. This story begins with the medical community's identification of the disease in the early 1980s, after the disease had slowly circulated in sub-Saharan Africa for years. In the first years of the HIV/AIDS pandemic, federal health authorities failed to act. HIV/AIDS patients and friends turned to activism and changed the way U.S. public health agencies work to serve their constituents. These activists built a novel international coalition of philanthropic organizations, clinicians, universities, federal health authorities, and large and small pharmaceutical companies to hear their concerns and build better treatments. Private and public actors in this coalition patented their technologies as they progressed, enabling a structure of licensing and acquisitions that facilitated the development of Truvada.

Each of the two active ingredients of Truvada, tenofovir and emtricitabine, were developed by university chemists looking to satisfy the unmet need for effective-yet-safe, once-daily anti-HIV medicines. The two Truvada active ingredients were each developed when large pharmaceutical companies shut down HIV treatment development and their HIV research leaders subsequently left for startup companies to address the painful AIDS crisis. The

42. *See Truvada® Package Insert*, *supra* note 40, at 30 (describing key clinical trial for Truvada for HIV treatment where 84% of the Truvada treatment group achieved < 400 HIV RNA copies/mL of blood, close to the CDC's current definition of "undetectable" as < 200 HIV RNA copies/mL of blood); *see also HIV Treatment as Prevention*, CDC, https://www.cdc.gov/HIV/risk/art/index.html (last visited Nov. 13, 2022) (defining "undetectable" HIV viral load as < 200 HIV RNA copies/mL of blood).

43. *See About PEP*, CDC (July 12, 2022), https://www.cdc.gov/HIV/basics/pep/about-pep.html (describing PEP for emergency treatment after an HIV exposure event); *see also* CDC, *PrEP Effectiveness*, https://www.cdc.gov/HIV/basics/prep/prep-effectiveness.html (last visited Nov. 13, 2022) (describing PrEP's clinical strengths in containing HIV spread).

two ingredients used together in the product Truvada proved a powerful anti-HIV combination therapy that enables those with HIV to live a full life; later, it became the first medicine with FDA approval to *prevent* HIV infection. Through success with Truvada, its development company Gilead Sciences, Inc. grew into the world's dominant anti-HIV drug manufacturer.

A. PHASE I—BEFORE TRUVADA: HIV/AIDS PANDEMIC EMERGES AND THE WORLD SLOWLY RESPONDS

In the 1980s, AIDS emerged among disadvantaged communities across the world, but governments were very slow to respond. HIV was identified as its cause several years into the pandemic, which provided a technological foothold for the world to begin systematically containing the virus' exponential spread by developing testing, treatments, and vaccines. The magnitude of death and suffering prompted AIDS patients and friends to build activist organizations that pushed U.S. public health authorities to rethink their approach to public health and form an innovation coalition with many public and private actors. This time provides foundational context for the development of Truvada in the late 1980s and 1990s.

1. Mysterious Disease Slowly Destroyed Communities "and the Band Played On"

Early in the summer of 1981, five gay men were hospitalized in Los Angeles with a rare combination of bacterial *Pneumocystis carinii* pneumonia and other opportunistic infections that ultimately killed the men within weeks of each other.[44] These were the first widely known cases of a novel, unidentified disease that would kill at least 130 people in the United States in 1981.[45] The death toll increased by a factor of four to almost 560 confirmed dead over the next two years before researchers identified the agent causing the disease.[46]

The disease, which quickly became known as "AIDS," had been circulating in sub-Saharan Africa since the 1950s.[47] The first cases in the United States and Europe were concentrated in travel medicine practitioners, Black youth, gay men of all ages, and hemophiliacs.[48] However, by the middle of 1983, 72%

44. *See* U.S. Dep't Health & Hum. Servs., *A Timeline of HIV and AIDS*, HIV.GOV, https://www.hiv.gov/hiv-basics/overview/history/hiv-and-aids-timeline (last visited Sept. 11, 2022).

45. *Id.*

46. *Id.*

47. *See generally* Michael Worobey et al., *Direct Evidence of Extensive Diversity of HIV-1 in Kinshasa by 1960*, 455 NATURE 661, 661–64 (2008) (showing the likelihood of HIV-1 circulating in humans in the 1910s).

48. *See A Timeline of HIV and AIDS*, *supra* note 22.

of the 1,100 AIDS cases in the United States were reported in gay men.[49] At this time, no one had a scientific understanding of the cause, so many cases went unreported. Nor was there any cure, or even a promising treatment; fear overcame these communities as many faced drawn-out deaths to AIDS.[50]

The U.S. federal government was slow to fund or otherwise support research to understand AIDS as the pandemic grew. The government did not approve any AIDS research grants in 1981–82, despite $8 million in Congressional appropriations for that purpose.[51] Over $55 million in proposed projects on AIDS research were submitted to the National Institutes of Health alone during this time.[52] A leader of the grassroots fight against AIDS compared this failure to launch needed AIDS research to the $10 million spent in a matter of weeks by the same federal health authorities to respond to the seven Tylenol poisonings in Chicago that same year, screaming in ink, "[w]e desperately need something from our government to save our lives, and we're not getting it."[53] It took four years of the pandemic raging before President Reagan publicly addressed its existence to a reporter in 1985 and two more years for him to issue the nation's first executive order to tackle to the AIDS pandemic in 1987.[54]

2. The World's Early Technologies Against HIV/AIDS

Researchers' first steps to contain the pandemic were to develop: (1) identification and testing methods for the pathogen that causes AIDS; (2) vaccines; and (3) effective treatments for HIV-positive patients. Only the first and third of these technologies initially resulted in meaningful HIV containment during first decade of the pandemic: the 1980s and early 1990s. This Section will describe each of the three technology fronts in that time.

a) Identification and Testing of HIV from Patient's Blood

French virologists Barré-Sinoussi and Montagnier at the Institut Pasteur in France collaborated with Dr. Robert Gallo (hereinafter, "Gallo") at the U.S. National Cancer Institute (NCI) in the first three years of the pandemic to

49. *See* Larry Kramer, *1,112 and Counting*, 59 N.Y. NATIVE (1983).
50. *Id.*
51. *Id.*
52. *Id.*
53. *Id.*
54. Joseph Bennington-Castro, *How AIDS Remained an Unspoken—But Deadly—Epidemic for Years*, HISTORY (updated Aug. 22, 2023), https://www.history.com/news/aids-epidemic-ronald-reagan; President Ronald Reagan, *Remarks at the American Foundation for AIDS Research Awards Dinner*, AM. PRESIDENCY PROJECT (May 31, 1987), https://www.presidency.ucsb.edu/documents/remarks-the-american-foundation-for-aids-research-awards-dinner [hereinafter President Reagan's Remarks at 1987 AIDS Research Awards Dinner].

identify HIV as the cause of AIDS.[55] After identifying HIV as a retrovirus that attacks lymphocytes, specifically T cells, each set of scientists raced to publish their findings and develop HIV test kits.[56] Barré-Sinoussi and Montagnier published their initial findings first in 1983. Gallo published one year later in 1984.[57]

HIV testing prompted an international patent and contract dispute. Barré-Sinoussi and Montagnier collaborated to file a U.S. patent on the first HIV antibody test kit in December 1983, just months after their ultimately-Nobel-prize-winning identification of HIV.[58] That summer, the Institut contracted with Gallo at NCI to collaborate and provide materials from Barré-Sinoussi's and Montagnier's innovative identification work. Gallo filed his own U.S. patent application on HIV antibody test kits in April 1984, just five months after Montagnier. Gallo's patent application granted while Montagnier's did not.[59] Gallo and collaborators at the U.S. Department of Health and Human Services went on to develop and mass produce HIV test kits, but initially did not share royalties with the Institut.[60] The Institut sued the United States for breach of contract to recover royalties. Simultaneously, the Institut pursued separate tort and Freedom of Information Act suits. To resolve these legal disputes, then-President Reagan and French Prime Minister Jacques Chirac negotiated an agreement to share inventorship and royalties for the HIV test kits and to create a new international AIDS foundation.[61] In 1987, Reagan announced jointly with Chirac the financial details of the plan and settlement:[62]

---

55. *See* Barré-Sinoussi, *supra* note 8; Gallo, *supra* note 9; *see also* Deborah M. Barnes, *AIDS Patent Dispute Settled*, 236 SCI. 17 (1987) (describing collaboration among the scientists for their respective studies).

56. *See* Barnes, *supra* note 55.

57. *Id.*

58. *Id.*

59. *See id.*

60. *See id.*; *see also HIV/AIDS Glossary: Enzyme-Linked Immunosorbent Assay (ELISA)*, CLINICAL INFO HIV.GOV, https://clinicalinfo.hiv.gov/en/glossary/enzyme-linked-immunosorbent-assay-elisa (last visited Feb. 16, 2024) (describing the French-American breakthrough invention for HIV testing).

61. *See* Barnes, *supra* note 55; *see also* Pasteur v. United States, 814 F.2d 624 (Fed. Cir. 1987) (reversing lower court's decision that French scientists did not state claim in HIV identification and patent dispute, prompting settlement between President Reagan and President Mitterrand to HIV test kit license terms).

62. President Ronald Reagan, *Remarks Announcing the AIDS Research Patent Rights Agreement Between France and the United States*, AM. PRESIDENCY PROJECT (Mar. 31, 1987), https://www.presidency.ucsb.edu/documents/remarks-announcing-the-aids-research-patent-rights-agreement-between-france-and-the-united [hereinafter President Reagan's Remarks on AIDS Testing Patent Settlement].

> The two medical groups will share the patent, and each party will contribute 80 percent of the royalties received to establish and support an international AIDS research foundation. This foundation, which will also raise private funds, will sponsor AIDS-related research and will donate 25 percent of the funds that they receive to education and research of AIDS problems in less developed countries.

When the French-American HIV test kits became broadly available in the United States in the mid-1980s, the focus in the burgeoning HIV/AIDS research field shifted to treatments for the millions already infected, as well as public health messaging to slow the spread.[63]

b) Early Failures: AZT and HIV Vaccines

Failure was a common and frustrating feature of early public health attempts to treat or prevent HIV. In the 1990s, at least one researcher published the conclusion that the first ART treatment against HIV—AZT (described in Section II.B: Antiretroviral Technology, *supra*)—was "highly toxic to human cells" and difficult for patients to adhere to the prescribed dosing for their lifetimes.[64]

Separately, vaccine trials began in earnest the same year AZT went to market in 1987, with the National Institutes for Allergy and Infectious Diseases leading the first vaccine trial to prevent AIDS.[65] In 2004, the international alliance known as The Group of Eight, or "G8," set forth a call to establish a Global HIV Vaccine Enterprise.[66] However, despite worldwide spending of more than $500 million on HIV/AIDS vaccine research almost every year since 2000, researchers have yet to develop an effective HIV vaccine.[67]

c) Therapies After AZT

Scientists considered many different combinations of compounds with anti-retroviral activity to achieve HIV treatment goals: an ART that would (1) change HIV/AIDS from a death sentence to a manageable chronic disease; (2) perform (1) without reducing the life expectancy of the patient due to ART

63. *See A Timeline of HIV and AIDS*, *supra* note 22.

64. Chiu & Duesberg, *supra* note 21, at 107–08.

65. *See In Their Own Words*, *supra* note 16.

66. G8 Sea Island Summit 2004, *G8 Action to Endorse and Establish a Global HIV Vaccine Enterprise*, *in* UNIV. TORONTO G8 INFO. CTR., http://www.g8.utoronto.ca/summit/2004seaisland/hiv.html (last visited Sept. 11, 2022).

67. *See* Jeffrey E. Harris, *The Repeated Setbacks of HIV Vaccine Development Laid the Groundwork for SARS-CoV-2 Vaccines* (Nat'l Bureau Econ. Rsch, Working Paper No. 28587, 2021).

toxicity; and (3) improve adherence to ART regimens with once-a-day dosing to avoid viral resistance to the drugs.[68] Truvada succeeded because it largely achieved all of these goals where its ART competitors had not (discussed *infra*, Section III.C).[69]

3. The Collaboration and Competition Ecosystem for Anti-HIV Treatments

As the AIDS crisis unfolded in the 1980s and early 1990s in the United States, federal health and innovation agencies, AIDS community activists, universities, small and large pharmaceutical companies, as well as large philanthropies worked to create therapeutic options.

a) The Role of the U.S. Executive Branch and Federal Agencies

U.S. federal health authorities gradually became leaders in responding to the AIDS crisis through special projects and newly created divisions (several of which are highlighted in Table 3 below) to specifically to combat the growing pandemic:

68. *See* THE EVOLUTION OF HIV/AIDS THERAPIES, (Chemical Heritage Foundation & Science History Institute 2012), https://vimeo.com/59281508 (containing clip of Norbert Bischofberger, EVP of R&D at Gilead Sciences, sharing motivations and goals for Atripla and Truvada for HIV treatment at the 20-minute mark).

69. *Id.*

Table 3: Sample of U.S. federal agency actions in response to AIDS crisis.

Agency	Example Action(s) in Response to AIDS Crisis
NIH	Began approving AIDS research grants in 1983.[70]
NIAID	Maintained from 1984 onward, at Dr. Anthony Fauci's direction, a special AIDS division to engage in outreach and long-term studies of the HIV/AIDS population.[71]
CDC	Closely monitored the spread of the virus, developed treatment resources, and began to engage in co-coordination of international clinical trial projects.[72]
FDA	Approved AZT in 1987 on accelerated basis due in part to AIDS community cries for help.[73]
Presidents' Executive Actions	Reagan: used executive orders in 1987–88 to motivate Congress to appropriate the first federally legislated AIDS research funding programs,[74] including the NIH's Institute for AIDS Research.[75]
	George W. Bush: secured in 2004 Congressional approval to create PEPFAR, the President's Emergency Program For AIDS Relief, to combat the pandemic by funding the equitable distribution of HIV treatments to developing nations globally.[76]
USPTO	Created a centralized AIDS Patent Project in the 1990s to facilitate global knowledge-sharing related to AIDS treatments and research together with the European and Japan Patent Offices.[77]
	Launched in the 2010s the Patents for Humanity acceleration & awards project, which has included HIV/AIDS technologies, among others.[78]

70. *See* Kramer, *supra* note 49.

71. *See* NIH.gov, *In Their Own Words… NIH Researchers Recall the Early Years of AIDS: Mobilizing*, https://history.nih.gov/display/history/Mobilizing (last visited Nov. 13, 2022).

72. *See A Timeline of HIV and AIDS*, *supra* note 48.

73. *See* National Institutes of Health, *In Their Own Words… NIH Researchers Recall the Early Years of AIDS: Anthony S. Fauci, M.D. – Transcript of Interview 03* at 19, https://history.nih.gov/display/history/Dr.+Anthony+S.+Fauci+Transcript?preview=/8881339/8881336/Fauci93.pdf (last accessed Apr. 8, 2024).

74. *See* President Reagan's Remarks at 1987 AIDS Research Awards Dinner, *supra* note 54.

75. *See* 42 U.S.C. § 300cc.

76. *See A Timeline of HIV and AIDS*, *supra* note 48.

77. *See* USPTO, *1996 Annual Review – Our Progress*, USPTO.GOV (1996), https://www.uspto.gov/about-us/performance-and-planning/annual-reports/1996-annual-review-our-progress (last visited Nov. 19, 2022).

78. *See* USPTO, *Patents for Humanity*, USPTO.GOV (2022), https://www.uspto.gov/ip-policy/patent-policy/patents-humanity (last visited Nov. 19, 2022).

b) The Role of International Government and Philanthropic Institutions

Global governmental and philanthropic organizations have also been a core part of the AIDS treatment innovation ecosystem.[79]

In the late 1990s, it became clear that ARTs were not reaching developing countries heavily hit by the HIV/AIDS pandemic, especially those in sub-Saharan Africa.[80] UNAIDS, the United Nations' strategic response team to the pandemic, launched in 1996 to address this concern.[81] The 2000 International AIDS Conference, held in South Africa, highlighted tensions about how to resolve this issue: the international healthcare philanthropic organization Medecins Sans Frontieres was quietly working with developing countries' leaders to find ways to send them HIV/AIDS medicine at heavy, under-the-table discounts to respond to the rising humanitarian crisis.[82] HIV/AIDS leaders from the United States and Europe called for a transparent approach—for well-resourced nations to openly fund and facilitate the delivery of critical anti-HIV treatments in developing nations. Within four years, two philanthropic agencies were created for this purpose: the Global Fund (largely based on funds from the United Kingdom and other parts of Europe) formed in 2001 and PEPFAR formed in 2004.[83]

International organizations also played policymaking and philanthropic roles in the AIDS treatment space. Responding to that contentious 2000 International AIDS Conference, the World Trade Organization (WTO)'s 2001 Fourth Ministerial Conference addressed the rights of nations to access critical medicines under the WTO's 1994 Agreement on Trade-Related Aspects of Intellectual Property Rights (TRIPS) through the 2001 Doha Declaration on TRIPS and Public Health.[84] The Doha Declaration provided that every WTO member state "has the right to grant compulsory licences and the freedom to determine the grounds upon which such licences are granted," where any granted "compulsory licence" is a demand by a member state for delivery of the public health technology (such as HIV/AIDS treatments) without

79. *See* THE EVOLUTION OF HIV/AIDS THERAPIES, *supra* note 68 (describing at the thirty minute mark rationale for creation of the Global Fund and PEPFAR).

80. *Id.*

81. *See* UNAIDS, *Who We Are: Saving Lives, Leaving No One Behind*, UNAIDS.ORG, https://www.unaids.org/en/whoweare/about (last visited Nov. 21, 2022).

82. *See* THE EVOLUTION OF HIV/AIDS THERAPIES, *supra* note 68 (describing at the thirty minute mark rationale for creation of the Global Fund and PEPFAR).

83. *Id.*

84. *See* WTO, *Declaration on the TRIPS Agreement and Public Health*, DOHA DECLARATIONS at 24-25, https://www.wto.org/english/res_e/booksp_e/ddec_e.pdf (last visited Nov. 21, 2022).

negotiation with the intellectual property owner.[85] The Doha Declaration brought the world's governments to the collaboration table with HIV/AIDS research and treatment innovators and businesses.[86]

Lastly, non-governmental philanthropies played a key role in enabling HIV/AIDS treatment development, including Truvada (described in Phases II and III, *infra*, Sections III.B and III.C). In the mid- to late-2000s, the Bill and Melinda Gates Foundation funded at least two different global clinical trials for Truvada as a prevention measure against HIV. It gave more than $13 million to the nonprofit, Family Health International, which oversaw the first trial (in sub-Saharan Africa) and provided more than $15.7 million to the J. Gladstone Institutes which oversaw the second clinical trial, testing Truvada in patients from developed and developing countries.[87]

c) The Role of AIDS Activists

Dr. Anthony Fauci (hereinafter "Fauci") and other staff from these federal health agencies credit AIDS community activists with motivating government action on AIDS in the 1980s and 1990s, when widespread stigma and misunderstanding otherwise slowed government investment.[88] Activists like Larry Kramer, the most famous co-founder of AIDS Coalition to Unleash Power ("*ACT UP*"), repeatedly took to the press to criticize the U.S.

85. *Id.* at 25; *see also* WTO, *Compulsory licensing of pharmaceuticals and TRIPS*, TRIPS AND HEALTH: FREQUENTLY ASKED QUESTIONS, https://www.wto.org/english/tratop_e/trips_e/public_health_faq_e.htm (last visited Apr. 11, 2024) (providing WTO's definition of compulsory licensing).

86. *See Doha+10: More People Accessing HIV Treatment*, UNAIDS.ORG (Nov. 22, 2011), https://www.unaids.org/en/resources/presscentre/featurestories/2011/november/20111123doha#:~:text=The%20Declaration%20clarified%20the%20scope,drugs%20for%20AIDS%2Drelated%20illnesses.

87. *See* Peterson et al., *Tenofovir Disoproxil Fumarate for Prevention of HIV Infection in Women: A Phase 2, Double-Blind, Randomized, Placebo-Controlled Trial*, 2 PLOS CLINICAL TRIALS 27 (2007) (failing to find statistically significant protection with Tenofovir-only as PrEP regimen across cohorts of African women with FHI and Gates Foundation financial support); *see also* Robert M. Grant et al., *Preexposure Chemoprophylaxis for HIV Prevention in Men Who Have Sex with Men*, 363 NEW ENG. J. MED. (27) 2587 (2010) (sharing the NIAID-led, Gates Foundation-supported, and Gilead-assisted iPrEx clinical Truvada for PrEP study results from men in Peru, Ecuador, Brazil, San Francisco, Boston, Thailand, and South Africa); *Committed Grants*, BILL & MELINDA GATES FOUND., https://www.gatesfoundation.org/about/committed-grants (last visited Mar. 11, 2023) (providing on downloadable spreadsheet the grant information for these two trials under grant opportunity codes OPP19789, OPP19789_01, and OPP48162).

88. *See* National Institutes of Health, *In Their Own Words… NIH Researchers Recall the Early Years of AIDS: Anthony S. Fauci, M.D. – Transcript of Interview 03* at 18–19, https://history.nih.gov/display/history/Dr.+Anthony+S.+Fauci+Transcript?preview=/8881339/8881336/Fauci93.pdf (last accessed Apr. 8, 2024).

government for its inaction.[89] Kramer and other ACT UP activists personally targeted leaders of federal agencies (such as by calling Fauci a "murderer") in op-eds,[90] occupied the FDA campus,[91] protested at the National Institutes of Health (NIH) campus,[92] and in performed other political actions.[93] These efforts earned AIDS activists seats at the table with public and private institutions leading efforts to combat the virus. Fauci recalled that "a major part of [his] work in [the HIV/AIDS] epidemic [had] been opening the doors and breaking down the barriers between the activist groups and the scientific community . . . allow[ing] [them] to see the impact of the disease at the grassroots level . . . changing the way that [they] do business[.]"[94] In response to the AIDS activism, in 1992, the FDA created a new process for accelerated drug approval that lasts to this day.[95] This unlikely coalition of activists and institutions would work together in the 1990s and 2000s to develop highly active ARTs.[96]

d) The Role of Universities

Universities performed much of the fundamental chemistry research necessary to develop AIDS treatments such as Truvada and lamivudine, a separate and competing NRTI therapy (discussed in "Emory Scientists Synthesize Emtricitabine and License it to Burroughs-Wellcome," *infra*, Section III.B.2.a). The AIDS crisis began just as the effects of the Bayh-Dole Act of 1980 were being felt across American universities.[97] The Act enabled the modern transfer of technologies from university settings to startup and larger commercial enterprises through new incentives for university patent ownership.[98]

89. *See* Kramer, *supra* note 49.

90. *See* Larry Kramer, *An Open Letter to Dr. Anthony Fauci*, SAN FRANCISCO EXAMINER (June 26, 1988), https://aep.lib.rochester.edu/node/49111.

91. *See* Douglas Crimp, *Before Occupy: How AIDS Activists Seized Control of the FDA in 1988*, ATLANTIC (Dec. 6, 2011), https://www.theatlantic.com/health/archive/2011/12/before-occupy-how-aids-activists-seized-control-of-the-fda-in-1988/249302/.

92. *See ACT UP ACCOMPLISHMENTS–1987–2012*, ACT UP NY, https://actupny.com/actions (last accessed Apr. 8, 2024).

93. *Id.*

94. *See In Their Own Words*, *supra* note 88.

95. *See Understanding the History and Use of the Accelerated Approval Pathway*, AVALERE (Jan. 4, 2022), https://avalere.com/insights/understanding-the-history-and-use-of-the-accelerated-approval-pathway.

96. *Id.*

97. *See generally Bayh-Dole Act*, DREXEL UNIV. OFF. RSCH. & INNOVATION, https://drexel.edu/research/innovation/technology-commercialization/bayh-dole-act/ (last visited Nov. 21, 2022).

98. *See id.*

e) The Role of Pharmaceutical Companies

Pharmaceutical companies of all sizes—from university-initiated startups to big pharma—began engaging in HIV/AIDS treatment development in the 1980s, beginning with pharmaceutical company Burroughs Wellcome's AZT in 1987.[99] The company that would become leading antiviral manufacturer in the HIV/AIDS space as the maker of Truvada, Gilead Sciences, Inc., was only a brand-new small startup at the time.

The coalition to end HIV through increasingly effective treatments therefore has included a very wide swath of public and private actors, organizations, and institutions.

B. PHASE II—THE AIDS INNOVATION ECOSYSTEM YIELDS TWO PROMISING COMPOUNDS

Of the many ARTs targeting HIV, two are critical to the story of Truvada:[100] (1) tenofovir (trade name Viread); and (2) emtricitabine (originally trade-named Coviracil, now under the trade name Emtriva).[101] The invention stories for these two compounds follow similar paths: (1) chemists at universities developed what would become life-saving compounds; (2) the chemists quickly published and patented their compounds for their ART activity; (3) the chemists licensed their patented compounds to small and large pharmaceutical companies for clinical development and regulatory approval; and (4) large pharmaceutical companies abandoned drug development licenses in the uncertain HIV market which allowed smaller pharmaceutical companies to step in and develop breakthrough ARTs.

1. Viread: Tenofovir Disoproxil Fumarate (TDF)

This Section will cover the invention of the first component of Truvada: tenofovir. In the mid-1980s, Czech chemist Dr. Antonín Holý (hereinafter, "Holý") at the Czechoslovak Academy of Sciences in Prague achieved his dream of creating an effective antiviral compound when he developed with Belgian physician and biologist Dr. Eric De Clercq (hereinafter, "De Clercq") the antiviral compound tenofovir.[102] Although Holý initially intended

99. *See* Alice Park, *The Story Behind the First AIDS Drug*, TIME, https://time.com/4705809/first-aids-drug-azt (last visited Nov. 21, 2022).

100. U.S. Food & Drug Administration, *Drug Approval Package: Truvada® (Emtricitabine and Tenofovir Disoproxil Fumarate) Tablets*, https://www.accessdata.fda.gov/drugsatfda_docs/nda/2004/021752s000_TruvadaTOC.cfm (last visited Sept. 11, 2022).

101. '397 Patent, *supra* note 2 (describing combination in the Abstract).

102. *See* Michal Hocek, *Prof. RNDr. Antonín Holý, DrSc., dr. h. c. mult. – 75th Birthday – Foreword*, COLLECTION CZECHOSLOVAK CHEM. COMMC'NS (2011), http://cccc.uochb.cas.cz/virtual_issues/holy/foreword/ (last visited Nov. 23, 2022).

tenofovir as a herpes simplex virus therapeutic, Holý and De Clercq's invention of tenofovir successfully treated HIV infections.[103] A small biopharmaceutical startup called Gilead Sciences, Inc. ("Gilead") licensed tenofovir from Holý and De Clercq when they noticed the initial tenofovir license to a large pharmaceutical company lapsed (as discussed in Section III.B.1.b, *infra*). Gilead developed tenofovir into the clinically useful NtRTI for HIV treatment called tenofovir disoproxil fumarate.

a) Holý and De Clercq Synthesize TDF and License to Bristol-Myers

Holý was initially interested in building chemical analogues of the DNA and RNA building blocks, known as nucleotides (discussed in Section II.B, Antiretroviral Technology, *supra*), to inhibit transcription of herpes simplex virus (HSV) DNA into RNA in host human cells.[104] He found a research partner in Belgium, De Clercq, who was interested in clinically studying the antiviral effects of such compounds to treat infections and cancer.[105] In 1978, they succeeded by synthesizing their first antiviral compound, one active against HSV: dihydroxypropyladenine (DHPA).[106]

In addition to HSV, the research team hypothesized their nucleoside analog technology could have antiviral activity against a wide range of viruses in humans and experimented with additional chemical modifications to DHPA. Holý and De Clercq produced three additional highly effective antiviral nucleoside analogs based by modifying DHPA: (1) cidofovir, used today to treat eye infections by cytomegalovirus in AIDS patients; (2) adefovir, used today to treat hepatitis B infection (HBV); and, perhaps most crucially, (3) tenofovir (9-(2-Phosphonyl-methoxypropyly)adenine (PMPA)[107]), used today to treat HIV and/or HBV infections.[108] In 1985 and 1986, Holý submitted patent applications on these DHPA-derived nucleoside analogs,

103. *See id.*

104. *See id.*

105. *See id.*

106. *See id.*; *see also* Erik De Clercq et al., *(S)-9-(2,3-Dihydroxypropyl)adenine: An Aliphatic Nucleoside Analog with Broad-spectrum Antiviral Activity*, 200 SCI. 563, 563–65 (1978) (presenting De Clercq and Holý's first DHPA work).

107. *See, e.g.*, Steven G. Deeks et al., *Safety, Pharmacokinetics, and Antiretroviral Activity of Intravenous 9-[2-(R)-(Phosphonomethoxy)propyl]adenine, a Novel Anti-Human Immunodeficiency Virus (HIV) Therapy, in HIV-Infected Adults*, 42(9) ANTIMICROBIAL AGENTS & CHEMOTHERAPY 2380, 2380–84 (1998) (sharing Gilead's first human trials of PMPA later rebranded tenofovir, one of the two core drugs in Truvada).

108. *Id.*

which drew the attention of the global pharmaceutical industry.[109] The patents claimed compounds with broad activity against many viruses—including retroviruses—and were granted in the United States, which enabled a series of licensing deals for the technologies.[110]

Bristol-Myers was the first major pharmaceutical company to license the DHPA-derivatives from Holý and De Clercq and launched preclinical trials in 1987.[111] A clause in the license agreement contained an out for the researchers invested in the compounds' development into powerful treatments: "In the event development is discontinued, all rights must be returned to [the Czech Academy of Sciences] together with all materials, obtained results, and documentation."[112] When Squibb merged with Bristol-Myers to form Bristol-Myers Squibb in 1989, the new company cut development of the DHPA derivatives and other HIV antivirals.[113] But their director of antiviral chemistry, John Martin, disagreed with the decision. He believed in the compounds' value as antiviral treatments, so when termination clause was triggered in 1990, Martin sought to continue the drugs' development elsewhere. Martin moved his team of scientists to the then-small biotechnology development company, Gilead Sciences, Inc.[114]

b) Beginnings of Gilead Sciences, Inc. and Its License for TDF Development

Doctor-turned-venture-capitalist Dr. Michael Riordan (hereinafter, "Riordan") founded Gilead in Foster City, California in 1987.[115] Riordan's interest in developing antiviral treatments began with a personal experience with dengue fever—a mosquito-borne virus—that knocked him "flat on [his] back for three weeks" while on a Luce scholarship to East Asia working in a children's malnutrition clinic before beginning medical school.[116] Prior to founding Gilead, Riordan earned degrees in biology, chemical engineering, medicine, and business and sought to use his training to build a world-leading

109. *See Antonín Holý 85 – Story of tenofovir*, INST. ORGANIC CHEMISTRY & BIOCHEMISTRY CZECH ACAD. SCIS. (Sept. 1, 2021), https://www.uochb.cz/en/news/342/antonin-holy-85-story-of-tenofovir.

110. *See*, *e.g.*, U.S. Patent No. 4,808,716 (belonging to Czech Academy of Sciences and later Gilead Sciences, Inc. by assignment for synthesis of tenofovir compounds) (expired 2006) [hereinafter '716 Patent].

111. *See Antonín Holý 85 – Story of tenofovir*, *supra* note 109.

112. *Id.*

113. *Id.*

114. *Id.*

115. Kathryn S. Brown, *Balms from Gilead* at 31, 33, WASH. UNIVERSITY MAG. (1997), https://riordangileadsciencesarticle.wordpress.com (last visited Nov. 23, 2022).

116. *See id.*

antiviral therapy company.[117] He did so by starting Gilead in the Bay Area with $2 million in help from his Menlo Ventures venture capital firm partners[118]—one of whom, H. DuBose Montgomery, also was very frustrated by the lack of treatments available for the common cold while he had been experiencing a particularly bad one. [119] Gilead initially focused on "antisense" oligonucleotide-based therapeutics, but upon recruiting Bristol-Myers' Martin as Chief Scientist in 1990, the Gilead team refocused on candidates Martin viewed as most likely to succeed: the small molecule DHPA derivatives Martin started to develop at Bristol-Myers.[120] Gilead entered into license agreements with the Czech Academy of Sciences and began advancing all three DHPA derivatives as potential antiviral treatments in 1991–92.[121]

Gilead quickly embarked on preclinical trials of subcutaneous tenofovir to demonstrate the tenofovir compound's effectiveness against HIV.[122] Gilead partnered with nearby universities and hospitals—the University of Washington, the University of California, San Francisco, and San Francisco General Hospital—to study HIV in animals and in HIV/AIDS patients.[123] As intravenous injection of tenofovir into humans proceeded to human clinical trials,[124] Gilead worked to address challenges in formulating tenofovir in a more convenient oral form.

The two primary challenges Gilead faced in turning tenofovir into a practical oral HIV treatment were: (1) poor absorption of tenofovir by the digestive system; and, once absorbed, (2) poor transfer across cell membranes

117. *See id.*

118. *See id.*

119. *See The Golden Age of Antiviral Drugs*, FORBES (Oct. 27, 2003), https://www.forbes.com/global/2003/1027/090.html?sh=caaa6d7753b3.

120. *See* FORBES, *supra* note 119.

121. *Id.*; *see also* John C. Martin, *License Agreement – Gilead Sciences Inc., the Institute of Organic Chemistry and Biochemistry of the Academy of Sciences of the Czech Republic, and Rega Institute for Medical Research*, GILEAD SCIS., INC. (Dec. 27, 2000), https://corporate.findlaw.com/contracts/operations/license-agreement-gilead-sciences-inc-the-institute-of.html.

122. *See, e.g.*, Che-Chung Tsai et al., *Prevention of SIV Infection in Macaques by (R)-9-(2-phosphonylmethoxypropyl)adenine*, 270 SCI. 1197 (1995) (describing the first simian trial co-coordinated by Gilead to demonstrate effectiveness of tenofovir against HIV infection or replication).

123. *See, e.g.*, Patricia Barditch-Crovo et al., *Phase I/II Trial of the Pharmacokinetics, Safety, and Antiretroviral Activity of Tenofovir Disoproxil Fumarate in Human Immunodeficiency Virus-Infected Adults*, 45 ANTIMICROBIAL AGENTS & CHEMOTHERAPY 1 (2001) (last visited Nov. 23, 2022) (including co-authors from San Francisco General Hospital, UCSF, and the University of Washington).

124. *See* Deeks et al., *supra* note 107.

into cells, where tenofovir is able to block viral replication.[125] Under Riordan and Martin, Gilead led development on chemical modifications to the tenofovir molecule to make a prodrug that improved cellular uptake for the first half of the 1990s.[126] Years of attempts by Gilead at oral prodrugs for tenofovir/PMPA yielded, in 1997, one lead compound out of eight prodrugs that had advanced to preclinical studies in dogs.[127] Initially called bis-POC PMPA, Gilead renamed the most effective prodrug to tenofovir disoproxil fumarate (TDF) during the subsequent human trials.[128] Immediately, Gilead patented many of the promising tenofovir prodrug compositions, including TDF, as well as their synthesis.[129]

Gilead achieved a commercial breakthrough when the FDA approved TDF for adults (trade name Viread) in 2001, only six months after Gilead filed a New Drug Application under the FDA's accelerated approval pathway.[130] By this time, Riordan had retired from Gilead and placed the direction of the company in Martin's hands.[131] Riordan saw the company grow from his initial idea to a biopharmaceutical company with a workforce of over 250 employees and a valuation of $850 million by his 1997 retirement. Martin led Gilead until his retirement in 2019, and he grew the company into a large biopharmaceutical manufacturer with more than 10,000 employees and a valuation in the tens of billions of dollars.[132]

Viread faced challenges upon FDA marketing approval. First, the FDA had concerns about effects on bone density and renal toxicity when it approved Viread in 2001 on a fast-track basis, conditioning the approval on continued clinical studies by Gilead to evaluate these side effects.[133] Second,

125. *See* Chanie Wassner et al., *A Review and Clinical Understanding of Tenofovir: Tenofovir Disoproxil Fumarate versus Tenofovir Alafenamide*, 19 J. INT'L ASS'N PROVIDERS AIDS CARE 1 (2020).

126. *See* Jeng-Pyng Shaw et al., *Metabolism and Pharmacokinetics of Novel Oral Prodrugs of 9-[(R)-2-(phosphonomethoxy)propyl]adenine (PMPA) in Dogs*, 14 PHARMACEUTICAL RSCH. 1824 (1997).

127. *See id.*

128. *See* Barditch-Crovo et al., *supra* note 123.

129. *See, e.g.*, U.S. Patent No. 5,935,946 (granted to Gilead Sciences, Inc.; expired 2017).

130. *See* U.S. Food & Drug Admin., *Drug Approval Package: VIREAD® (Tenofovir Disoproxil Fumarate) Tablets* (Oct. 26, 2001), https://www.accessdata.fda.gov/drugsatfda_docs/nda/2001/21-356_Viread.cfm#:~:text=Approval%20Date%3A%2010%2F26%2F01 (last visited Apr. 8, 2024).

131. *See* FORBES, *supra* note 119.

132. *See Gilead Sciences Inc: Overview*, GLOBALDATA.COM (2022), https://www.globaldata.com/company-profile/gilead-sciences-inc/ (last visited Nov 23, 2022); *see also* Press Release, Gilead Scis., Inc., Gilead Sciences Comments on the Passing of John C. Martin, PhD (Mar. 31, 2021) (describing John Martin's legacy at Gilead).

133. *See Drug Approval Package: VIREAD®*, *supra* note 130.

the Doha Declaration issued that year empowered countries to issue compulsory licenses on drugs critical for public health like Viread; the Declaration therefore incentivized Gilead to launch a face-saving, proactive approach of *voluntary* licensing of TDF (and its future HIV ARTs) to governments in need internationally.[134] While several countries later threatened or demanded that Viread be licensed to them via compulsory licenses, this was very rare considering the global reach Viread had in treating HIV.[135] As borne out by Martin's record of rapid growth at Gilead as its leader, the company was able to manage both of these challenges with TDF/Viread.[136]

2. Coviracil: Emtricitabine, Marketed Now as Emtriva

While Holý and De Clercq initiated negotiations with Martin and Riordan for Gilead to license tenofovir in 1990, Emory University chemist Dr. Dennis Liotta ("Liotta"), a "serial entrepreneur,"[137] synthesized emtricitabine—the compound that would become the second component of Truvada. With a collaborative team including Liotta's chemistry group at Emory, an Emory virologist (Dr. Raymond Schinazi, hereinafter "Schinazi"), and scientists at pharmaceutical companies of both large (Dr. George Painter, hereinafter "Painter," and Dr. David Barry, hereinafter "Barry," at Burroughs-Wellcome) and small (Dr. David Barry's startup, Triangle Pharmaceuticals) sizes, emtricitabine entered clinical development into an ART against HIV.[138]

a) Emory Scientists Synthesize Emtricitabine and License to Burroughs-Wellcome

Liotta's motivation to pursue nucleoside analogs as antivirals began in 1989, when his collaborator Schinazi shared about an interesting conference poster he saw disclosing the synthesis of a new cytidine analog, later called 3TC, with "anti-HIV activity with no apparent cytotoxicity [toxicity to cells]"

134. *See* UNAIDS.ORG, *supra* note 86; *see also* THE EVOLUTION OF HIV/AIDS THERAPIES, *supra* note 68 (at approximately the 38-minute mark, containing Gilead executive vice president Gregg Alton's explanation of Gilead's extensive voluntary licensing system).

135. *See, e.g.*, IHS Global Insight, *Indonesia Issues Compulsory Licenses Against Seven HIV, Hepatitis Drugs*, S&P GLOBAL MKT. ANALYSIS (Oct. 12, 2012), https://www.spglobal.com/marketintelligence/en/mi/country-industry-forecasting.html?ID=1065972339.

136. *See* GLOBALDATA.COM, *supra* note 132.

137. *See* Dr. Dennis Liotta, *About Dr. Dennis Liotta*, LIOTTA RSCH. GRP., https://liottaresearch.org/ (last visited Nov. 24, 2022) (showing Liotta's trademarked lab group logo and describing how Liotta "co-founded more than ten biotech companies" and sits on advisory boards for "more than a dozen biotech companies and venture capital firms.").

138. *See generally* Dennis C. Liotta & George R. Painter, *Discovery and Development of the Anti-Human Immunodeficiency Virus Drug, Emtricitabine (Emtriva®, FTC)*, 49 ACCOUNTS CHEM. RSCH. 2091 (2016), (providing Liotta and Painter's first-hand account of their research process and relevant anecdotes from their development of emtricitabine).

in cell-culture studies.[139] Liotta and Schinazi were aware of the toxicity problems of the early HIV nucleoside analog ARTs and agreed to work together at Emory to develop low-toxicity NRTIs.[140]

Liotta first attempted to replicate the synthesis of the cytidine analog that Schinazi told him about. The published synthesis was "inefficient," so he applied organic chemistry skills to develop a more efficient synthesis.[141] Cytosine is a nucleobase and a portion of the nucleoside cytidine; cytosine alone lacks the ribose base that allows cytidine to be included in an RNA chain.[142] Liotta's synthesis resulted in a pair of analogs to cytidine that are mirror images of each other, referred to in organic chemistry as enantiomers.[143]

Schinazi confirmed the anti-HIV activity and low-toxicity of Liotta's racemic 3TC mixture and invited his long-standing collaborator Painter, a researcher at Burroughs-Welcome interested in NRTI development, to verify the same.[144] This first low-toxicity cytosine analog, named by Liotta "3TC," would quickly be developed as a component of other important HIV drugs, such as lamivudine.[145] As interest in cytosine analogs as anti-HIV therapeutics spread, Liotta and Schinazi competed with researchers at Yale, the University of Georgia, and pharmaceutical companies like GlaxoSmithKline (GSK) to isolate the (-) enantiomer from the more toxic (+) enantiomer efficiently. Simultaneously, Liotta had been working on syntheses for fluorinated versions of 3TC and found the resultant racemic mixture ("FTC") *more* potent against HIV and HBV but similarly or *less* toxic than the original 3TC. Importantly, neither FTC enantiomer was more toxic than the other, though one enantiomer was "100 times more potent" than the other.[146] The "(-)"-coded enantiomer of "FTC" became known as emtricitabine.[147] Liotta and his

139. *Id.* at 2091–92; *see also* Théo Bourgeron & Susi Geiger, *(De-)assetizing Pharmaceutical Patents: Patent Contestations Behind a Blockbuster Drug*, 51 ECON. & SOC'Y 23, 30–31 (2021) ("In 1989 . . . Schinazi learned of an interesting new compound, called 3TC, being developed by Canadian biotech firm, BioChem Pharmaceuticals.").

140. *See* Liotta & Painter, *supra* note 138, at 2092 ("Given the side effect profiles of the approved NRTIs and the rapid development of resistance to them . . . it was clear that additional drugs were needed.").

141. *Id.*

142. *See* Lee W. Janson & Marc E. Tischler, *Nucleosides, Nucleotides, DNA, and RNA*, *in* THE BIG PICTURE: MEDICAL BIOCHEMISTRY (2018).

143. *See* Liotta & Painter, *supra* note 138, at 2092–94. In organic chemistry, enantiomers are a set of two molecules that are mirror images of each other in 3D space. As a result, isolating the two from each other may show each has slightly different chemical activity. *See id.* at 2093.

144. *See id.* at 2093.

145. *Id.*

146. *Id.* at 2094.

147. *Id.* at 2092.

assignee Emory filed a patent application for emtricitabine in 1991 and the PTO granted it in 1995.[148] The Canadian scientist's company whose work inspired Liotta and Schinazi challenged in district court Liotta's equitable conduct when prosecuting the patent before the U.S. Patent and Trademark Office (USPTO) given the inspiration. After years of litigation, Liotta and colleagues retained the rights to their FTC patent.[149]

Before that inventorship and novelty dispute, Burroughs-Welcome licensed emtricitabine from Emory to conduct the requisite preclinical studies for an Investigational New Drug Application (IND) with the FDA.[150] Ahead of filing their IND that year, Glaxo offered to purchase Burroughs-Wellcome and the two ultimately merged into one entity, Glaxo-Wellcome.[151] Glaxo-Wellcome decided to abandon the emtricitabine IND and prioritize 3TC development because the 3TC candidate was ahead of FTC in the FDA approval process.[152]

b) Barry Leaves Big Pharma to Develop Emtricitabine with His Own Company, Triangle

Dr. David Barry (hereinafter, "Barry") was a scientific leader of Burroughs-Wellcome's antiviral development team when it found and commercialized AZT in 1987.[153] In 1995, Barry was the head of HIV treatment discovery and development at Burroughs-Wellcome.[154] Barry eventually left Glaxo-Wellcome in 1996 to form his own company which would restart development of emtricitabine in collaboration with Liotta.[155] Like Holý's initial license to develop tenofovir with Bristol-Myers (discussed in Section III.B.1: Viread, *supra*), Liotta's initial license to develop emtricitabine to Burroughs-Wellcome (and later Glaxo-Wellcome) terminated if the company shelved the project.[156] Barry used this termination clause to his advantage. In 1996, he formed Triangle Pharmaceuticals, Inc. in Durham, North Carolina, and Triangle

148. *See generally* U.S. Patent No. 5,210,085 (filed (expired 2010) (claiming initial FTC compound and initial uses) [hereinafter '085 Patent].

149. *See generally* Emory Univ. v. Glaxo Wellcome Inc., No. 1:96-CV-1868-GET, 1997 WL 817342 (N.D. Ga. July 14, 1997) (denying Glaxo's motion for summary judgment to invalidate Liotta's and Emory's 3TC patent); *see also Emory Case Study: Dispute Details – Awards/Legal Rulings*, IPADVOCATE, http://ipadvocatefoundation.org/studies/emory/8.cfm (last visited Mar. 12, 2023).

150. *See* Liotta & Painter, *supra* note 138, at 2095.

151. *Id.*

152. *Id.*

153. *See id.*

154. *See id.*

155. *Id.*

156. *See id.*

licensed Emory's emtricitabine IP to develop the drug into a commercial product.[157]

Triangle eagerly picked up emtricitabine development where Burroughs-Wellcome left off. Triangle leveraged the earlier preclinical data supporting emtricitabine to submit a renewed IND in 1997 and, given emtricitabine's potential for once-daily dosing and promising early trials, the FDA granted it "Fast Track" status in 1998.[158] In the same period, Barry successfully took Triangle public.[159] Over the next four years, clinical trials would show emtricitabine reduced HIV viral load more than the already-marketed 3TC products; Triangle submitted a New Drug Application (NDA) to the FDA in 2002 based on this data, under the trade name Coviracil.[160] During that time, Emory sued Glaxo-Wellcome and Biochem Pharma for infringement of Emory's 3TC patents and, separately, sued the same defendants to claim Emory's patent inventorship and ownership of emtricitabine; the eventual settlements gave Emory both cash and a license to the patent rights to emtricitabine, while Glaxo-Wellcome's successor GlaxoSmithKline received a license to 3TC.[161] With this settlement in 2002, regulatory approval and commercialization of emtricitabine became unencumbered by patent litigation.

Unexpectedly, Barry died while travelling for business in January 2002, only months before Triangle submitted the full emtricitabine NDA to the FDA.[162] News of his death rocked the small company, the Research Triangle (the Raleigh-Durham-Cary tri-city region in North Carolina), the AIDS innovation community he helped lead, and the pharmaceutical industry. Though another Triangle officer took on his role, a power vacuum formed at Triangle without its founder-leader and its high-potential anti-HIV & anti-HBV emtricitabine made it an attractive candidate for acquisition.[163]

C. PHASE III—TRUVADA AS THE LEADING METHOD OF HIV TREATMENT AND PREVENTION

Gilead Sciences, Inc. moved aggressively after FDA approval of Viread to create what would become one of the best-selling HIV drugs, Truvada.

157. *Id.*

158. *Id.*

159. *See* Yale Class of 1965, *David Walter Barry*, YALE CLASS 1965: LUX ET VERITAS, https://yale1965.org/david-walter-barry/ (last visited Nov. 24, 2022).

160. *See* Liotta & Painter, *supra* note 138, at 2096.

161. *Id.*

162. *See* Yale Class of 1965, *supra* note 159.

163. *See* Rick Smith, *The sad saga of David Barry, Triangle Pharmaceuticals nears a close*, WRAL TECHWIRE (June 25, 2010), https://wraltechwire.com/2010/06/25/the-sad-saga-of-david-barry-triangle-pharmaceuticals-nears-a-close/.

Between 2002 and 2005, Gilead acquired the intellectual property rights to emtricitabine by acquiring Triangle and purchasing Emory's patent rights in exchange for a hefty sum. By 2004, Gilead had secured FDA approval of both Emtriva (formerly Coviracil) and a combination ART, a co-formulation of emtricitabine and TDF: Truvada. Truvada quickly dominated the HIV treatment market. Public health administrations adapted their existing Truvada clinical trials to methods of HIV *prevention*. The CDC eventually patented a new method of treatment with Truvada for Pre-Exposure Prophylaxis (PrEP). An unprecedented patent litigation over the rights to PrEP reasonable royalties between the U.S. government and Gilead ensued in 2019; meanwhile, millions of Americans received Truvada to prevent or treat HIV infection.[164]

1. *Method One: Combining TDF with Emtricitabine for HIV Treatment as Truvada*

Truvada, more potent and safer than previous treatments, came to dominate the HIV ART market due to aggressive strategies by Gilead. Gilead committed fully to the second active ingredient of Truvada, emtricitabine, by acquiring (as opposed to licensing) relevant intellectual property and existing clinical operations. Gilead then used its regulatory expertise and approved one-component drugs, Viread and Emtriva, to receive accelerated approval for Truvada as bioequivalent to Viread and Emtriva. Gilead turned into the behemoth pharma company it is known for today largely thanks to this success.

a) Gilead Purchases Triangle for Emtricitabine

In 2002, Gilead was riding the newfound commercial success of tenofovir (Viread).[165] But, Gilead's leaders observed doctors would commonly prescribe many different ARTs at once to avoid the kind of viral resistance and HIV rebound first encountered by HIV/AIDS patients on AZT alone in the late

164. *See, e.g.*, United States v. Gilead Scis., Inc., 515 F. Supp. 3d 241, 244 (D. Del. 2021) (denying Government's motion to strike affirmative defenses and dismiss Gilead's counterclaims of non-infringement & invalidity in Government's patent infringement suit against Gilead regarding Gilead's marketing of Truvada for PrEP); *see also* The Editorial Board, *Gilead Sciences Defeats the CDC*, WALL ST. J. (May 10, 2023), https://www.wsj.com/articles/cdc-federal-jury-gilead-sciences-truvada-patent-4ae9fa8e (sharing the jury verdict of noninfringement and CDC patent invalidity).

165. *See* THE EVOLUTION OF HIV/AIDS THERAPIES, *supra* note 68 (discussing Truvada's initial successes at approximately the 20-minute mark, 38-minute mark, and 50-minute mark).

1980s and early 1990s.[166] Many criticized this practice as wasteful and risky, since no clinical studies tested combinations of treatments.[167]

Gilead's leaders thought they should make a single product doctors could prescribe for an HIV patient to achieve and safely maintain "undetectable" status for their lifetime.[168] It struck the leaders of Gilead that there was an enormous opportunity for such a drug to succeed. Gilead held regular meetings with HIV/AIDS patients and AIDS community activists. What struck Gilead scientists the most was how any meeting spanning the hours of 4:00 AM or PM, 8:00 AM or PM, or 12:00 AM or PM would involve the crowd of AIDS patients having alarms go off to take their once-every-four-hours set of medications.[169]

For Gilead, the opportunity presented by Triangle and its emtricitabine product was too good to pass over. Emtricitabine had negligible toxicity to cells,[170] while Gilead's TDF presented known toxicities to bone density and kidney systems in humans.[171] Thus, emtricitabine was advantageous over many other NtRTIs (as well as NRTIs) as a candidate to combine with TDF for a combination treatment to address viral resistance and HIV rebound concerns. Emtricitabine and the tenofovir in TDF both inhibit the replication action of the same HIV enzyme, but in two different ways (as cytidine and adenosine imitators, respectively). Gilead scientists hypothesized their combination should have a strong clinical synergistic effect of HIV inhibition.[172] Emtricitabine was a new potent NRTI product expected to enter the market in the next year with lesser-known branding (in its trademark, Coviracil, and manufacturer, Triangle).[173] Triangle had just suffered the tragic loss of its visionary leader, leaving the Triangle team open to new leadership through a merger or acquisition.[174]

On December 4, 2002, Gilead and Triangle announced a "definitive agreement" for Gilead to purchase Triangle via a two-step tender offer.[175]

166. *See id.*

167. *See* Alice Tseng et al., *The Evolution of Three Decades of Antiretroviral Therapy: Challenges, Triumphs and the Promise of the Future*, 79 BRIT. J. CLINICAL PHARMACOLOGY 182, 182–94 (2015).

168. *See* THE EVOLUTION OF HIV/AIDS THERAPIES, *supra* note 68 (containing clip of Norbert Bischofberger, EVP of R&D at Gilead Sciences, sharing motivations and goals for Atripla and Truvada for HIV treatment at the 20-minute mark).

169. *Id.*

170. *See* Liotta & Painter, *supra* note 138, at 2094.

171. *See Drug Approval Package: VIREAD®*, *supra* note 130.

172. *See supra* Section II.B.

173. *See* Liotta & Painter, *supra* note 138.

174. *See* Smith, *supra* note 163.

175. *See* Gregg Alton, *Schedule TO-C Triangle Pharmaceuticals Inc.: Tender Offer Statement under Section 14(d)(1) or 13(e)(1) of the Securities Exchange Act of 1934*, GILEAD SCIS., INC., SECURITIES

Gilead purchased Triangle, including its intellectual property portfolio and North Carolina headquarters, for $464 million.[176] As a part of the emtricitabine purchase, Gilead took the unusual step of purchasing the full patent rights to emtricitabine from their original owners, Emory University, for a single payment of $525 million, instead of maintaining a license with Emory.[177] Gilead made clear its primary intention in acquiring Triangle in its 2002 announcement: Gilead intended to both commercially launch the delayed Coviracil and build a combination therapy of Viread and Coviracil.[178]

b) Gilead Seeks Accelerated Approval for Anti-HIV Combination Therapy Truvada

Gilead quickly worked with worldwide health agencies to launch both an emtricitabine-only HIV treatment and a combination treatment of emtricitabine-tenofovir.[179] To gain more rapid approval for the combination therapy, Gilead pursued a clinical study route acceptable to American and European regulators for combination therapies of existing drugs: a single "bioequivalence" study, in lieu of the standard phases I through III of clinical trials for novel medicines.[180] Further, the American AIDS health agencies were excited and confident about the potential of this combination therapy and organized trials of their own with Gilead's supporting input before FDA approval of the combination therapy.[181]

In March 2004, only eight months after emtricitabine was approved by the FDA, Gilead filed a New Drug Application for the combination anti-HIV

EXCHANGE COMMISSION (Dec. 4, 2002), https://www.sec.gov/Archives/edgar/data/882095/000104746902005573/a2095407zscto-c.htm (last visited Nov. 24, 2022).

176. *See id.*

177. *See* Press Release, Emory Univ., Gilead Sciences and Royalty Pharma Announce $525 Million Agreement with Emory University To Purchase Royalty Interest for Emtricitabine, (July 18, 2005), https://www.emory.edu/news/Releases/emtri.

178. *See* Alton, *supra* note 175.

179. In 2003, Gilead updated the NDA for Coviracil to reflect a replacement trade name: Emtriva. *See* U.S. Food & Drug Admin., *Drug Approval Package: Emtriva® (emtricitabine) 200 mg Tablets*, https://www.accessdata.fda.gov/drugsatfda_docs/nda/2003/021500_emtriva_toc.cfm#:~:text=Approval%20Date%3A%2007%2F02%2F2003 (last visited Nov. 24, 2022). The FDA granted approval for Emtriva that same summer; *Id.*

180. *See id.* (containing clinical trial basis in the Clinical Pharmacology and Biopharmaceutics Review report); *see also* European Medicines Agency, *Scientific Discussion: Truvada®, MINN-Emtricitabine/Tenofovir disoproxil fumarate*, https://www.ema.europa.eu/en/documents/scientific-discussion/Truvada-epar-scientific-discussion_en.pdf (last visited Nov. 25, 2022).

181. *See* National Institute of Allergy and Infectious Diseases (NIAID), *Safety of Tenofovir Disoproxil Fumarate (TDF) and Emtricitabine/TDF in HIV Infected Pregnant Women and Their Infants*, U.S. NAT'L LIB. MED.: CLINICALTRIALS.GOV (2004), https://clinicaltrials.gov/ct2/show/NCT00076791 (last visited Nov. 25, 2022).

therapy of emtricitabine and TDF under the trade name Truvada.[182] Gilead also filed the first patent, followed by several continuation applications, on daily treatment of HIV with 500 milligrams of Truvada that year.[183] Gilead would go on to receive three additional patents on treatment of HIV with Truvada, each with a terminal disclaimer to the first patent; all four patents have been listed in the FDA Orange Book drug patent listings for Truvada.[184]

The AIDS innovation and regulation ecosystem was eager to deploy the new Truvada. Only five months later, in August, the FDA would approve Truvada for HIV treatment;[185] however, the FDA approved it conditionally based on Gilead's continued study of the toxicity and efficacy of Viread, especially related to the drug's renal effects.[186] In February 2005, the European Commission approved Truvada for HIV treatment too.[187] In October that year, Gilead announced its year-over-year third quarter revenue increased by 51%, with a record product sales of $467.2 million during the third quarter of 2005 "driven primarily by Gilead's HIV product franchise, including the continued strong uptake of Truvada® . . . since its U.S. launch in August of 2004."[188]

However, Gilead and the AIDS innovation ecosystem collaborating with it had even higher aims for Truvada. Gilead sought to combine Truvada with yet a third anti-HIV compound to treat the most severe HIV infections with a

182. *See Drug Approval Package: Truvada®*, *supra* note 30 (containing timeline of application and approval on page 1 of the linked Approval Letter).

183. *See* '397 Patent, *supra* note 2, at 1 (showing discrepancy between filing date of granted patent with first application on page 1).

184. *See Orange Book: Approved Drug Products with Therapeutic Equivalence Evaluations – Patent and Exclusivity for: N021752*, FDA, https://www.accessdata.fda.gov/scripts/cder/ob/patent_info.cfm?Product_No=001&Appl_No=021752&Appl_type=N (last visited Mar. 12, 2023) (listing Gilead's four patents on the 500 mg dose of Truvada set to expire in 2024).

185. *Id.*; *see also* 21 C.F.R. § 314.510 (defining process for FDA to grant marketing approval for a new drug based on a "surrogate endpoint that is reasonably likely" based on past evidence, in the Truvada case on evidence from FTC & TDF's independent trials, with the condition to continue clinical studies for verification post-marketing).

186. *See Drug Approval Package: Truvada®*, *supra* note 30 (containing post-marketing conditions of approval on pages 2–4 of the linked Approval Letter).

187. Press Release, Gilead Scis., Inc. European Commission Approves Truvada®, a Once-a-Day Tablet Containing Gilead Sciences' Anti-HIV Drugs Emtriva® and Viread® (Feb. 23, 2005), https://www.gilead.com/news-and-press/press-room/press-releases/2005/2/european-commission-approves-truvada-a-onceaday-tablet-containing-gilead-sciences-antihiv-drugs-emtriva-and-viread.

188. Press Release, Gilead Scis., Inc., Gilead Sciences Announces Third Quarter 2005 Financial Results (Oct. 18, 2005), https://www.gilead.com/news-and-press/press-room/press-releases/2005/10/gilead-sciences-announces-third-quarter-2005-financial-results.

once-daily pill.[189] Gilead ultimately succeeded in doing so in partnership with Bristol-Myers Squibb by making the product Atripla.[190] The U.S. Public Health Service recommended Truvada for post-exposure prophylaxis (post-HIV-exposure emergency treatment to reduce the risk of infection).[191] Audaciously, many of the AIDS institutions partnered with Gilead to embark on a promising, entirely new area of tackling the HIV pandemic: prevention of HIV infection.

2. *Method Two: TDF with Emtricitabine as Truvada for PrEP Preventing HIV Infection*

Public health authorities, as discussed in this Section, were leading global trials on methods to prevent HIV infection from the late 1990s into the late 2000s, especially through continuous use of ART in HIV-negative but vulnerable populations. When Truvada was first approved for HIV treatment in 2004, the public health authorities leading the prevention clinical trials noticed the new drug's potential as a preventive. After clinical trials with other ARTs, including tenofovir alone, failed to show a PrEP regimen could work, public health authorities turned to Truvada. The CDC accessed Truvada with a Material Transfer Agreement (MTA) with Gilead, but the trials were funded by taxpayers and philanthropies. Finding success, the CDC patented Truvada for PrEP as a method of treatment to prevent HIV infection. After Gilead received FDA approval for the second indication of Truvada as Truvada for PrEP, access to the medicine by vulnerable populations has been limited. AIDS activists successfully pushed the U.S. government to enforce its patents against Gilead, though the government in 2023 lost a jury trial in its unprecedented patent litigation. There, the government had sought resource concessions from Gilead—in the form of one billion dollars in royalties—to help fund increased public assistance for the still-suffering HIV/AIDS community.[192]

189. *See* THE EVOLUTION OF HIV/AIDS THERAPIES, *supra* note 68 (discussing Gilead's goals for Truvada at the 20, 38, and 54 minute marks).

190. *See id.*

191. *See* Adelisa L. Panlilio et al., *Updated U.S. Public Health Service Guidelines for the Management of Occupational Exposures to HIV and Recommendations for Postexposure Prophylaxis*, NAT'L CTR. FOR INFECTIOUS DISEASES, CDC (Sept. 30, 2005), https://www.cdc.gov/mmwr/preview/mmwrhtml/rr5409a1.htm.

192. *See* Christopher Yasiejko & Michael Shapiro, *Gilead Beats US in Billion-Dollar Trial on Anti-HIV Patents (1)*, BLOOMBERG LAW (May 9, 2023), https://news.bloomberglaw.com/ip-law/gilead-beats-us-in-billion-dollar-trial-on-anti-hiv-patents; *see also* Press Release, Statement from Prep4All and PIPLI on the Disappointing Verdict in US v. Gilead, PREP4ALL (May 17, 2023), https://prep4all.org/statement-from-prep4all-and-pipli-on-the-disappointing-verdict-in-us-v-gilead/ ("If the government prevails and obtains a royalty from Gilead, the proceeds

a) Breakthrough: Government, Philanthropy, Big Pharma Clinical Trials

At the time of the Truvada launch for HIV treatment in 2004, the HIV/AIDS innovation coalition leaders were starting to think seriously about the concept of PrEP for prevention of HIV infection in at-risk populations.[193] The CDC's first PrEP investigation using only tenofovir compounds in an animal trial in 1995 produced mixed results.[194] Though veteran clinical leaders that had been in the fight against AIDS since the 1980s openly questioned if PrEP was a high-value strategy to contain the lasting HIV pandemic,[195] interest in trying to develop PrEP again surged after the Viread approval. In 2004, at least six trials were planned to evaluate PrEP against HIV infection around the globe, though initially only through use of TDF (Viread).[196] One of the largest Viread for PrEP trials ongoing at the time was a study in Botswana coordinated by two of the world's largest global health philanthropies (the Bill & Melinda Gates Foundation as sponsors and Family Health International (FHI), in collaboration with Gilead for materials).[197] However, that trial would also fail to find clinically significant HIV protection from Viread alone.[198]

---

could provide badly-needed funding to expand access to PrEP, HIV testing, and related care.").

193. *See* Greg Szekeres et al., *Anticipating the Efficacy of HIV Pre-Exposure Prophylaxis (PrEP) and the Needs of At-Risk Californians*, CTR. FOR HIV IDENTIFICATION, PREVENTION, & TREATMENT SERVS. (2004), http://www.uclaisap.org/documents/PreP_Report_FINAL_11_1_04.pdf (last visited Nov. 25, 2022).

194. Che-Chung Tsai et al., *Prevention of SIV Infection in Macaques by (R)-9-(2-phosohonylmethoxypropyl)adenine*, 270 SCI. 1197, 1199 (1995); *see also Leigh* Peterson et al., *Tenofovir Disoproxil Fumarate for Prevention of HIV Infection in Women: A Phase 2, Double-Blind, Randomized, Placebo-Controlled Trial*, 2 PLOS CLINICAL TRIALS 27 (2007) (failing to find statistically significant protection with Tenofovir-only as PrEP regimen across cohorts of African women with Gates Foundation financial support).

195. *See The Evolution of HIV/AIDS Therapies*, CHEMICAL HERITAGE FOUND. & SCI. HIST. INST. (2012), https://vimeo.com/59281508 (containing clip of at the minute mark Norbert Bischofberger, EVP of R&D at Gilead Sciences, and Dr. Paul Volberding of UCSF discussing the relatively low value of PrEP to containing the pandemic with its simultaneous importance to high-risk individuals' ability to protect themselves).

196. *See* Szekeres et al., *supra* note 193.

197. *See* Press Release, Bill & Melinda Gates Found., Family Health International Receives Grant to Evaluate Once-Daily Antiretroviral as a Potential Method of HIV Prevention, https://www.gatesfoundation.org/ideas/media-center/press-releases/2002/10/family-health-international-receives-grant (last visited Apr. 8, 2024); *see also* Peterson et al., *supra* note 194 (failing to find statistically significant protection with Tenofovir-only as PrEP regimen across cohorts of African women with Gates Foundation financial support).

198. *See* Peterson et al., *supra* note 194 (failing to find statistically significant protection with Tenofovir-only as PrEP regimen across cohorts of African women with Gates Foundation financial support).

In 2004, the CDC was interested in exploring combination ARTs as PrEP candidates and reached out to Gilead for its emtricitabine and tenofovir materials as well as basic guidance. The CDC signed a MTA with Gilead to enable the CDC to complete a study of emtricitabine and tenofovir as PrEP against HIV in animals.[199] The CDC's trial of Truvada for PrEP against HIV infection ("Truvada for PrEP"), the first of many Truvada for PrEP studies funded primarily by U.S. taxpayers through NIH grants, was very successful.[200] Contrary to the terms of the CDC's MTA with Gilead, which stipulated neither party could file for patents arising from the resulting CDC trial, CDC scientists—possibly unaware of that clause—began filing method of treatment patents on Truvada for PrEP in 2006.[201] The CDC alerted Gilead to the trial's success, but made minimal mention of the patent filings or otherwise decided not to pursue enforcement of them for more than a decade;[202] instead, the CDC encouraged Gilead and other organizations starting to run or running tenofovir-as-PrEP clinical trials globally to shift to clinical trials of Truvada for PrEP in the late 2000s.[203]

The Bay Area hub of the broader AIDS innovation coalition led the way again (this time in regards to PrEP) with Dr. Robert Grant at UCSF spearheading the largest Truvada for PrEP study, dubbed the "iPrEx" study, beginning in 2006–07.[204] Grant's study, which included observing almost 2500 men across seven distinct locations across the globe for three years, was supported by $50 million in federal grants from the NIH and $17 million in additional funding from the Bill & Melinda Gates Foundation, with minimal

199. *See* Gilead Scis., Inc. v. United States, 155 Fed. Cl. 336, 339 (2021).

200. *See* J. Gerardo García-Lerma et al., *Prevention of Rectal SHIV Transmission in Macaques by Daily or Intermittent Prophylaxis with Emtricitabine and Tenofovir*, 5 PLOS MED. 28 (2008) (finding statistically significant protection with combination therapy of tenofovir and emtricitabine, forming basis of CDC inventorship claim to Truvada as HIV PrEP).

201. *See, e.g.*, U.S. Patent No. 9,044,509 (granted June 2, 2015) (claiming tenofovir disoproxil fumarate + emtricitabine as a method of treatment for prevention of HIV infection based on simian trials) [hereinafter '509 Patent].

202. *See Gilead Scis.*, 155 Fed. Cl. at 340.

203. *See, e.g.*, Press Release, Ctrs. for Disease Control & Prevention, CDC Trial and Another Major Study Find PrEP Can Reduce Risk of HIV Infection among Heterosexuals, https://www.cdc.gov/nchhstp/newsroom/2011/prepheterosexuals.html (last visited Sep. 11, 2022) (sharing another PrEP study that the CDC supported after its initial agreement with Gilead).

204. *See* Robert M. Grant et al., *Preexposure Chemoprophylaxis for HIV Prevention in Men Who Have Sex with Men*, 363 NEW ENG. J. MED. 2587 (2010) (sharing the NIAID-led, Gates Foundation-supported, and Gilead-assisted iPrEx clinical Truvada for PrEP study results from men in Peru, Ecuador, Brazil, San Francisco, Boston, Thailand, and South Africa).

materials support from Gilead.[205] The study found that Truvada for PrEP reduced the risk of transmission of HIV to those following the regimen by as much as 92%.[206] The wild success of the clinical trial prompted a call from President Obama in November 2010 to congratulate Grant and the rest of the NIH team for the remarkable findings.[207]

During this time, Gilead was simultaneously fighting a smear campaign by many AIDS activists against PrEP. At FDA hearings about the potential new Truvada for PrEP indication, the AIDS Healthcare Foundation, which represents AIDS care providers and patients globally, protested loudly: that the drug had problematic side effects and costs to patients; that the PrEP approach would incentivize unsafe sex despite continued circulation of other STIs; and that irregular adherence to the daily PrEP regimen would lead to Truvada-resistant HIV strains.[208] Gilead did not fund, but only gave requested materials, for the leading trials that found Truvada to be effective as PrEP; in fact, Gilead was initially hesitant to pursue PrEP development, given its close collaboration in its HIV therapies with AIDS activists that disagreed with the concept, but the public health authorities pushed for Truvada to be made available as a preventive.[209]

b) Gilead Obtains FDA Approval and Markets Truvada for PrEP

The clear results of the iPrEx study in 2010, in addition to the similarly-successful "Partners PrEP" study (lead by AIDS coalition members the CDC and the University of Washington and with Gates Foundation financial support),[210] prompted Gilead to begin the development necessary to file a supplementary New Drug Application (sNDA) and new trade name for a second FDA-approved indication of Truvada: Truvada for PrEP.[211] Gilead filed its sNDA for Truvada for PrEP in December 2012, relying on the two

205. Liz Highleyman, *CDC Has Patents on PrEP, Advocates Find*, POZ (Mar. 28, 2019), https://www.poz.com/article/cdc-patent-prep-advocates-find.

206. *See* Grant et al., *supra* note 204, at 2597.

207. *See* Christopher Glazek, *Why Is No One on The First Treatment to Prevent H.I.V.?*, NEW YORKER: ANNALS TECH. (Sept. 13, 2013), https://www.newyorker.com/tech/annals-of-technology/why-is-no-one-on-the-first-treatment-to-prevent-h-i-v.

208. *See id.*

209. *See id.*

210. *See* Jared M. Baeten et al., *Antiretroviral Prophylaxis for HIV Prevention in Heterosexual Men and Women*, 367 NEW ENG. J. MED. 399 (2012) (sharing results of the Partners PrEP study evaluating Truvada for use in serodiscordant partners).

211. *See* Press Release, Gilead Scis., Inc., Gilead Sciences Submits Supplemental New Drug Application to U.S. Food and Drug Administration for Truvada® for Reducing the Risk of Acquiring HIV (Dec. 15, 2011), https://www.gilead.com/news-and-press/press-room/press-releases/2011/12/gilead-sciences-submits-supplemental-new-drug-application-to-us-food-and-drug-administration-for-Truvada-for-reducing-the-risk-of-acquiring-hiv.

studies supported by the Gates Foundation and other members of the AIDS innovation coalition.[212]

Eight months later, in July 2012, Gilead secured FDA approval for the second indication for Truvada: Truvada for PrEP against HIV.[213] Though Grant had expected "a stampede" of demand for the drug to be prescribed as PrEP, even pre-approval, the controversy regarding PrEP's adoption (discussed in Section III.C.2.a, *infra*) slowed the uptake of Truvada for PrEP. In 2013, a year after FDA approval, only a few thousand Americans were taking Truvada for PrEP, despite "at least half a million Americans" being good candidates due to their risk profiles.[214]

Gilead predicted in 2013 that it would take five to ten years for PrEP to become more widely accepted and used in communities vulnerable to HIV's spread.[215] Over the next seven years, profits for Truvada increased by billions of dollars as uptake of Truvada for PrEP gradually increased; however, the number of HIV infections annually would hold steady at about 40,000 per year.[216]

c) United States Enforces PrEP Patents Against Manufacturer Gilead

Carrying on the tradition of driving access to HIV/AIDS medicines, AIDS activists uncovered the CDC's patents on Truvada for PrEP in 2018 and pushed for the CDC to take enforcement action.[217] James Krellenstein, co-founder of a modern AIDS activism organization called PrEP4All Collaboration, claimed "[t]he CDC has all these patents and is allowing Gilead to rip off the American people at the expense of public health."[218] The modern AIDS activists asked the CDC to enforce its patents on Truvada for PrEP to

212. *See id.*

213. Press Release, Gilead Scis., Inc., U.S. Food and Drug Administration Approves Gilead's Truvada® for Reducing the Risk of Acquiring HIV (July 16, 2012), https://www.gilead.com/news-and-press/press-room/press-releases/2012/7/us-food-and-drug-administration-approves-gileads-Truvada-for-reducing-the-risk-of-acquiring-hiv.

214. *See* Glazek, *supra* note 207.

215. *See id.*

216. *See* Christopher Rowland, *An HIV Treatment Cost Taxpayers Millions. The Government Patented It. But a Pharma Giant Is Making Billions*, WASH. POST (Mar. 26, 2019), https://www.washingtonpost.com/business/economy/pharma-giant-profits-from-hiv-treatment-funded-by-taxpayers-and-patented-by-the-government/2019/03/26/cee5afb4-40fc-11e9-9361-301ffb5bd5e6_story.html.

217. *See id.*

218. *Id.*

help the CDC fund Medicaid-based PrEP education and heavily-discounted PrEP distribution programs.[219]

Reports on the AIDS activists' calls for action spurred a congressional hearing on May 16th, 2019, where the House Committee on Oversight and Government Reform called the Gilead CEO Daniel O'Day, Grant, and HIV/AIDS activists to testify. [220] For hours, House Representatives interrogated the panel about the pricing of Truvada and the taxpayer funds that went into Grant's studies in relation to the CDC's patents. [221] Representative Alexandria Ocasio-Cortez, who had pushed the Committee to hold the hearing, entered into the congressional record a Yale Law report asserting the validity and enforceability of the CDC's patents. Through her questions, she began to make the case that the patents should be enforced against Gilead so that the government could seek lower-price guarantees or more need-based access programs from the manufacturer.[222] After the hearing, Committee Chair Elijah E. Cummings and Representative Ocasio-Cortez wrote to the Department of Health and Human Services Secretary Alex Azar requesting more information about the CDC's patents.[223] In November, the U.S. Department of Justice Civil Division on behalf of the Department of Health and Human Services took the unprecedented step of bringing suit against its longtime AIDS innovation partner, Gilead, for willful infringement of the four CDC patents.[224]

Gilead vigorously defended the patent infringement claims—including seeking (to no avail) Patent Trial and Appeal Board *inter partes* review of the patents.[225] In 2021, Gilead countersued for breach of contract regarding the CDC's PrEP patents arguing the CDC violated the terms in the CDC-Gilead Material Transfer Agreement that stipulated the CDC could not seek patents

219. *Id.*

220. *See* Press Release, House Committee on Oversight & Accountability, Committee to Hold Hearing on Gilead's Exorbitant Price for HIV Prevention Drug (May 14, 2019), https://oversightdemocrats.house.gov/news/press-releases/committee-to-hold-hearing-on-gilead-s-exorbitant-price-for-hiv-prevention-drug.

221. *Id.*

222. *See HIV Prevention Drug: Billions in Corporate Profits after Millions in Taxpayer Investments: Hearing Before the Committee on Oversight and Reform*, 116 Cong. 14-16 (May 16, 2019), https://docs.house.gov/meetings/GO/GO00/20190516/109486/HHRG-116-GO00-Transcript-20190516.pdf.

223. Eric Sagonowsky, *Lawmakers Clash as Gilead CEO Takes Congressional Hot Seat to Defend Truvada®*, FIERCE PHARMA (May 17, 2019), https://www.fiercepharma.com/pharma/gilead-s-o-day-takes-congressional-hot-seat-to-defend-Truvada.

224. United States v. Gilead Scis., Inc., 2019 WL 5942984 (D. Del.) (Trial Pleading).

225. The United States of America v. Gilead Sciences, Inc. 1:19CV02103 (referring to a sealed Motion for Summary Judgment at Docket Entry 360).

from Gilead's sharing of their Truvada.[226] The judge ruled that the CDC did breach the MTA.[227] In May 2023, a jury found for Gilead in the patent suit, finding both the CDC's patents invalid and not infringed by Gilead's sale of Truvada for PrEP.[228]

IV. ANALYSIS OF INNOVATION DRIVERS

The motivations and impediments to the actors in the three-decade-long story of Truvada innovation changed throughout the HIV/AIDS pandemic. At the pandemic's start in the United States in the early 1980s, vulnerable communities and federal health authorities were forced to reckon with the most lethal yet transmissible virus in recorded human history, yet they knew nothing about the disease itself. AIDS activists, quietly ostracized and blamed by conservative society for their plight, cried out and protested for help. Interest in the international scientific community to address the massive AIDS crisis by engaging with patients and health authorities birthed an organized AIDS innovation ecosystem.

In the late 1980s and early 1990s, the ongoing crisis and the new ecosystem of AIDS activists and researchers helped motivate university chemists to synthesize what would become the two compounds in the Truvada combination therapy. The university scientists had motivations and challenges unique to their projects and personalities, but they each sought patent protection of their novel ARTs and leveraged the patents to commercialize their technologies via licenses to pharmaceutical companies for clinical development. Pharmaceutical companies managed dueling interests of responding to the public health crisis and fulfilling their fiduciary duties to corporate shareholders in gradually developing the components of Truvada.

After Truvada was marketed, AIDS activists and health authorities maintained the innovation ecosystem for decades to: further efforts to continue reducing case numbers; continue increasing the longevity of HIV patients; and spur trials for PrEP to prevent HIV infection. HIV became manageable, but many of the same motivations driving innovation in mid-1981 remain today: to stop HIV from spreading and to help those with less resources combat the virus.

226. *See* Gilead Scis., Inc. v. United States, 151 Fed. Cl. 742 (2020).

227. Andrew Karpan, *Claims Court Finds CDC Broke Gilead Deal Over HIV Research*, LAW360 (Nov. 22, 2022), https://www.law360.com/articles/1551976/claims-court-finds-cdc-broke-gilead-deal-over-hiv-research.

228. *See* The Editorial Board, *Gilead Sciences Defeats the CDC*, WALL ST. J. (May 10, 2023) (sharing the jury verdict of noninfringement and CDC patent invalidity), https://www.wsj.com/articles/cdc-federal-jury-gilead-sciences-truvada-patent-4ae9fa8e.

A. THE 1980S: INNOVATION IN RESPONSE TO ACUTE CRISIS

The chaos of the first decade of the U.S. HIV/AIDS epidemic created many innovation drivers behind the development of Truvada. The then-unprecedented nature of the pandemic motivated regular citizens to call on the government to act. The government, though slowed by stigma and misunderstanding, eventually responded. Private actors—scientists and pharmaceutical companies—turned their research quickly to finding solutions for the ballooning problem of HIV/AIDS. As the scale of the humanitarian crisis unfolded in this first decade, international bodies and nonprofits increasingly formed and became leaders in this innovation ecosystem. These actors together started a unique ecosystem of innovation to end the HIV/AIDS pandemic.

1. Activism Borne from Communities' Unanswered Cries for Help

As of early 2023, HIV/AIDS is the deadliest pandemic in human history (COVID-19 has killed only about 20% as many people globally as AIDS has as of early 2023[229]), largely because of the rapid spread of HIV/AIDS in the decade immediately following the U.S. onset of the pandemic in 1981.[230] The sheer number of dead in vulnerable communities—men who have sex with men ("MSM"), people with close contact to people in sub-Saharan Africa, hemophiliacs, and intravenous drug users—has *devastated* these communities.[231] However, most of these communities in Western society were already disadvantaged: gay men, Black Americans, and people with disabilities, though gay men quickly became the largest patient population in the United States.[232] A temporary official name for the virus ("Gay-Related Immune Disorder") only added to existing homophobia and transphobia.[233]

The situation was even more dire in sub-Saharan Africa, where most deaths due to HIV/AIDS have occurred since the pandemic began.[234] While HIV spread mostly in a select few marginalized communities in the United

229. *See* Steven W. Thrasher, *Why COVID Deaths Have Surpassed AIDS Deaths in the U.S.*, SCI. AMERICAN (Dec. 1, 2021), https://www.scientificamerican.com/article/why-covid-deaths-have-surpassed-aids-deaths-in-the-u-s/#:~:text=While%20COVID%20deaths%20are%20now,who%20have%20died%20of%20AIDS.

230. *See supra* Section II.A.

231. *See supra* Section III.A.1; *see also* Shilts, *supra* note 10, at 42, 72.

232. *See supra* Section III.A.1.

233. One of the CDC's first names for the AIDS condition was Gay-Related Immune Disorder, or GRID, only adding to the blaming and shaming of the MSM community. *See, e.g.*, Lawrence K. Altman, *New Homosexual Disorder Worries Health Officials*, N.Y. TIMES (May 11, 1982), https://www.nytimes.com/1982/05/11/science/new-homosexual-disorder-worries-health-officials.html (discussing GRID in a way that added to stigma of the MSM community).

234. *See* Thrasher, *supra* note 229.

States and other Western countries, in sub-Saharan Africa it spread among the broader population, including through childbirth.[235] These communities faced hunger, lacked access to Western medicine (including early HIV treatments), and confronted many other challenges largely avoided by Western society making HIV/AIDS containment especially difficult.[236]

Facing serious impediments by their own governments, people in affected communities across the world had no choice in this period but to advocate for their own survival.[237]

2. *The U.S. Federal Government and International Diplomacy Slowly Step Up*

The association of AIDS with disadvantaged groups, especially MSM, was a major impediment to the U.S. government's public health response. In 1981, the federal government was riding a new socially conservative wave following the decades focused on social tolerance in the 1960s and 1970s.[238] Social conservatives were in charge of the Presidency and the Senate for much of the crisis' first decade in the United States.[239] Federal action therefore required conservative, often religious, constituencies to recognize the plight of Americans conservatives often looked down on, blamed for the burgeoning crisis, or both.[240] President Reagan only publicly acknowledged the crisis for the first time in 1985 and only first signed legislation and an executive order creating public health research initiatives to fight AIDS in 1987, six years after the pandemic began in the United States.[241] In that time, nearly fifty thousand Americans had already died from AIDS-related complications.[242] Prejudices seemed to impede the U.S. government from caring for its own people.

The silence of the U.S. federal government in those early days turned patients, doctors, families, and friends of HIV/AIDS patients into activists.

---

235. *See id.*

236. *See id.*

237. *See supra* Section III.A.3.c.

238. *See generally The People vs. America*, AL JAZEERA, https://interactive.aljazeera.com/aje/2017/the-people-vs-america.html (last visited May 21, 2023) (providing a chronology of sociopolitical development in the 20th century United States by decade).

239. *See The People vs. America: 1980s – A new era of conservatism*, AL JAZEERA, https://interactive.aljazeera.com/aje/2017/the-people-vs-america/1980s.html (last visited May 21, 2023).

240. *See* President Reagan's Remarks at 1987 AIDS Research Awards Dinner, *supra* note 54; *see also supra* Section III.A.3.c.

241. *See supra* Section III.A.1.

242. Centers for Disease Control and Prevention, *Morbidity and Mortality Weekly Report: HIV and AIDS — United States, 1981-2000*, CDC.GOV (June 1, 2001), https://www.cdc.gov/mmwr/preview/mmwrhtml/mm5021a2.htm.

These communities needed care that generally did not yet exist or, if it did, patients were not receiving it.[243] AIDS activism, especially the in-person protests at each of the major health authorities—NIH, National Institute of Allergy and Infectious Diseases (NIAID), FDA, CDC—is credited by leaders in those agencies as creating federal support for research and development of HIV medicines.[244] The FDA created its first accelerated drug approval processes in response to AIDS pandemic, but, more directly, in response to the ACT UP protestors shutting down their building.[245] The AIDS activists' work on this front paid off in the 1990s and later in the accelerated approval of Truvada and its component drugs, Viread and Emtriva, for HIV treatment.[246] Many activists passed away in the 1980s and 1990s fighting for the care they would not receive.

3. Growing Crisis Motivated a Unique Public-Private Innovation Ecosystem

The AIDS innovation coalition built itself slowly in this period in response to the patients' and physicians' cries for help. With "highly toxic" AZT being the first treatment brought (six years into the pandemic), the existing HIV therapy options were wildly inadequate well into the mid-1990s.[247] However, pharmaceutical companies increasingly sought to capture the HIV therapy market[248] and annual International AIDS Conferences shared discoveries among innovators in public health and private companies.[249]

AIDS increased dramatically in sub-Saharan Africa concurrent with and persisting beyond the pandemic in developing nations.[250] The expanding humanitarian crisis prompted massive philanthropy and international policymaking to increase access to AIDS treatments globally.[251] Philanthropic and non-governmental organizations were truly driven by the scope of suffering due to AIDS in developing parts of the world.[252] These nations

243. *See supra* Section III.A.1; *see also supra* Section III.A.2.b.

244. *See supra* Section III.A.3.a.

245. *See id.*; *see also supra* Section III.A.3.a.

246. *See supra* Section III.A.3.c; *see also supra* Section III.C.1.b.

247. *See supra* Table 1 (showing HIV drug approval dates as mostly in 1990s and later); *see also supra* Table 2 (showing toxicity concerns with many of the early drugs listed in Table 1).

248. *See, e.g.*, THE EVOLUTION OF HIV/AIDS THERAPIES, *supra* note 12 (sharing Gilead's motivations for getting into the HIV treatment marketplace primarily at the 20 minute mark, and its expansion of HIV treatment voluntary licensing globally at the 38 minute mark).

249. *See* Khai Tram, *A Brief History of the International AIDS Conference*, GATESNOTES (July 18, 2012), https://www.gatesnotes.com/A-Brief-History-of-the-International-AIDS-Conference#:~:text=Atlanta%2C%201985%3A%20The%20first%20IAC,on%20the%20emerging%20new%20disease.

250. *See supra* Section IV.A.1.

251. *See supra* Section III.A.3.b.

252. *See id.*

became the primary sites for federal health authorities and pharmaceutical companies to prove the effectiveness of HIV therapies in humans via clinical trials.[253]

Therefore, the African and other developing nations most severely afflicted by the HIV/AIDS pandemic were highly motivated when they began a diplomatic effort in this period to drastically improve access to the novel and limited Western medicines against HIV. This diplomacy would culminate in the 2001 Doha Declaration regarding the international TRIPS Agreement allowing nations to issue compulsory licenses to patented technologies critical to the health and welfare of a nation's people.[254] This agreement had a tremendous impact on how pharmaceutical companies, such as Gilead, would choose to enter voluntary license agreements with developing countries for valuable HIV treatments. Voluntary licensing programs encouraged peaceful, increased distribution of the lifesaving drugs while avoiding the consequences of a nation issuing a compulsory license for a company's technology. Without the Doha Declaration on TRIPS, it is not clear that pharmaceutical companies like Gilead would have had as much motivation to offer these voluntary licenses in the first place.[255]

Drivers in the marketplace—patient adherence, desirable lifelong treatments, minimizing drug toxicities, profitability of treatments, and altruism—began to become clear in this dire period. First, prior to Truvada, HIV/AIDS patients took several, even a dozen or more medications daily for HIV treatment, often multiple times per day, making treatment adherence challenging.[256] Second, HIV, by its nature, was (and still is) difficult, if not impossible, to cure.[257] A lifelong prescription presents a large business opportunity. Third, combination use of therapies was often prescribed off-label, with the potential for high toxicity for those in advanced stages of the disease.[258] Many initial HIV treatments bore long-term adverse effects or

253. *See, e.g.*, *supra* Section III.C.2.a.

254. *See supra* Section III.A.3.b.

255. *See id.*

256. *See, e.g.*, THE EVOLUTION OF HIV/AIDS THERAPIES, *supra* note 12 (describing near the 16 minute mark the strict dosing schedule faced by most AIDS activists that met with Gilead in the 1990s); *see also* '397 Patent, *supra* note 2, at col. 19:27-30 ("Combinations of the present invention [Truvada] enable patients greater freedom from multiple dosage medication regimens and ease the needed diligence required in remembering and complying with complex daily dosing times and schedules.").

257. *See supra* Section II.A.

258. *See supra* Table 2 (showing the many toxicities for many individual HIV treatments and does not list all the adverse interactions among their combinations).

toxicities that harmed patients' health and discouraged treatment adherence.[259] Other HIV treatments contributed to "viral resistance," where a fought-down HIV viral load would rebound and become resistant to the prior treatment because of a lack of effective combination therapy that the virus couldn't dodge evolutionarily.[260] Pharmaceutical inventors and companies saw a huge business opportunity: a once-a-day, one-a-day combination therapy pill to treat HIV could dominate the market.[261] Desperate customers and a genuine public health crisis made for strong motivators for scientists and pharmaceutical companies to research novel treatments in this area.

Yet there were still impediments to HIV treatment development that the ecosystem collaborated to remove in this period. First, the ecosystem was new and required time and talent to form. Unfortunately, established pharmaceutical companies found these new HIV departments higher-risk ventures and de-prioritized them in high-profile mergers and acquisitions, such as those mergers between Glaxo and Burroughs-Wellcome and between Bristol-Myers and Squibb.[262] Second, the regulatory burdens in place by the FDA and USPTO for HIV/AIDS inventions were just as high in the first years of the pandemic as for all other drugs. The FDA passed "Subpart H" for accelerated approval of life-saving drugs (such as HIV therapies) in direct response to the AIDS activism at their doorstep in the late 1980s and early 1990s.[263] This FDA regulatory change enabled the innovation ecosystem to launch many life-saving ARTs in the mid-1990s.[264]

B. THE INNOVATORS BEHIND TRUVADA FOR HIV TREATMENT

The innovators behind each part of the breakthrough HIV treatment drug Truvada at times revealed how their innovations were driven: (1) in university laboratories, by strokes of genius, brute force, concern for the crisis, and entrepreneurial spirit; and (2) in commercialization, by risk-taking startups

259. *See id.* (providing HIV treatment toxicity / adverse effect information by drug class and drug name).

260. *See id.*

261. *See* THE EVOLUTION OF HIV/AIDS THERAPIES, *supra* note 12 (sharing Gilead's motivations for getting into the HIV treatment marketplace at the 20 minute mark).

262. *See supra* Section III.B.1.b; *see also supra* Section III.B.2.b.

263. *See Understanding the History and Use of the Accelerated Approval Pathway*, *supra* note 96; *see also Accelerated and Restricted Approvals Under Subpart H (drugs) and Subpart E (biologics)*, FDA.GOV (Aug. 6, 2014), https://www.fda.gov/drugs/drug-and-biologic-approval-and-ind-activity-reports/accelerated-and-restricted-approvals-under-subpart-h-drugs-and-subpart-e-biologics.

264. *See Accelerated and Restricted Approvals Under Subpart H (drugs) and Subpart E (biologics)*, FDA.GOV (Aug. 6, 2014), https://www.fda.gov/drugs/drug-and-biologic-approval-and-ind-activity-reports/accelerated-and-restricted-approvals-under-subpart-h-drugs-and-subpart-e-biologics.

believing in the size of the market, expressing altruistic concern for the situation, engaging in regulatory accelerated approval pathways, and seeking regulatory exclusivity. Moreover, patents were used by every inventor and pharmaceutical development leader at every stage of the Truvada development process. A recurring theme emerges from the tenofovir, emtricitabine, and combination therapy stories: patent licensing was key to the series of pharmaceutical mergers and acquisitions that enabled company growth—and more importantly, high-quality HIV treatment development.

1. Creators of Tenofovir

Innovation drivers, such as genius and brute force, underpinned the academic chemists' synthesis of tenofovir; impediments, such as inconsistent collaboration with a large pharmaceutical company, Bristol-Myers, slowed their progress. These are often distinct from the drivers (like agility and brute force), or the impediments (like limited financing) faced by their biopharmaceutical company development partner, Gilead Sciences, Inc.[265]

a) Holý of the Czech Academy of Sciences

Holý's work on tenofovir was driven by many forces of innovation: genius, brute force, patent ambitions, curiosity, and more. He also faced challenges pursuing the invention.

i) Holý's Drivers

Holý created an antiviral molecule by modifying a nucleoside analogue, DHPA, and sought to apply it to many viral diseases (herpes simplex virus, hepatitis B virus, and HIV).[266] In this way, Holý had a stroke of genius for realizing transcription enzymes of many different viruses could be inhibited by the same DHPA-based compounds.

Holý's efforts also required brute force. He tried small tweaks to DHPA against a wide swath of viruses, choosing not to limit his research to only his initial target virus, herpes simplex (though DHPA derivatives were successful against HSV as well).[267] Tenofovir, one of Holý's DHPA derivatives, ended up proving a more targeted antiviral than DHPA.[268] In the end, his modifications

265. *See generally supra* Section III.B.1.

266. *See id.*; *see also* Hocek, *supra* note 103.

267. *See* Hocek, *supra* note 103 (summarizing Holý's major inventions and other accomplishments over his career); *see also* De Clercq et al., *supra* note 106, at 563–65.

268. *See* Erik De Clercq & Guangdi Li, *Approved Antiviral Drugs over the Past 50 Years*, 29 CLINICAL MICROBIOLOGY REVS. 695, 721 (2016).

of the DHPA molecule led to treatments for HIV (including the tenofovir component of Truvada), cytomegalovirus, hepatitis B, and herpes.[269]

Holý was also motivated to build a patent portfolio for his work as a chemist. He was quick to file patents on the DHPA and tenofovir technologies.[270] Over the course of his decades-long career, Holý filed over 60 patent applications, many of them granted.[271] This patent portfolio could indicate personal fortune through licensing his patents, institutional reputation, professional promotion, or all the above motivated him. The Czech Academy of Sciences, where he developed the chemistry supporting the first patents to tenofovir, was assigned all the rights to these patents.[272] In this manner, the Academy managed patent rights in a similar capacity to universities in the United States under the Bayh-Dole Act, where American universities are assigned the patent rights of employed innovators to encourage universities to commercialize their innovations.[273]

Holý may have been motivated by further professional recognition or career advancement, but there is limited evidence to available to the public on these points—after all, he was already the chair of his department when he filed the first U.S. patent.[274] Though there is limited evidence in public that he was specifically motivated by an altruistic desire to help end the HIV crisis, his curiosity and desire to cure herpes simplex virus combined with thorough testing of other virus' reactions to DHPA derivatives imply he was also motivated to address as many public health virological issues as he could.[275]

Due to Holý's position as chair of the biochemistry department at the Czech Academy of Sciences while developing DHPA, he had few impediments to accessing necessary research tools.[276] Given his leadership position at the time, it is less clear that Holý would develop this thread of antiviral technologies for mostly financial reward instead of genuinely trying to address public health.

269. *See id.*; *see also* Hocek, *supra* note 103 (summarizing Holý's major inventions and other accomplishments over his career).

270. *See, e.g.*, '716 Patent, *supra* note 270.

271. *See, e.g.*, *id.*; *see also* Hocek, *supra* note 103.

272. *See, e.g.*, '716 Patent, *supra* note 270.

273. *See generally Bayh-Dole Act*, *supra* note 97.

274. *See* Hocek, *supra* note 103.

275. *See supra* Section III.B.1.a.

276. *See* Hocek, *supra* note 103.

ii) Impediments to Holý's Tenofovir Research

Holý faced a challenge when Bristol-Myers stopped preclinical development of tenofovir as an antiviral for HIV in 1989.[277] However, this impediment was brief. Gilead restarted this work within the next two years.[278]

b) Drivers for Bristol-Myers and Gilead

Bristol-Myers and Gilead, the two companies that worked in series on the preclinical and clinical development of tenofovir for HIV treatment, had some similar and some distinct motivations and impediments in their work on tenofovir.[279] Bristol-Myers was an established large pharmaceutical company; Gilead was only a small biopharmaceutical startup at the time. Both were motivated to find a tenofovir prodrug that would allow for an oral drug formulation. Some scientists moved from larger companies to a smaller company to develop HIV drug candidates with less strategic resistance to their vision of the value of new HIV treatments. Gilead, as a small and new company, could nimbly explore many prodrugs, within somewhat more constrained resources.

i) Motivations and Impediments for Bristol-Myers

Bristol-Myers initiated tenofovir development through licensing patents from the Czech Academy of Sciences in the late 1980s. It sought to develop an HIV ART that was safer and more effective than AZT and others coming to the market. Yet in the 1989 merger with Squibb, Bristol-Myers decided to gut the HIV therapy development department.[280] Reasons for this decision were not publicized but may have included to pursue lower-risk product portfolios due to the then-nascent field of HIV science. The director of that department, Martin, wanted to continue the development of HIV therapies. Martin had become a part of the AIDS innovation ecosystem and felt a connection to the public health crisis. To the impediment of Bristol-Myers' individual development of other life-saving drugs, Martin found an opportunity to continue this life-saving work at then-startup Gilead.[281]

ii) Motivations for Gilead

Gilead, as a startup, was motivated to find the breakthrough technologies that would put them on the map with investors and then turn a profit by

277. *See id.*
278. *See supra* Section III.B.1.b.
279. *See generally supra* Section III.B.1.
280. *See id.*
281. *See id.*

developing them clinically. Their motivations reflect the aggressive actions they took to execute these strategies.

The first innovation driver for Gilead was their ability to hire leading HIV researchers due to Bristol-Myers' cuts, including Martin.[282] With the flexibility and agility of a fledgling Silicon Valley startup, Gilead's founding CEO Riordan hired Martin and listened to his advice on where to take the startup from a technology standpoint. Together they took Gilead in the direction of NRTI/NtRTI development and away from the "antisense" technology upon which Riordan had founded Gilead.[283]

A second innovation driver for Gilead was the availability of licenses due to Bristol-Myers' cuts. Because Bristol-Myers shelved most HIV projects after the merger with Squibb, including development of tenofovir, a clause in the license agreement with Czech Academy of Sciences allowed the Academy to generate a new exclusive tenofovir patent license, which gave Martin and Gilead an opening to license tenofovir technology.[284]

Gilead's most critical innovation driver was its brute force development of many prodrugs of tenofovir. TDF and other Gilead prodrugs such as tenofovir alafenamide fumarate (TAF) are both now staple products in HIV and even hepatitis B virus treatment.[285]

Gilead patented many prodrug combinations for tenofovir, including TDF. Gilead successfully commercialized TDF alone as Viread.[286]

iii) Impediments for Gilead

Gilead faced headwinds as a startup, from its initial technology platform selection to the financing challenges often faced by startups.

The "anti-sense" technology that Riordan envisioned for the fledgling company was challenging to develop. Fortunately, Riordan course-corrected by hiring Martin and listening to his ideas about how Gilead could become the world's best antiviral company.[287]

Limited funding and people constrained Gilead during the bulk of the tenofovir preclinical development. However, Gilead attracted sufficient investors by doing its work finding safe ARTs.[288]

282. *See id.*
283. *See id.*
284. *See supra* Section III.B.1.b.
285. *See id.*
286. *See id.*
287. *See id.*
288. *See id.*

2. Creators of Emtricitabine

The chemists at Emory University had distinct motivations and faced distinct impediments in their work synthesizing the emtricitabine NRTI product from the motivations and impediments faced by their series of pharmaceutical company development partners, Burroughs-Wellcome, Triangle, and Gilead.

a) Liotta's Motivations and Impediments in the Synthesis of Emtricitabine

Liotta's work on tenofovir was driven by many forces of innovation: entrepreneurial spirit, genius, incremental advances on existing research, brute force, curiosity, serendipity, wide patent ambitions, and more. Yet, Liotta too faced challenges pursuing the invention to commercialization, especially in the form of patent litigation.

i) Liotta's Motivations

Liotta has considered himself a "serial entrepreneur"—consistently creating molecules to try to be the next big drug, not just for fundamental research, and building ties to venture capital and large pharmaceutical companies as potential licensing partners.[289] In this way, Liotta appears to have been motivated to some extent either by the rush of starting new businesses from scratch, the potential profits from such activities, the reputational benefit to his laboratory for doing so, or a combination of the three.[290] This entrepreneurial skill helped Liotta launch emtricitabine before his competitors because he could leverage a "long-standing collaboration" with Burroughs-Welcome scientist Painter to help initiate preclinical trials and other development steps.[291]

Liotta partnered with Schinazi, a virologist also at Emory University. Schinazi observed a cytosine analogue molecule presented as a racemic mixture of two enantiomers at the 1989 International AIDS Conference and suggested Liotta create a more efficient synthesis that purified it further into each enantiomer to develop a powerful anti-HIV ART.[292] Through their novel synthesis and isolation process to obtain only one enantiomer, 3TC, where the

289. *See* Dr. Dennis Liotta, *supra* note 137.
290. *See id.*
291. *See* Liotta & Painter, *supra* note 138, at 2093.
292. *See id.* at 2092.

presenter had not, Liotta and Schinazi acted under both the innovation drivers of genius and of building on others' discoveries.[293]

Liotta applied brute-force methods of attempting many different synthesis paths for the cytosine analogues. He applied his organic chemistry expertise to develop a more-efficient emtricitabine synthesis than his Yale, the University of Georgia, and Glaxo competitors in the race to innovate the best cytosine/cytidine analogs as antiviral drug candidates.[294] This way, he found that fluorinating (adding fluorine) a starting enantiomer mixture created a racemic mixture that was just as effective, or more effective, than the (-) enantiomer of the non-fluorinated cytosine analog.[295] Liotta had been attempting "a variety . . . of nucleoside analogs and evaluating their anti-HIV profiles" but it was pure serendipity that one of those attempts—the fluorinated version—was also *better* metabolized by a patient's cells than the reference cytosine analogue.[296] Liotta had serendipitously created the breakthrough HIV drug FTC, or emtricitabine.

Liotta was also an avid believer in the patent system. As of 2023, he holds more than 100 patents[297] and has fought many patent litigations directly, to both his and Emory University's financial benefit. Emory University owned the first patents to emtricitabine and its precursors and won a patent litigation against the Canadian scientist who presented the precursor molecule at the 1989 International AIDS Conference inspiring Liotta's work.[298] Liotta, who remains at Emory, would help Emory negotiate a sale of the patent rights on emtricitabine to Gilead Sciences.[299]

Liotta was less clearly motivated by the search for tenure at the time of the invention, because he was Chair of Emory's Chemistry Department from 1993–96.[300] He appears to be partially driven by recognition and esteem in his field, having won the Perkin Medal in 2022.[301] Liotta's prior statements suggest he had curiosity in creating emtricitabine and other antivirals driven partly by

293. *See* Emory Univ. v. Glaxo Wellcome Inc., No. 1:96-CV-1868-GET, 1997 WL 817342 (N.D. Ga. July 14, 1997), at *4, *9 (describing how Emory's patent claimed isolation of FTC where Glaxo's patent only claimed the racemic mixture, not FTC in isolation, and denying Glaxo summary judgment partially on this basis).

294. *See supra* Section III.B.2.a.

295. *See* Liotta & Painter, *supra* note 138, at 2094.

296. *See id.*

297. *See* Dr. Dennis Liotta, *supra* note 137.

298. *See supra* Section III.B.2.a.

299. *See id.*

300. *See* Dr. Dennis Liotta, *supra* note 137.

301. *See id.*

a desire to address the terrible AIDS public health crisis and other "viral diseases of global concern."[302]

ii) Impediments Faced by Liotta in Synthesis of Emtricitabine

Liotta's primary impediments to his development and commercialization of emtricitabine came in the form of several patent litigations arising from the early stages of emtricitabine development: both (1) the infringement as well as the ownership and inventorship disputes related to the 1989 International AIDS Conference; and (2) from his work to license emtricitabine to Barry's startup Triangle Pharmaceuticals after Burroughs-Wellcome stopped pursuing emtricitabine's development during the merger with Glaxo.[303] Though the litigations drained Liotta's time and slowed Triangle's progress on emtricitabine, he did ultimately prevail in each suit.[304]

b) Drivers and Impediments for Burroughs-Wellcome and Triangle

The innovation drivers in the commercialization of emtricitabine share many similarities with those in the commercialization of tenofovir. Large pharmaceutical company Burroughs-Wellcome sought to merge with a competitor, Glaxo, and, to minimize risk, cut Glaxo's HIV therapy development projects, including emtricitabine. The spearhead for that division at Burroughs-Wellcome, Barry, would go on to form his own small pharmaceutical company, Triangle, to continue emtricitabine development.

i) Motivations and Impediments for Burroughs-Wellcome

Burroughs-Wellcome shared the same drivers to commercialize emtricitabine that its peer company Bristol-Myers had to commercialize tenofovir: access to a promising technology via licensing; an altruistic desire to develop a clinically safe and effective breakthrough HIV treatment; a large and profitable market opportunity; and bring profit to its shareholders through a merger with a competitor, though this last motivation was equally an impediment to emtricitabine's short-term development.[305]

Also, like Bristol-Myers, Burroughs-Wellcome faced a contractual impediment: if it stopped pursuing clinical development from its licensed patent with Liotta, Liotta and Emory had the right to re-license the patent exclusively to another entity to restart the drug development.[306] However, this

302. *See id.*
303. *See* Liotta & Painter, *supra* note 138, at 2096.
304. *See id.*
305. *See supra* Section IV.B.1.b.
306. *See supra* Section III.B.2.a.

license agreement clause enabled Liotta and Emory University to take emtricitabine's development elsewhere: to Triangle Pharmaceuticals, Inc.

ii) Motivations for Triangle

Barry, an HIV scientist at Burroughs-Wellcome and part of the original team of AZT creators, wanted to continue pursuing emtricitabine's clinical development when Burroughs-Wellcome terminated the project after the merger with Glaxo.[307] When Burroughs-Wellcome abandoned development of emtricitabine, Barry left—just as Martin departed from Bristol-Myers.[308] He exhibited entrepreneurial spirit and founded his own small pharmaceutical company: Triangle. Burroughs-Wellcome, like Bristol-Myers, triggered a release clause in their patent license agreement (for emtricitabine, licensed from Emory), allowing re-license of the molecule from Emory, in this case, to Triangle.[309]

Barry may have been specially motivated to continue HIV therapy development to improve upon his initial helpful (yet toxic) AZT drug at Burroughs-Wellcome.[310]

iii) Impediments Faced by Triangle

Triangle, as a startup, faced challenges that Gilead had encountered only a few years earlier—limited funding and manufacturing capacity to make rapid progress.[311] Yet, Triangle faced distinct challenges in the patent litigations brought against it, Liotta, and Emory University, by Glaxo and the scientist who inspired Liotta's work.[312] Further, Barry died tragically early, leaving the fledgling company without its specially motivated leader. It was beneficial for the company, then, that Gilead found Triangle and its emtricitabine technology to be promising and worthy of acquisition.[313]

C. TRUVADA COMMERCIALIZATION: GILEAD AND PUBLIC SECTOR INNOVATION

Gilead took center stage for HIV treatments in 2001–02, when it received FDA approval for its potent TDF drug (Viread) and negotiated the acquisition of Triangle to fully commercialize emtricitabine and combine it with TDF as Truvada. As public health organizations and agencies driven to mitigate the

307. *See supra* Section III.B.2.b.
308. *See supra* Section IV.B.1.b.
309. *See supra* Section III.B.2.b.
310. *See id.*
311. *Compare id. with* Section IV.B.2.
312. *See supra* Section IV.B.2.a.
313. *See supra* Section III.B.2.b; *see also supra* Section III.C.1.a.

HIV pandemic in new ways took notice of Gilead's HIV treatments, the organizations incorporated Gilead's treatments into trials for public health's next big goal in HIV treatments for that decade: to find a preventive technology. The AIDS innovation ecosystem finally succeeded in doing so with Truvada for PrEP.

1. Truvada as HIV Treatment: Gilead the David Turned Gilead the Goliath

Many innovation drivers motivated and assisted Gilead to launch its blockbuster combination ART against HIV (Truvada). They include: an interest in carrying out a specific brand vision for the company; curiosity; leaders' expertise in HIV therapeutic development; resources to build targeted intellectual property portfolios; institutional collaboration across the AIDS innovation ecosystem; unmet patient need for a once-a-day single pill form of HIV treatment; and resources to acquiring companies and technologies to achieve these broader goals. Gilead's main challenges in this process have arisen out of the Doha Declaration and patent litigation on the Truvada active ingredients or methods of use.

a) Gilead's Motivations for Truvada

Gilead was founded by Riordan and expanded dramatically under Martin, who both sought to build the world's leading antiviral company. Riordan sought to leverage his degrees in engineering, medicine, and business as Gilead's founder.[314] The leaders' goal for Gilead to be the best antiviral maker was consistent with Riordan's initial vision of Gilead as finding treatments for viruses like the flu, common cold, and other common viruses that get in everyday people's way.[315] However, Martin had high ambitions for Gilead to be the leader in ART treatments against HIV, restarting his work from his time at Bristol-Myers on tenofovir to take Gilead down that path.[316] One of Martin's first actions as the second CEO of Gilead (after Riordan retired) was Gilead's acquisition of Triangle to develop market-leading combination therapy for HIV (as Truvada and later Atripla).[317]

The local community in which Gilead has based its operation likely was a driver of its innovation in the HIV space. Gilead's headquarters in San Francisco enabled it to connect with the large Bay Area queer community and HIV patient population, to learn their needs, and to learn how Gilead medicines including ARTs that patients will want to take, could improve their

314. *See supra* Section III.B.1.b.
315. *See id.*
316. *See id.*
317. *See supra* Section III.C.1.a.

quality of life.[318] Gilead developed relationships with AIDS activists during Viread development and leveraged them in the decades that followed to help growth of their HIV product line (including Truvada, Truvada for PrEP, and more).[319] These relationships motivated Gilead to develop a once-a-day, one-pill treatment. Gilead leadership was aware of the loud and sad four-eight-twelve dose alarms that most HIV patients interacting with them used to consistently take their cocktails of multiple HIV treatments.[320] From this angle, Gilead could also see the profit potential from the higher concentration of suffering in the HIV patient community locally than elsewhere.

Gilead was motivated by and secured regulatory exclusivities on its HIV products as they came to market. Gilead received New Chemical Entity status on tenofovir ("Viread") and fast-tracked FDA approval in 2001; they also received both for emtricitabine ("Emtriva"), approved in 2003.[321] Gilead was able to secure accelerated approvals of Truvada through simple bioequivalence studies with its established tenofovir and emtricitabine products, allowing rapid Truvada FDA approval in 2004.[322]

The highly accelerated approvals also reflected public health institutions' support of Gilead in helping each product hit the market. This institutional support for Gilead's work was also shown by the agencies' collaboration with Gilead on PrEP development—including agencies such as NIH/NIAID, the Bill and Melinda Gates Foundation, and other nonprofits.[323] Gilead signed material transfer agreements (MTAs) with public health authorities to provide Truvada-related supplies for clinical trials for PrEP globally in 2001–11.[324] Through this process, the public health authorities began pushing for PrEP and patenting it on their own. The CDC either intentionally or inadvertently patented Truvada for PrEP and recently lost a patent infringement litigation against Gilead.[325]

It appears that for brand or market power or both, Gilead chose a strategy of horizontal integration, opting to buy or license from companies making

318. *See, e.g.*, THE EVOLUTION OF HIV/AIDS THERAPIES, *supra* note 12 (containing clip of Norbert Bischofberger, EVP of R&D at Gilead Sciences, sharing motivations and goals for Atripla and Truvada for HIV treatment at the 20-minute mark).

319. *See supra* Section III.B.1.b.

320. *See* THE EVOLUTION OF HIV/AIDS THERAPIES, *supra* note 12 (describing the 4-8-12 dosing regimen of the first anti-HIV treatments near the 16 minute mark).

321. *See Drug Approval Package: Emtriva® (emtricitabine) 200 mg Tablets*, *supra* note 179; *see also Drug Approval Package: VIREAD® (Tenofovir Disoproxil Fumarate) Tablets*, *supra* note 130.

322. *See Drug Approval Package: Truvada® (Emtricitabine and Tenofovir Disoproxil Fumarate) Tablets*, *supra* note 30.

323. *See supra* Section III.C.2.a.

324. *See id.*

325. *See id.*

ideal active ingredients to use in combination anti-HIV therapies. Buying Triangle for emtricitabine for roughly $400 million and paying outright for the patent rights (around $500 million to Emory) supports this theory.[326] It is notable that Gilead took this unusually aggressive step instead of partnering with Triangle to make combination drugs with emtricitabine, which may have been cheaper to manage for a year or two, but not for the life of the patented invention.[327]

Gilead also made a point to gather patents and other intellectual property (IP) from other sources to help build a targeted portfolio. Gilead turned to Emory and Triangle for acquiring emtricitabine, but also licensed from Czechoslovak Academy of Sciences in Prague under a long-term agreement to develop and commercialize tenofovir.[328] Gilead's extensive testing of different prodrugs of tenofovir for effective metabolism could also be used to support this theory, as they now have a wide array of prodrugs (and corresponding IP protection) to use to expand their product line.[329]

b) Impediments to Gilead's Commercialization of Truvada

Gilead chose to address a public health crisis with its development of HIV treatment, so it has had to respond to international law and policy related to the AIDS crisis. The most major development on this front, TRIPS—the international compulsory licensing system under the World Trade Organization and its 2001 Doha Declaration—pushed Gilead to create a global voluntary licensing program. This program includes licensing their ARTs to third-party local manufacturers in developing nations to produce the same medications at lower cost. In this program, Gilead has negotiated lower rates on its HIV ARTs with developing countries so that it could minimize the number of compulsory license demands by governments, who have only acted on their compulsory license rights a few times for the Truvada active ingredients.[330]

Gilead has had to fend off patent litigation from the CDC and others over the Truvada technology, including design defect suits due to the availability of other prodrugs. However, Gilead has largely succeeded in these cases and managed to avoid major compulsory license fights, so these impediments have not severely hindered its growth.[331]

326. *See supra* Section III.C.1.a.
327. *See id.*
328. *See supra* Section III.B.
329. *See supra* Section III.B.1.b.
330. *See id.*
331. *See supra* Section III.C.2.c; *see also infra* Epilogue (describing the Truvada design defect tort case).

2. *Truvada for PrEP: Public Health Goals Mix with Wide Profitability Potential*

International philanthropic organizations like the Bill and Melinda Gates Foundation were eager to provide support for new technologies that could contain the HIV/AIDS pandemic. Public health institutions were coalescing at the time of the FDA's approval of Viread in 2001 around the idea that HIV ARTs should be attempted as post-exposure prophylaxis (preventive drugs after exposure). Investments in the then-proposed target population coincidentally benefitted PrEP treatment research, which Gilead eventually pursued despite being advised against doing so by certain AIDS activists concerned with changes in the MSM community if PrEP became prevalent.

a) Public Health Goals

The AIDS innovation ecosystem had many motivations to find and launch a PrEP product against HIV. First, the actors involved all wanted to protect vulnerable communities from HIV transmission. The ecosystem wanted to stem the persistent tide of new infections each year, even decades later. This has been especially true for the vulnerable populations in sub-Saharan Africa that have been massively afflicted by the HIV/AIDS pandemic and where most AIDS deaths have been since the 1990s.[332]

However, experts questioned whether this strategy would actually bring case rates down in the United States.[333] Unfortunately, those experts have largely been correct about case rates post-PrEP in the United States so far.[334]

Public health agencies were also motivated to coordinate large-scale international clinical trials with safety and integrity. One of the ways the CDC engages in this costly process is to occasionally patent its clinical methods and to seek licensing partnerships for future clinical trials. The CDC helped conceived of (and pushed for) PrEP to prevent HIV infection and patented Truvada for PrEP against HIV during the PrEP global clinical trials. The CDC specifically patented the treatment of macaques for simian-analogue HIV while they were carrying out an experimental trial on Truvada for PrEP.[335] The CDC's patent rights were later used (to no avail) as an enforcement tool in 2019 to push Gilead to provide more free supplies and services to communities

332. *See supra* Section IV.A.1.

333. *See* THE EVOLUTION OF HIV/AIDS THERAPIES, *supra* note 12 (containing at the 54-minute mark public health experts' brief opinion that PrEP was never intended to really bring the overall pandemic to a new low of transmission or case rates, but is still helpful for the vulnerable communities).

334. *See* Casey, *supra* note 1.

335. *See supra* Section III.C.2.c.

in need of PrEP via a high-stakes patent litigation brought by the CDC and Department of Justice.[336]

However, the health agencies and international philanthropies collaborating on these trials also have serious impediments to their work. Their funding is almost entirely from charitable donations, with some U.S. taxpayer assistance through the CDC and PEPFAR. Also, clinical trials routinely fail to show clinical effectiveness, as demonstrated in the Bill and Melinda Gates-sponsored trial of tenofovir-only as PrEP. These organizations must continually seek funding to support the high cost of this critical work—tens of millions of dollars for each of the major PrEP trials that lead to Truvada for PrEP.[337]

b) PrEP's Unique Commercialization Motives (Gilead)

From a commercialization perspective, Gilead accessed a much larger patient base with a drug to *prevent* HIV infection—gay men, people in sub-Saharan Africa, and other vulnerable community members who do *not* yet have HIV could take the drugs. This presented Gilead with a much greater profitability opportunity for its tenofovir-based products—to use them in otherwise healthy people.

Gilead was pressed by public health authorities, especially after the success of the iPrEx PrEP clinical trial in 2010, to pursue FDA approval of the PrEP indication.[338] Offering discounted PrEP to communities in need would and has helped Gilead improve its image with its consumer bases. Yet, many in the communities vulnerable to HIV believe Gilead is not doing enough to expand access to PrEP to those who need it. A hotbed of AIDS activism kick-started CDC enforcement of Truvada for PrEP patents in 2019, largely due to Congressional hearings with Gilead and CDC scientists who worked on PrEP.[339] Gilead won the enforcement patent litigation, but with HIV case rates persisting at about 30,000–40,000 annually in the United States, there is a strong argument that Gilead could be doing more to improve access to effective PrEP and educational resources to encourage its broader uptake in vulnerable communities.[340]

336. *See id.*
337. *See id.*
338. *See supra* Section III.C.2.a.
339. *See supra* Section III.C.2.c.
340. *See id.*

V. EPILOGUE

The HIV pandemic persists in 2023, with almost the same rate of new infections as since the availability of Truvada for PrEP in 2012: at least one every fifteen minutes.[341] Access to Truvada and its descendant medications for either treatment or PrEP indications has been slowed at least by: (1) stigma from outside and within the communities hit hardest by the pandemic; and (2) a Texas federal judge ruling in 2022 that the Affordable Care Act's mandatory coverage of PrEP medication infringes upon rights created by the Religious Freedom Restoration Act.[342] HIV/AIDS activists continue to raise alarms over the lack of affordable access and the need for improved education around sexual health in affected communities to further reduce the incidence of HIV and other STIs.[343]

Truvada, while imperfect, has greatly improved the lives for people either seeking treatment for HIV or prevention of HIV infection. The kidney and bone system toxicities associated with Truvada have been understood since its component drug, Viread, was associated with those same toxicities years before. Consumers of Truvada have brought many product liability lawsuits against Gilead based on these adverse effects.[344] However, those with access to Truvada can protect themselves from HIV infection or, after infection, rapidly become "undetectable" to stave off AIDS for a normal lifetime. This is no small achievement when compared to the death sentence that HIV/AIDS was for tens of millions in the 1980s and early 1990s.[345]

Though Truvada was not a silver bullet to end HIV/AIDS, leaders in the AIDS innovation ecosystem did not expect it to be.[346] Instead, Truvada and its

341. *See* COMMITTEE ON OVERSIGHT & ACCOUNTABILITY, *supra* note 222, at 11–13 (containing the statement of Dr. Lord to the committee).

342. Braidwood Mgmt. Inc. v. Becerra, No. 4:20-CV-00283-O, 2022 WL 4091215 (N.D. Tex. Sept. 7, 2022) (holding mandatory PrEP coverage by insurance per the Affordable Care Act to be a violation of the Religious Freedom Restoration Act).

343. *See* Rowland, *supra* note 216.

344. *See, e.g.*, Evans v. Gilead Scis., Inc. (D. Hawaii, Aug. 31, 2020, No. 20-CV-00123-DKW-KJM) 2020 WL 5189995 (dismissing Truvada product liability claim citing effective warnings on labels based on clinical trial data); *but see* Gaetano v. Gilead Scis., Inc., 529 F. Supp. 3d 333 (D.N.J. 2021) (denying motion to dismiss Truvada design defect tort claim for Gilead's failure to commercialize their known safer alternative drug design, the tenofovir prodrug called TAF now marketed as Descovy, instead of the tenofovir prodrug called TDF in Truvada).

345. *See* Shilts, *supra* note 7, at 496.

346. *See* THE EVOLUTION OF HIV/AIDS THERAPIES, *supra* note 12 (containing at the 54 minute mark public health experts' brief opinion that PrEP was never intended to really bring the overall pandemic to a new low of transmission or case rates, but is still helpful for the vulnerable communities).

component medicines have had an impressively positive impact on reducing the severity of the HIV/AIDS pandemic, especially in improving the lives of people living with HIV and helping to reduce the stigma associated with having the disabling illness by making PrEP available to at-risk communities.

Truvada represents decades of fundamental research, public policymaking, clinical experience, licensing, mergers and acquisitions, manufacturing, and marketing made possible by a uniquely large public-private coalition of individuals dedicated to a cause. The Truvada story illustrates how both private and public institutions can use the patent system, with all the rights and knowledge-sharing benefits it confers, to drive innovation forward towards more powerful medicines and methods of treatment. The uniquely intersectional AIDS innovation coalition certainly has a role to play in ending the HIV/AIDS pandemic once and for all.

VI. APPENDIX 1: TRUVADA SUMMARY TIMELINE

Year(s)	Key Events
1950s-70s	HIV circulates quietly in sub-Saharan Africa.[347]
1978	In Europe, Holý and De Clercq synthesize DHPA, an antiviral with activity against herpes. DHPA was foundational to their development of tenofovir in the decade after.[348]
1981	First U.S. hospitalizations and deaths due to mysterious disease (later known as AIDS) occur in Los Angeles.[349]
1982	CDC initially names AIDS the "Gay-Related Immune Disorder," contributing to lasting stigma.[350] Congress had appropriated, but the Reagan administration had not spent, $8 million towards AIDS research grants.[351]
1983	Larry Kramer criticizes the U.S. government's inaction on AIDS in his essay *1,112 and Counting*, helping to lead a grassroots movement of AIDS activism.[352] French virologists Barré-Sinoussi and Montagnier isolate HIV, a novel retrovirus, from AIDS patients' cells.[353]

347. *See* Worobey et al., *supra* note 47, at 661–64.
348. *See* De Clercq et al., *supra* note 106, at 563–65.
349. *See A Timeline of HIV and AIDS*, *supra* note 44.
350. *See* Altman, *supra* note 233.
351. Kramer, *1,112 and Counting*, *supra* note 49.
352. *See id.*
353. *See* Barré-Sinoussi et al., *supra* note 8.

Year(s)	Key Events
1984	American scientists also isolate HIV from AIDS patients' cells, confirming the French virologists' findings and building consensus that HIV causes AIDS.[354]
1985	In response to a reporter's question, President Reagan first publicly acknowledges the existence of AIDS.[355] Holý files his first European patent on a class of DHPA-derived nucleoside analogs that included PMPA, known now as "tenofovir."[356]
1986	Holý files his U.S. patent on the class of DHPA derivatives that include PMPA, known now as "tenofovir."[357]
1987	President Reagan gives his first speeches addressing HIV/AIDS, six years into the U.S. crisis, announcing executive orders and Congressional action[358] and settling a dispute among French and U.S. scientists over patent inventorship and ownership of HIV/AIDS test kits.[359] The FDA approves the first treatment for HIV/AIDS: AZT, which was originally created as a cancer treatment.[360] Bristol-Myers licenses Holý and De Clercq's DHPA derivatives for preclinical trials and drug development.[361]
1988	AIDS activist group ACT UP leader Larry Kramer writes *An Open Letter to Dr. Anthony Fauci* in the *San Francisco Examiner*, accusing Fauci of murder (and winning Fauci's attention).[362] ACT UP storms the FDA headquarters in 1988 to demand acceleration of HIV/AIDS treatment R&D and approval.[363] President Reagan and Congress work together to create and fund the first federally legislated AIDS research programs, including the Institute for AIDS Research at NIH.[364]

354. *See* Gallo et al., *supra* note 9; *see also* Levy et al., *supra* note 9.
355. Bennington-Castro, *supra* note 54.
356. *See* '716 Patent, *supra* note 110.
357. *Id.*; *see also Antonín Holý 85 – Story of tenofovir*, *supra* note 109.
358. *See* President Reagan's Remarks at 1987 AIDS Research Awards Dinner, *supra* note 54.
359. *See* President Reagan's Remarks on AIDS Testing Patent Settlement, *supra* note 62.
360. *See Antiretroviral Drug Discovery and Development*, *supra* note 14.
361. *See Antonín Holý 85 – Story of tenofovir*, *supra* note 109.
362. *See* Kramer, *An Open Letter to Dr. Anthony Fauci*, *supra* note 90.
363. *See* Douglas Crimp, *supra* note 91.
364. *See* 42 U.S.C. § 300cc, *supra* note 11; *see also* President Reagan's Remarks at 1987 AIDS Research Awards Dinner, *supra* note 54.

Year(s)	Key Events
1989	Squibb merges with Bristol-Myers to form Bristol-Myers Squibb, and the new company stops development of Holý and De Clercq's DHPA derivatives as well as other HIV antivirals.[365] Schinazi attends the Fifth International Conference on AIDS and observes a poster describing the synthesis of racemic 3TC, a compound with anti-HIV activity, and reports back to his Emory University colleague Liotta suggesting the synthesis can be improved.[366] The two begin research on 3TC synthesis.
1990	Activists with ACT UP storm the NIH, demanding more treatments brought to market than just AZT.[367]
1991	Startup company Gilead Sciences, Inc., at recommendation of its recently hired Bristol-Myers alumnus Martin, licenses Holý and De Clercq's DHPA derivatives for drug development after the Bristol-Myers DHPA license lapsed in 1989.[368] Liotta and Schinazi file a patent on the method of synthesis and prodrug analogs of FTC,[369] later known as emtricitabine.
1992	The FDA announces the Accelerated Approval Program for small-molecule drugs that "fill an unmet," yet serious, "medical need"—primarily in response to AIDS activism.[370]
1995	Gilead's simian trial of tenofovir is the first to demonstrate tenofovir's effectiveness in preventing HIV replication.[371] Liotta and Schinazi file the composition and method of treatment patent on FTC,[372] later known as emtricitabine. Glaxo purchases Burroughs-Wellcome—the pharma company that Liotta's team had licensed emtricitabine development rights to in the 1992–94 timeframe—laying off thousands of workers and abandoning its emtricitabine clinical development and IND application in the process.[373]
1996	Burroughs-Wellcome HIV team leader Barry leaves Glaxo-Wellcome to found Triangle which licenses anew Liotta and company's emtricitabine for clinical development.[374]

365. *See Antonín Holý 85 – Story of tenofovir*, *supra* note 109.
366. *See* Liotta & Painter, *supra* note 138, at 2092.
367. *See A Timeline of HIV and AIDS*, *supra* note 22.
368. *See* FORBES, *supra* note 119; *see also* John C. Martin, *supra* note 121.
369. *See* '085 Patent, *supra* note 148.
370. *See* AVALERE, *supra* note 95.
371. *See* Tsai et al., *supra* note 122.
372. U.S. Patent No. 6,642,245 B1 (filed June 7, 1995) (assigned to Emory University).
373. *See* Liotta & Painter, *supra* note 138, at 2095.
374. *See id.*

Year(s)	Key Events
	UNAIDS, the UN's strategic response organization for AIDS, launches to assist the growing scale of the pandemic in developing countries.[375]
1997	Gilead's years of prodrug development for tenofovir pay off with the identification of an effective prodrug, tenofovir disoproxil fumarate (TDF), from preclinical studies in dogs.[376] Triangle submits a renewed IND for emtricitabine.[377]
1998	Emtricitabine receives "Fast Track" status with the FDA.[378] Gilead publishes clinical study results showing tenofovir's effectiveness in treating HIV in humans.[379]
2000	The 2000 International AIDS Conference is contentious, as developing nations, especially those in sub-Saharan Africa, plead with wealthy nations and aid organizations for help with the growing HIV/AIDS crisis in their nations.[380]
2001	The WTO adopts the Doha Declaration on TRIPS and Public Health, providing for WTO member states the right issue compulsory licenses for "national emergencies" and other "urgent" circumstances.[381] The FDA approves Gilead's TDF under the trade name Viread, just six months after Gilead filed the New Drug Application, under the Accelerated Approval Program.[382]
2002	Triangle submits its New Drug Application to the FDA for emtricitabine to treat HIV, the same year Emory settled patent litigation over disputed inventorship, ownership, and infringement of the same drug.[383] After Triangle founder Barry died in early 2002, Gilead in December 2002 offered to purchase Triangle, primarily to build a combination therapy of tenofovir and emtricitabine.[384]
2003	Gilead secures FDA approval for emtricitabine with the trade name Emtriva, having maintained the "Fast Track"-status New Drug Application that Triangle started the year before.[385]

375. *See* UNAIDS, *supra* note 81.
376. *See* Shaw et al., *supra* note 126.
377. *See* Liotta & Painter, *supra* note 138, at 2095.
378. *See id.*
379. *See* Deeks et al., *supra* note 107.
380. *See* THE EVOLUTION OF HIV/AIDS THERAPIES, *supra* note 68 (describing at the thirty minute mark rationale for creation of the Global Fund and PEPFAR).
381. *See* DOHA DECLARATIONS, *supra* note 84, at 24–25.
382. *See Drug Approval Package: VIREAD® (Tenofovir Disoproxil Fumarate) Tablets*, *supra* note 130.
383. *See* Liotta & Painter, *supra* note 138, at 2096.
384. *See* Alton, *supra* note 175.
385. *See Drug Approval Package: Emtriva® (emtricitabine) 200 mg Tablets*, *supra* note 179.

Year(s)	Key Events
2004	Gilead completes New Drug Application paperwork and later that same year receives approval for Truvada, the combination HIV treatment of tenofovir disoproxil fumarate and emtricitabine.[386] President Bush creates PEPFAR to combat the HIV/AIDS pandemic by funding the equitable distribution of treatments to developing nations globally.[387] Gilead enters into the first MTA with the CDC to support the CDC's clinical trials of Truvada for PrEP—Truvada consumed daily to *prevent* HIV infection, not just treat it.[388]
2005	Gilead fully purchases, instead of licenses, the patent rights to emtricitabine from Emory University for $525 million.[389]
2006	The CDC begins filing method of treatment patents on Truvada for PrEP using the findings of its clinical trials.[390]
2010	The iPrEx clinical trial concludes and initially reports regular Truvada consumption is 92% effective at preventing the spread of HIV (the effectiveness is later found to be 99%).[391]
2011	Gilead files a Supplementary New Drug Application with the FDA for a new indication of Truvada: Truvada for PrEP.[392]
2012	Gilead secures FDA approval for Truvada for PrEP.[393]
2019	Congress holds hearings interrogating Gilead and HIV scientists about Truvada's slow uptake as PrEP, where Representative Ocasio-Cortez makes the case for the U.S. government to enforce the CDC's patents against Gilead.[394] The U.S. Department of Justice sues Gilead for infringement of the CDC's patents on Truvada for PrEP.[395]
2023	A jury found invalid, and nevertheless that Gilead did not infringe, the CDC's patents.[396]

386. *See Drug Approval Package: Truvada® (Emtricitabine and Tenofovir Disoproxil Fumarate) Tablets*, *supra* note 30.

387. *See A Timeline of HIV and AIDS*, *supra* note 48.

388. *See* Gilead Scis., Inc. v. United States, 155 Fed. Cl. 336, 339.

389. *See* Emory Univ., *supra* note 177.

390. *See* '509 Patent, *supra* note 201.

391. *See* Grant et al., *supra* note 204, at 2597.

392. *See* Glazek, *supra* note 207.

393. *See* U.S. Food and Drug Administration Approves Gilead's Truvada® for Reducing the Risk of Acquiring HIV, *supra* note 213.

394. *See* House Committee on Oversight & Accountability, *supra* note 220.

395. *See* United States v. Gilead Scis., Inc., 2019 WL 5942984 (D. Del.) (Trial Pleading).

396. *See* The Editorial Board, *supra* note 228.

HOW KETAMINE BECAME AN ANTIDEPRESSANT

Vincent Joralemon[†]

TABLE OF CONTENTS

DOI: https://doi.org/10.15779/Z38W08WH8B

† J.D. Candidate, University of California, Berkeley, School of Law, Class of 2024; Petrie-Flom Student Fellow, Harvard Law School. This article benefitted from helpful comments from Peter Menell, Allison Schmitt, and Caressa Tsai.

I. INTRODUCTION

This Article examines the anomalous story surrounding the use of ketamine to treat depression. Although first discovered, developed, and patented half a century ago (albeit for use as an anesthetic), use of ketamine is now seen by many clinicians as "one of the most significant advances in the field of depression" in recent years.[1] Yet challenges related to intellectual property protection, regulatory exclusivity and approval, and insurance coverage are hampering further research on and deployment of ketamine for depression treatment. Despite these obstacles, access to ketamine is expanding. This expansion creates concerns about a lack of oversight, but also showcases the ingenuity of clinicians and researchers working to broaden access to the drug.

Part II of this Article traces the history of the recognition of depression as a treatable condition and the development of treatment approaches during the mid to late 20th century. Part III discusses the promises and pitfalls of ketamine as a depression treatment. Part IV explores the complex institutional impediments to ketamine's wider study and use for depression. Part V analyzes how entrepreneurs and clinicians are innovatively expanding access to ketamine, despite these obstacles.

II. THE HISTORY OF DEPRESSION AND DEPRESSION THERAPIES IN THE UNITED STATES

Depression is one of the most prevalent diagnosed conditions in the world. Yet, clinicians have protean views on a precise definition and what constitutes effective treatment. Over the centuries, clinicians have implemented a wide range of physical and psychological interventions with varying degrees of success. However, pharmacologic advances in the 20th century saw marked improvements in treatment, which culminated in the widespread adoption of selective serotonin reuptake inhibitors (SSRIs). Despite these advances, gaps in treatment persisted. Scientists thus looked beyond the monoamine focus that defined mid-1900s antidepressant pharmaceutical interventions, precipitating a shift towards glutamate-modulating drugs like ketamine.

1. Ronald S. Duman & George K. Aghajanian, *Neurobiology of Rapid Acting Antidepressants: Role of BDNF and GSK-3β*, 39 NEUROPSYCHOPHARMACOLOGY 233, 233 (2014).

A. DEFINING DEPRESSION

Depression has been defined in various terms since at least the time of Hippocrates.[2] While the first and second editions of the *Diagnostic and Statistical Manual of Mental Disorders* (DSM), DSM-I (1952)[3] and DSM-II (1968),[4] contained diagnostic criteria for "depressive reaction" and "depressive neurosis," respectively, the fourth edition (DSM-IV) codified the modern definition of depression in 1994.[5] The DSM-IV defined depression based on the presence of clinical features such as depressed mood, fatigue, and loss of interest or pleasure.[6] The DSM-IV diagnosis also acknowledged the possibility of both psychological and biological causes.[7]

Major Depressive Disorder (MDD) is now the most commonly diagnosed mood disorder in the United States and one of the most prevalent disabilities in the world.[8] According to the DSM-V (the fifth and current iteration of the DSM), individuals with MDD exhibit a minimum of five depressive symptoms nearly every day for at least two weeks, which are newly presented or clearly worsened prior to the onset of the depressive episode.[9] The symptoms include a depressed mood, loss of interest or pleasure, fatigue, feelings of worthlessness, diminished ability to concentrate, and suicidal ideation.[10] For a diagnosis of MDD, these symptoms must rise to the level of significantly impairing social or occupational functioning, and must also not be attributed to substance abuse or better explained by other psychological disorders (e.g., schizophrenia, bipolar, etc.).[11]

---

2. Eugene S. Paykel, *Basic Concepts of Depression*, 10 DIALOGUES IN CLINICAL NEUROSCIENCE 279, 279 (2008). Hippocrates characterized depression as "melancholia" defined by "fears and despondencies." HIPPOCRATES, APHORISMS § 6.23.

3. AMERICAN PSYCHIATRIC ASSOCIATION, DIAGNOSTIC AND STATISTICAL MANUAL OF MENTAL DISORDERS (1st ed. 1952).

4. AMERICAN PSYCHIATRIC ASSOCIATION, DIAGNOSTIC AND STATISTICAL MANUAL OF MENTAL DISORDERS (2nd ed. 1968).

5. Paykel, *supra* note 2, at 280; AMERICAN PSYCHIATRIC ASSOCIATION, DIAGNOSTIC AND STATISTICAL MANUAL OF MENTAL DISORDERS 339 (4th ed. 1994).

6. Paykel, *supra* note 2, at 280–81.

7. *Id.*

8. Todd M. Hillhouse & Joseph H. Porter, *A Brief History of the Development of Antidepressant Drugs: From Monoamines to Glutamate*, 23 EXPERIMENTAL & CLINICAL PSYCHOPHARMACOLOGY 1, 1 (2015); Anna Beyeler, *Do Antidepressants Restore Lost Synapses?*, 364 SCI. 129, 129–30 (2019).

9. AMERICAN PSYCHIATRIC ASSOCIATION, DIAGNOSTIC AND STATISTICAL MANUAL OF MENTAL DISORDERS (5th ed. 2013).

10. *Id.*

11. *Id.*

B. THE EVOLUTION OF MODERN DEPRESSION THERAPIES

Since the early diagnoses of "melancholia," clinicians have explored a wide range of interventions to treat depression. Early interventions included plant extracts from poppy (opium), nightshade (belladonna), hemp, and St. John's wort.[12] These were often used alongside other psychotherapeutic measures, such as music, dancing, theatre, and sleep therapies.[13] The 1800s saw the evolution of pharmaceutical interventions for depression, with documented uses of bromine salts (1826), codeine (1832), chloral hydrate (1869), and paraldehyde (1882).[14] Finally, barbiturates, which work primarily through sedation, gained popularity in the late 1800s as treatments for "agitated" patients suffering from depression.[15]

The late 1800s also saw the advent of Western modern psychotherapy and Freudian psychoanalysis. Early psychoanalysts such as Freud and Jung pioneered therapeutic interventions that aimed to improve patients' suffering from a range of mental disorders, including depression.[16] In the 1920s, behaviorism gained traction as a remedy for depression, based on theories outlined by B. F. Skinner and others researching operant and classical conditioning.[17]

In the 20th century, clinicians began implementing physiological interventions for patients suffering from mental illness.[18] These included recreational, occupational, and physical treatments, including electroconvulsive therapy.[19] Then, in 1944, penicillin demonstrated efficacy in a large-scale clinical trial, launching a new era of pharmaceutical interventions for psychiatric illnesses.[20] Researchers were soon on the hunt for novel drug therapies to treat depression.[21]

---

12. T. R. Payk, *Treatment of Depression*, 7 J. GERIATRIC PSYCHIATRY 3, 3 (1994).
13. *Id.*
14. *Id.*
15. *Id.*
16. Suzanne K. Haddad et al., *Depression and Internally Directed Aggression: Genetic and Environmental Contributions*, 56 J. AM. PSYCHOANALYTIC ASS'N 515, 515–18 (2008); Warren Steinberg, *Depression: A Discussion of Jung's Ideas*, 34 J. ANALYTIC PSYCHOLOGY 339, 339–42 (1989).
17. Paulo Roberto Abren & Carlos E. Santos, *Behavioral Models of Depression: A Critique of the Emphasis on Positive Reinforcement*, 4 INT'L J. BEHAV. CONSULTATION & THERAPY 130 (2008).
18. CHRISTOPHER M. CALLAHAN & GERMAN E. BERRIOS, REINVENTING DEPRESSION: A HISTORY OF THE TREATMENT OF DEPRESSION IN PRIMARY CARE, 1940–2004 88–89 (2004).
19. *Id.* at 89.
20. *Id.* at 92.
21. *Id.* at 92.

As the field of pharmacology developed, researchers synthesized more drugs that helped alleviate the symptoms of mental illness. By the second half of the 20th century, antidepressant medications became the primary tools to combat depression.[22] Drugs such as Prozac and Lexapro proved inexpensive, effective, and relatively safe.[23]

Understanding the development and progression of these drug therapies sets the stage for the use of ketamine as an antidepressant today. Many of the discoveries associated with ketamine's antidepressant qualities were made possible by attentive researchers, who followed up based on observations of their trial patients. Amidst these stories, a recurrent theme of clinical diligence emerges, highlighting the value of thorough observation and controlled experimentation to pursue curious scientific leads. The following Sections provide a history of seven notable 20th century therapeutics that preceded ketamine's ultimate discovery as an antidepressant.

22. Joshua Gordon, *New Hope for Treatment-Resistant Depression: Guessing Right on Ketamine*, NAT'L INST. MENTAL HEALTH DIRECTOR'S MESSAGES (Aug. 13, 2019), https://www.nimh.nih.gov/about/director/messages/2019/new-hope-for-treatment-resistant-depression-guessing-right-on-ketamine.

23. *Id.*

Table 1: Notable 20th Century Antidepression Pharmacologic Therapeutics.

Drug	Indication	Year Discovered	FDA Approval for Depression	Years Used as an Antidepressant
Lithium	Depression, bipolar disorder	1948	1970	1970 – present
Monoamine Oxidase Inhibitors	Depression	1952	1958 (iproniazid)	1972 – present
Tricyclic Antidepressants	Depression, neuropathic pain, migraine, etc.	1951	1959 (imipramine)	1957 – present
Meprobamate	Anxiety	1950	1959	1959 – present
Benzodiazepines	Anxiety, insomnia, seizures, muscle relaxant, etc.	1950	1960	1960 – present
Diazepam	Anxiety, sedation, etc.	1959	1963	1963 – present
Selective Serotonin Reuptake Inhibitors	Depression, OCD, panic attacks, etc.	1972	1987	1986 – present

1. Lithium

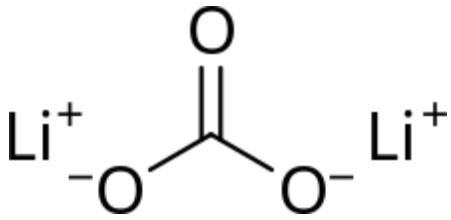
The discovery story of lithium as a therapeutic vividly demonstrates how coincidence followed by scientific diligence can lead to novel therapies. During World War II, Japanese troops captured and interned John F. Cade for over three years at a prisoner-of-war camp at Changi in Singapore.[24] A physician by training, Cade was put in charge of the camp's psychiatric section. While there, he noted a link between certain food deficiencies and diseases in some of the patients.[25] After the war, he homed in on one of those correlations to test his hypothesis that depression might result from "an abnormally low level" of uric acid in the bloodstream.[26]

24. Douwe Draaisma, *Lithium: The Gripping History of a Psychiatric Success Story*, 572 NATURE 584, 584 (2019).

25. *Id.*

26. Edward Shorter, *The History of Lithium Therapy*, 11 CAN. INSTS. HEALTH RSCH. 1, 2–3 (2013).

Figure 1: Lithium Carbonate, Used for Depression and Bipolar Disorder Treatments.[27]



Working out of an abandoned pantry in an under-resourced mental hospital near Melbourne, Cade explored his hypothesis by injecting uric acid into patients and monitoring the effects. Because uric acid is so toxic in the bloodstream, Cade used lithium urate (a known pharmacologic treatment for gout at the time) as an alternative in initial animal studies, because lithium can help modulate the toxicity of uric acid in humans.[28] Although his initial findings showed promise, Cade diligently sought to control for the additives he included in his treatments. To assess whether the lithium component of the treatment itself induced the positive results, Cade injected pure lithium into his subjects and observed a prolonged "placid state."[29] In 1948, after he experimented on himself and ten other patients with a range of psychiatric diagnoses, Cade reported significant improvements in the patients' "agitation."[30]

Cade's research spawned further investigation into the psychopharmacological effects of lithium, including a breakthrough random control study by Erik Strömgren in 1952, which showed that the drug served as a useful alternative to electroconvulsive therapy for patients with bipolar disorder.[31] The FDA approved lithium as a depression treatment in the 1970s, and today, millions of patients use it as a mood stabilizer for bipolar disorder.[32]

Lithium is largely credited with setting off the "psychopharmacological revolution" of the 1950s that eventually led to the discovery of numerous antipsychotics and antidepressants.[33] Although lithium is FDA-approved and primarily prescribed for patients with bipolar disorder, it is frequently used to

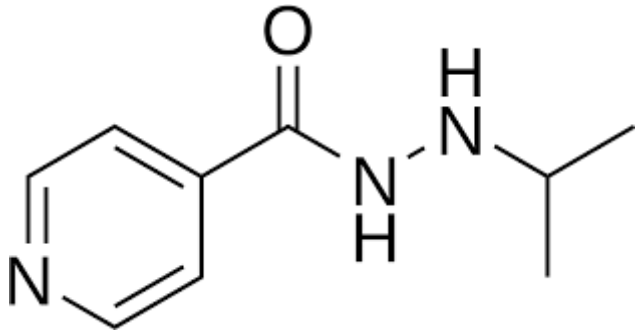
27. *Lithium (medication)*, WIKIPEDIA, https://en.wikipedia.org/wiki/Lithium_(medication) (last visited Nov. 1, 2023).
28. CALLAHAN & BERRIOS, *supra* note 18, at 95.
29. *Id.*
30. *Id.* at 95–96.
31. Shorter, *supra* note 26, at 3.
32. Draaisma, *supra* note 24, at 585.
33. *Id.*

treat depression.[34] Clinicians occasionally treat patients not responding to other antidepressants with lithium; some showcase promising results.[35] However, because of toxicity and efficacy concerns, it is typically not prescribed as an primary antidepressant.[36]

2. Monoamine Oxidase Inhibitors

The synthesis of monoamine oxidase inhibitors (MAOIs) follows a similar trajectory of observant clinicians exploiting unanticipated side effects of preexisting pharmaceuticals. In the aftermath of World War II, Germany had a large and inexpensive supply of hydrazine because the military used the compound as rocket fuel in the war.[37] Access to this compound led investigators to experiment with the use of hydrazine derivatives for a wide variety of applications, including treatment for tuberculosis.[38]

Figure 2: Iproniazid, the First MAOI Widely Used to Treat Depression.[39]



Clinicians using a hydrazine derivative for tuberculosis noted a peculiar side effect—many patients became euphoric when given the compound.[40] These unexpected effects motivated researchers to test the use of related compounds as a treatment for depression. Columbia University Professor Nathan Kline eventually established that these hydrazine derivatives—a class of drugs that came to be known as MAOIs—effectively treated depression in

34. Mark L. Ruffalo, *A Brief History of Lithium Treatment in Psychiatry*, PSYCHIATRIST (Oct. 12, 2017), https://www.psychiatrist.com/pcc/history-of-lithium-treatment-in-psychiatry/.

35. Tom Bschor, *Lithium in the Treatment of Major Depressive Disorder*, 74 DRUGS 855, 855 (2014).

36. Shorter, *supra* note 26, at 6.

37. CALLAHAN & BERRIOS, *supra* note 18, at 97.

38. *Id.*

39. *Iproniazid*, WIKIPEDIA, https://en.wikipedia.org/wiki/Iproniazid (last visited Nov. 1, 2023).

40. *Id.*

many patients.[41] One of these derivatives, iproniazid, was the first MAOI widely prescribed for depression.[42]

MAOIs help to alleviate depressive symptoms by blocking the monoamine oxidase enzyme responsible for breaking down neurotransmitters such as norepinephrine, serotonin, and dopamine.[43] Despite early promising treatment results, MAOIs caused undesirable side effects such as jaundice, headaches, and elevated blood pressure, causing the drugs to soon fall out of favor.[44] While doctors in the United States continue to prescribe MAOIs as antidepressants, these prominent side effects have prevented widespread adoption.[45]

3. Tricyclic Antidepressants

The discovery of tricyclic antidepressants (TCAs) continues this pattern of clinical diligence. The TCA story begins with chlorpromazine, a compound synthesized in 1951 as an antihistamine and potentiator for anesthetics.[46] As a medic in the French army, Henri Laborit discovered chlorpromazine's antidepressant effect while using the drug as a part of his "anesthetic cocktail."[47] Laborit observed that patients given chlorpromazine experienced "disinterest without loss of consciousness," and convinced his medical associates to try the drug with patients in a psychiatric setting.[48] Over repeated administrations, chlorpromazine effectively calmed "agitated" individuals. As a result, clinicians adopted the drug for a variety of psychiatric applications.[49]

Another researcher at an asylum in Switzerland, Roland Kuhn, also became interested in chlorpromazine. Faced with a limited budget, Kuhn contacted the pharmaceutical company Geigy to see if they had any available antipsychotic drugs to provide in exchange for his clinical data.[50] Geigy agreed, allowing Kuhn to commence experimental treatments for his schizophrenic patients with the chlorpromazine derivative imipramine.[51] Although

41. *Id.* at 98.

42. Hillhouse & Porter, *supra* note 8, at 4–5.

43. Tahrier Sub Laban & Abdolreza Saadabadi, *Monoamine Oxidase Inhibitors (MAOI)*, *in* STATPEARLS 1, 1 (2022).

44. CALLAHAN & BERRIOS, *supra* note 18, at 98.

45. *Id.*

46. *Id.* at 99.

47. Thomas A. Ban, *Fifty Years Chlorpromazine: A Historical Perspective*, 3 NEUROPSYCHIATRIC DISEASE & TREATMENT 495, 496 (2007).

48. *Id.*

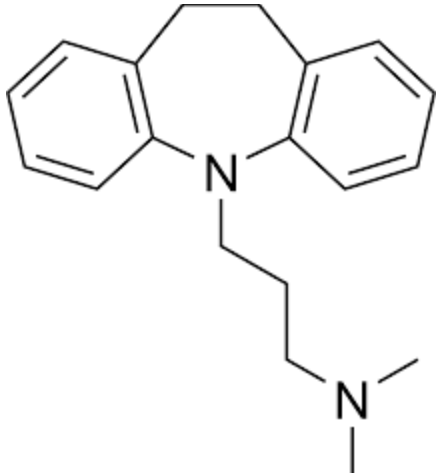
49. *Id.*

50. Charles Cahn, *Roland Kuhn, 1912–2005*, 31 NEUROPSYCHOPHARMACOLOGY 1096, 1096 (2006).

51. CALLAHAN & BERRIOS, *supra* note 18, at 99.

imipramine proved ineffective in his trials, he observed an excitatory effect that suggested to him that the drug might be used as an antidepressant.[52] In subsequent trials, Kuhn showed that imipramine was an effective antidepressant for many patients.[53]

Figure 3: Imipramine, the First FDA-Approved TCA.[54]

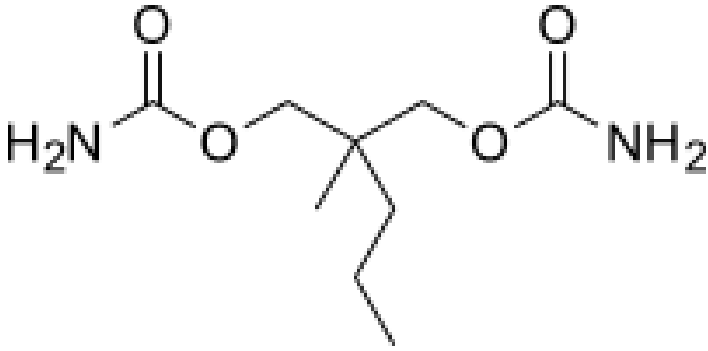


Imipramine established the class of "tricyclic antidepressants" (TCAs).[55] TCAs, like MAOIs, primarily aided the symptoms of depression through the reuptake inhibition of monoamines (namely, serotonin and norepinephrine).[56] The FDA approved imipramine for depression in 1959, and it—along with numerous other TCAs—is still prescribed for depression today.[57] Despite imipramine's efficacy, pharmaceutical companies did not aggressively market it or any other TCAs for depression because of concerns about time lag for efficacy and the narrow range of patients who might use the drug.[58]

52. *Id.*
53. *Id.* at 100.
54. *Imipramine*, WIKIPEDIA, https://en.wikipedia.org/wiki/Imipramine (last visited Nov. 1, 2023).
55. Hillhouse & Porter, *supra* note 8, at 6.
56. *Id.*
57. *Id.*
58. Imipramine has dangerous interactions with other medications, is not recommended for patients with a history of heart problems, and can cause side effects such as blurry vision, dry mouth, and eye pain. For these reasons, it is seldom used as an appropriate treatment for depression. *See* CALLAHAN & BERRIOS, *supra* note 16, at 100.

4. Meprobamate, Benzodiazepine, Diazepam, and the Search for Effective Antidepressants for Wider Populations

Figure 4: Meprobamate, One of the First Widely Used GABA-Modulating Antidepressants.[59]



Despite promising results from lithium, MAOIs, and TCAs, none of these drugs dominated the depression market due to inadequate safety and efficacy profiles.[60] So, scientists continued their search for drugs that could treat depression for a wide range of populations with limited side effects. In the late 1950s, Wallace Laboratories began to market and sell meprobamate for patients with mild to moderate psychiatric conditions.[61] It soon became one of the most widely prescribed drugs in the world, inspiring other pharmaceutical companies to market competing drugs.[62] Unlike the MAOIs and TCAs, meprobamate binds to gamma-aminobutyric acid (GABA) receptors, modulating GABA levels.[63] GABA is a neurotransmitter that blocks specific signals in the central nervous system, producing a calming effect.[64]

59. *Meprobamate*, WIKIPEDIA, https://en.wikipedia.org/wiki/Meprobamate (last visited Nov. 1, 2023).

60. *Id.*

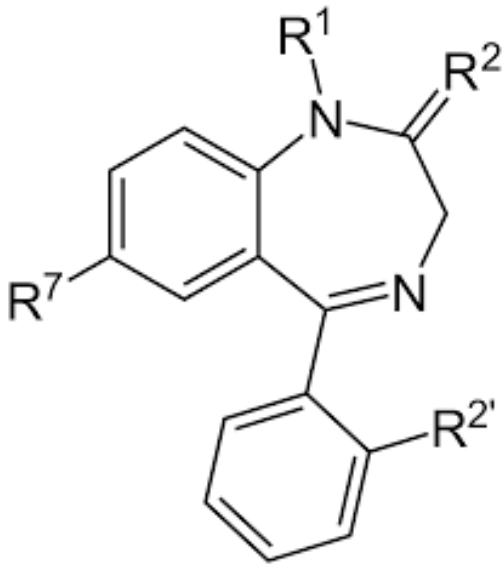
61. *Id.* at 106.

62. *Id.*

63. Manish Kumar & Glenn H. Dillon, *Assessment of direct gating and allosteric modulatory effects of meprobamate in recombinant $GABA_A$* receptor, 775 EUR. J. PHARMACOLOGY 149, 149 (2016).

64. Piril Hepsomali et al., *Effects of Oral Gamma-Aminobutyric Acid (GABA) Administration on Stress and Sleep in Humans: A Systematic Review*, 14 FRONTIERS IN NEUROSCIENCE 923, 923.

Figure 5: Benzodiazepine, the Most Frequently Prescribed Psychiatric Medication in the Late 1950s and Early 1960s.[65]



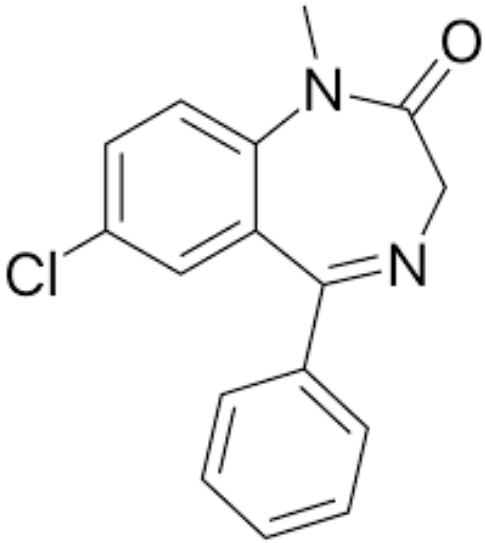
However, meprobamate was soon overtaken in popularity by another GABA-modulating drug—benzodiazepine. Leo Sternbach discovered benzodiazepine serendipitously, after accidentally leaving a meprobamate analog on the laboratory shelf for too long.[66] Benzodiazepine worked effectively to relax patients without sedation, and quickly overcame meprobamate as the most frequently prescribed psychiatric medication in the late 1950s and early 1960s.[67]

65. *Benzodiazepine*, WIKIPEDIA, https://en.wikipedia.org/wiki/Benzodiazepine (last visited Nov. 1, 2023).

66. CALLAHAN & BERRIOS, *supra* note 18, at 107.

67. *Id.*

Figure 6: Diazepam (Marketed as Valium), Which Proved More Effective as a Tranquilizer than an Antidepressant.[68]



Sternbach continued researching antidepressants and developed diazepam in the 1960s.[69] This drug, marketed under the brand name "Valium," quickly overcame benzodiazepine as the most widely prescribed antidepressant in the United States, and the most commonly prescribed drug in the world.[70] Like benzodiazepine, Valium is a GABA modulator.[71] Valium hit a "sweet spot" for psychiatrists and primary care providers by proving effective for large populations of patients with relatively few side effects.[72] However, clinicians primarily used Valium as a tranquilizer rather than an antidepressant.[73]

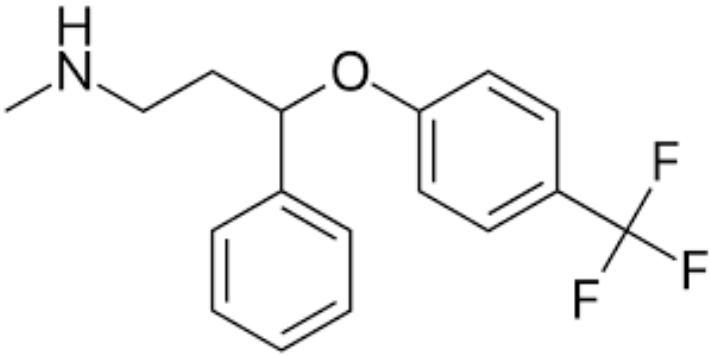
5. A Breakthrough Depression Treatment: Selective Serotonin Reuptake Inhibitors

Although physicians prescribed MOAIs, TCAs, and other pharmaceuticals such as Valium and lithium for depression through the 1970s, each drug

68. *Diazepam*, WIKIPEDIA, https://en.wikipedia.org/wiki/Diazepam (last visited Nov. 1, 2023).
69. *Id.*
70. *Id.*
71. Jaberpreet S. Dhaliwal et al., *Diazepam*, *in* STATPEARLS 1, 2 (Jan. 2022).
72. CALLAHAN & BERRIOS, *supra* note 18, at 107.
73. *Id.*

exhibited undesirable adverse effects or off-target pharmacological activity.[74] Researchers thus remained motivated to find a drug that could effectively treat a broad range of patients with depression while minimizing side effects.

Figure 7: Fluoxetine (Marketed as Prozac), Which Became the Most Prescribed Antidepressant in the United States by 1990.[75]



Inspired by the mechanisms of action of both the MAOIs and TCAs, pharmacologists at Eli Lilly spent much of the 1960s and 1970s searching for drug alternatives that might modulate neural serotonin levels.[76] At the time, various psychiatric conditions, including depression, were associated with reduced serotonin levels. So, the Eli Lilly researchers synthesized several compounds that they hypothesized might cause serotonin reuptake inhibition, which would lead to increased serotonin neurotransmission in patients suffering from depression.[77] Medicinal chemistry and animal studies eventually led to the discovery of a drug called fluoxetine, which served as a potent serotonin reuptake inhibitor with relatively few side effects in mice.[78]

Eli Lilly published the synthesis and activity of fluoxetine in 1974, and in 1983, Dista Products Company (a division of Eli Lilly) filed a New Drug

74. Laura Fitzpatrick, *A Brief History of Antidepressants*, TIME (Jan. 7, 2010), https://content.time.com/time/health/article/0,8599,1952143,00.html.

75. *Fluoxetine*, WIKIPEDIA, https://en.wikipedia.org/wiki/Fluoxetine (last visited Nov. 1, 2023).

76. David T. Wong et al., *Prozac (Fluoxetine, Lilly 110140), the First Selective Serotonin Uptake Inhibitor and an Antidepressant Drug: Twenty Years Since its First Publication*, 57 LIFE SCIS. 411, 416 (1995).

77. *Id.*

78. *Id.*

Application for fluoxetine with the FDA.[79] The FDA approved fluoxetine for use in depression in 1987, and it hit the market under the brand name "Prozac."[80]

Prozac was immediately successful. By 1989, the drug brought in more money than had been spent annually on all antidepressants combined in 1987, adjusted for inflation.[81] By 1990, Prozac was the most prescribed antidepressant in the United States.[82] By 1993, clinicians prescribed the drug to over ten million people globally, and *Newsweek* noted that "Prozac has attained the familiarity of Kleenex and the social status of spring water."[83]

Several other SSRIs marketed for depression treatment soon entered the market: sertraline (Zoloft) in 1991; paroxetine (Paxil) in 1992; fluvoxamine (Luvox) in 1994; citalopram (Celexa) in 1998; and escitalopram (Lexapro) in 2002.[84] At last, scientists had developed antidepressants that safely and effectively worked on wide populations of individuals.

However, gaps in treatment remained. Although SSRIs presented relative improvements over prior treatment options, these compounds were not a "magic bullet" for all patients—many still failed to achieve depression remission even with SSRIs. Further, SSRIs come with a litany of potential side effects, with gastrointestinal disturbances, sexual dysfunction, weight gain, and sleep disturbances among the most commonly reported adverse events.[85]

79. David T. Wong et al., *The Discovery of Fluoxetine Hydrochloride (Prozac)*, 4 NATURE REVS. DRUG DISCOVERY 764, 770 (2005).

80. *Id.* at 770–71.

81. Fitzpatrick, *supra* note 74.

82. *Id.*

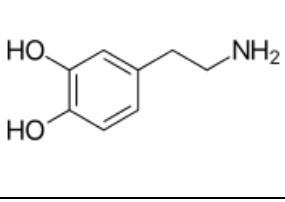
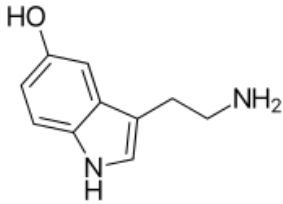
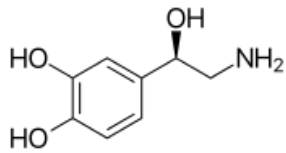
83. *Id.*

84. *See Orange Book: Approved Drug Products with Therapeutic Equivalence Evaluations*, U.S. FOOD & DRUG ADMIN., https://www.accessdata.fda.gov/scripts/cder/ob/results_product.cfm?Appl_Type=N&Appl_No=019839#3392 (Zoloft) (last visited Oct. 6, 2023); https://www.accessdata.fda.gov/scripts/cder/ob/results_product.cfm?Appl_Type=N&Appl_No=020031#3487 (Paxil) (last visited Oct. 6, 2023); https://www.accessdata.fda.gov/scripts/cder/ob/results_product.cfm?Appl_Type=N&Appl_No=020243#3660 (Luvox) (last visited Oct. 6, 2023); https://www.accessdata.fda.gov/scripts/cder/ob/results_product.cfm?Appl_Type=N&Appl_No=020822#4029 (Celexa) (last visited Oct. 6, 2023); https://www.accessdata.fda.gov/scripts/cder/ob/results_product.cfm?Appl_Type=N&Appl_No=021365#4290 (Lexapro) (last visited Oct. 6, 2023).

85. James M. Ferguson, *SSRI Antidepressant Medications: Adverse Effects and Tolerability*, 3 J. CLINICAL PSYCHIATRY 22, 24–25 (2001).

6. The Monoamine Hypothesis

Figure 8: The Primary Monoamines, the Target of Most 20th Century Antidepressants.[86]

		
Dopamine	Serotonin	Norepinephrine

In the wake of the SSRI explosion, clinicians solidified the "monoamine hypothesis" of depression.[87] By the 2000s, nearly all known antidepressants targeted monoamine neurotransmitters, including serotonin, norepinephrine, and dopamine.[88] Proponents of the theory postulated that drugs targeting those neurotransmitters should be the primary means for treating depression.[89]

The post-SSRI world saw some novel antidepressant innovations, including changes to: dosing (e.g., extended release and sustained release mechanisms); monoamine targets (e.g., serotonin-norepinephrine reuptake inhibitors [SNRIs]); and receptor effect (e.g., serotonin agonism instead of reuptake inhibition).[90] But while scientists accomplished incremental improvements with the antidepressant efficacy of these drugs in the 1980s and early 1990s, by the early 2000s, researchers were unable to significantly improve on the efficacy of existing antidepressants.[91] There are several hypotheses for this stalled progress, and many believed that monoamine-targeting drugs had reached a ceiling in terms of antidepressant capacity.[92]

86. *Monoamine Neurotransmitter*, WIKIPEDIA, https://en.wikipedia.org/wiki/Monoamine_neurotransmitter (last visited Nov. 1, 2023).

87. Robert M. A. Hirschfeld, *History and Evolution of the Monoamine Hypothesis of Depression*, 61 J. CLINICAL PSYCHIATRY 4, 4–6 (2000). Monoamines are named for the single amine group in their structure.

88. These include serotonin-norepinephrine reuptake inhibitors (SNRIs), which inhibit reuptake of norepinephrine as well as serotonin. As a result, SNRIs have a more stimulating effect than SSRIs. *Id.*

89. Raleigh McElvery, *The Past, Present and Future of Using Ketamine to Treat Depression*, SMITHSONIAN (May 24, 2022), https://www.smithsonianmag.com/science-nature/a-brief-history-of-ketamines-use-to-treat-depression-180980106/.

90. Hillhouse & Porter, *supra* note 8, at 6–7.

91. *Id.*

92. *Id.* at 7.

Motivated by the desire to develop drugs that worked with a broader range of individuals, had increased efficacy, and threatened fewer side effects, researchers began to question the simplicity of the monoamine hypothesis.[93]

7. The Glutamate Hypothesis

In the 1990s, many scientists turned their attention to glutamate, an excitatory neurotransmitter, as a potential target for the next generation of antidepressants. Glutamate is the primary excitatory neurotransmitter in the brain.[94] It activates neurons that drive a wide range of behaviors and is also a necessary precursor to the synthesis of GABA. As a "calming" neurotransmitter involved in sleep, relaxation, anxiety regulation and muscle function, GABA seemed to be a promising drug target.[95]

Research starting in the 1990s showed that patients with depression had increased concentrations of glutamate in blood plasma and cerebrospinal fluid.[96] Additionally, patients who experienced successful remission through antidepressants exhibited decreases in glutamate concentration throughout their treatment.[97] These results suggested that while monoamine-based treatments like SSRIs and SNRIs impacted the glutamatergic system in some way, other drugs could likely treat depression through alternative approaches.

Scientists hypothesized that one of the receptors that glutamate binds, N-methyl-D-aspartic acid (NMDA), could be a promising drug target. Several studies indicated changes to the NMDA receptor in patients with depression, leading scientists to hypothesize that NMDA receptor-modulating antidepressants could revolutionize the monoamine-dominated paradigm of the post-SSRI clinical landscape.[98] A paper published by Robert Berman, Dennis Charney, John Krystal, and others at Yale University in 2000 showed that ketamine, an NMDA antagonist that had previously been used as an anesthetic, might be one such drug.[99]

---

93. *Id.* at 4.

94. Yun Zhou & Niels C. Danbolt, *Glutamate as a Neurotransmitter in the Healthy Brain*, 121 J. NEURAL TRANSMISSION 799, 799–800 (2014).

95. Cleveland Clinic Health Library, *Glutamate*, CLEVELAND CLINIC (Apr. 25, 2022), https://my.clevelandclinic.org/health/articles/22839-glutamate.

96. Hillhouse & Porter, *supra* note 8, at 10.

97. Amir Garakani et al., *Cerebrospinal Fluid Levels of Glutamate and Corticotropin Releasing Hormone in Major Depression Before and After Treatment*, 146 J. AFFECTIVE DISORDERS 262, 262 (2013).

98. *See, e.g.*, Michelle J. Chandley et al., *Elevated gene Expression of Glutamate Receptors in Noradrenergic Neurons from the Locus Coeruleus in Major Depression*, 17 INT'L J. NEUROPSYCHOPHARMACOLOGY 1, 1–2 (2014).

99. Robert M. Berman et al., *Antidepressant Effects of Ketamine in Depressed Patients*, 47 SOC'Y BIOLOGICAL PSYCHIATRY 351, 351–54 (2000).

C. TREATMENT-RESISTANT DEPRESSION: GAPS IN DEPRESSION TREATMENT

One of the chief issues facing depression researchers in the late 1990s and early 2000s was the prevalence of patients with treatment-resistant depression (TRD). Clinicians categorize patients with MDD who do not respond to one or more antidepressant treatment as having TRD.[100] Despite several treatment options like SSRIs, MAOIs, and TCAs, 34–46% of MDD patients still do not adequately respond to antidepressant treatment.[101] Even amongst those who recover from a depressive episode, 50–80% will experience symptom recurrence (usually within five years of the initial episode).[102] Likewise, even for patients who do respond to currently available treatments, most experience a delayed onset of four to twelve weeks before adequate symptom remission.[103]

The current method of treatment for patients with TRD is called Sequence Treatment Alternatives to Relieve Depression (STAR*D).[104] STAR*D is a four-step escalating treatment plan: patients start with SSRIs and move to other antidepressant drugs (e.g., TCAs) until they experience remission.[105] The vast majority of these antidepressants target only monoamine neurotransmitters (including serotonin, norepinephrine, and dopamine).[106]

Despite the range of possible treatment options, over 30% of patients do not sufficiently respond to these interventions.[107] The toll of such poor treatment efficacy is extraordinary. In the United States, 36.7% of individuals diagnosed with MDD are either unemployed or out of the labor force, and in 2018, the total economic impact of MDD was $326 billion.[108]

---

100. Hillhouse & Porter, *supra* note 8, at 2.

101. *Id.*

102. Stephanie L. Burcuso & William G. Iacono, *Risk for Recurrence in Depression*, 27 CLINICAL PSYCHOLOGY REV. 959, 960 (2007).

103. Hillhouse & Porter, *supra* note 8, at 2–3.

104. *Id.* at 3.

105. Step (1) of the STAR*D plan starts patients on an antidepressant for 12–14 weeks. If a patient does not achieve remission, they move on to step (2), where they either switch to a new antidepressant or take an additional antidepressant on top of their step (1) treatment. Those who do not achieve remission in step (3), where they again either switch to a new antidepressant or take an additional one on top of their existing treatment. Those who do not achieve remission through step (3) move on to step (4), and are considered to have TRD. These patients are moved on to a new antidepressant, often an MAOI or another treatment that has not yet been a part of their plan *See generally* Maurizio Fava et al., *Background and Rationale for the Sequenced Treatment Alternatives to Relieve Depression (STAR*D) Study*, 26 PSYCHIATRIC CLINICS N. AM. 457 (2003).

106. McElvery, *supra* note 89.

107. *Id.*

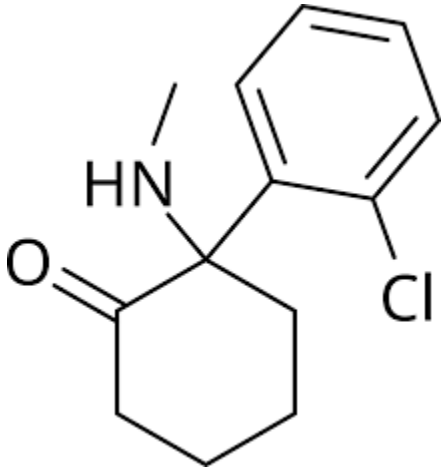
108. Paul E. Greenberg et al., *The Ecobonic Burden of Adults with Major Depressive Disorder in the United States (2019)*, 10 ADVANCES THERAPY 1, 2 (2023); Debra Lerner et al., *Research on the*

III. HISTORY OF KETAMINE

Discovered in the 1950s, ketamine's journey from a phencyclidine (PCP) derivative to a widely used anesthetic follows a similar pattern traced by many of the pharmaceuticals discussed in Part II, *supra*. The drug gained popularity as an anesthetic in surgical settings throughout the latter part of the 20th century. Researchers who observed ketamine's unexpected antidepressant effects in the 1990s helped to initiate an exploration into the drug's use outside of its previous analgesic purposes. This research led to what many clinicians heralded as "one of the most significant advances in the field of depression in recent years" as ketamine provided a much-needed leap forward for treatment of TRD.[109]

A. DISCOVERY AND INITIAL USE

Figure 9 Ketamine.[110]



Initially synthesized at Parke-Davis in 1956, ketamine proved to be an effective anesthetic. However, the drug's undesirable side effects limited the drug's widespread use. Ironically, these same dissociative side effects helped to propel ketamine's recreational use, leading to heightened government regulations.

Tufts Be Well at Work Program for Employees with Depression: 2005–2020, 72 PSYCHIATRIC SERVS. 1441, 1467–68 (2021).

109. Duman & Aghajanian, *supra* note 1, at 233.

110. *Ketamine*, WIKIPEDIA, https://en.wikipedia.org/wiki/Ketamine (last visited Nov. 1, 2023).

1. Synthesis at Parke-Davis

On March 26, 1956, while working for the pharmaceutical company Parke-Davis, V. Harold Maddox first synthesized phencyclidine (PCP) through his discovery of a new chemical Grignard reaction.[111] Maddox shared his findings with his Parke-Davis colleague, Graham Chen. On September 11, 1958, Chen found that use of PCP created a drunken state in rodents but an immobilized state in pigeons.[112] This led to further animal experimentation with PCP, where scientists found similarly "unusual" results.[113] Curious to explore the compound further, the Parke-Davis researchers set about conducting more comprehensive animal studies to understand the full range of PCP's pharmacological impact.[114]

In the early 1960s, Chen and Maddox contacted Maurice H. Seevers, who was the Head of Pharmacology at the University of Michigan; Seevers agreed to be their pharmacology consultant.[115] Parke-Davis then collaborated with Ferdinand E. Greifenstein, who was the Chair of Anesthesiology at Wayne State University in Detroit, to conduct human trials of PCP at Detroit Receiving Hospital.[116] The clinical trials found PCP to be an effective and safe anesthetic, but some patients experienced severe and prolonged post-surgery emergence delirium.[117]

Although this prolonged delirium was not acceptable, PCP still proved an effective anesthetic, so Cal Bratton, Head of Pharmaceutical Research at Parke-Davis, approved further synthesis of related compounds.[118] Calvin Stevens—a Professor of Organic Chemistry at Wayne State University and a chemical consultant to Parke-Davis—synthesized a PCP derivative that proved an effective anesthetic in animal models without the long-lasting delirium side effects of PCP.[119] This chemical, known then as CI-581, was eventually named "ketamine."[120]

111. V. Harold Maddox et al., *The Synthesis of Phencyclidine and Other 1-Arylcyclohexylamines*, 8 J. MED. CHEMISTRY 230 (1965).

112. Edward F. Domino, & David S. Warner, *Taming the Ketamine Tiger*, 113 ANESTHESIOLOGY 678, 679 (2010).

113. Graham Chen et al., *The Pharmacology of 1-(1-Phenylcyclohexyl) Piperidine-HCl*, 127 J. PHARMACOLOGY & EXPERIMENTAL THERAPEUTICS 241, 241 (1959).

114. *Id.*

115. Domino & Warner, *supra* note 112, at 679.

116. Ferdinand E. Greifenstein et al., *A Study of 1-Aryl Cyclo Hexyl amine for Anesthesia*, 37 ANESTHESIA & ANALGESIA 283 (1958).

117. Domino & Warner, *supra* note 112, at 679.

118. *Id.*

119. *Id.*

120. *Id.*

Edward Domino and Guenter Corssen, two University of Michigan professors working at the Parke Davis Research Unit at Jackson Prison in Michigan, intravenously administered the first human dose of ketamine on August 3, 1964.[121] The drug proved an effective anesthetic with minimal delirium side effects.[122] However, many subjects described feeling "spaced out" like they were "floating in outer space," with no feeling in their arms and legs.[123] Concerned about clinicians classifying these responses as "schizophrenomimetic" (hampering the drug's marketability), Parke-Davis researchers instead described ketamine as a "dissociative anesthetic."[124] The label stuck, and ketamine soon acquired approval for clinical trials.

2. Clinical Trials and FDA Approval

Clinicians published the first clinical study of ketamine as a human anesthetic in 1966.[125] The drug proved particularly safe because, as opposed to opiate-based anesthetics, patients in a ketamine-induced dissociative state maintained both an airway reflex and respiratory drive.[126] Corseen and Domino's initial human studies with ketamine showed that ketamine could produce rapid and effective anesthesia with a limited duration of effect that could safely be re-administered for prolonged surgical operations.[127]

The FDA approved the first preparation of ketamine in 1970 under the name "Ketalar" as a short-acting anesthetic in humans.[128] The drug was, and still is, widely employed in human and veterinary medicine.[129] In clinical settings, the drug is typically administered intravenously, although several alternate delivery routes exist.[130]

3. Recreational Use and Abuse Potential

Ketamine also became a popular recreational drug in the mid-1990s.[131] The drug is typically used at subanesthetic doses, which produces thirty to sixty

121. *Id.*

122. Linda Li & Phillip E. Vlisides, *Ketamine: 50 Years of Modulating the Mind*, 10 FRONTIERS HUM. NEUROSCIENCE 1, 2 (2016).

123. Domino & Warner, *supra* note 112, at 679.

124. *Id.* at 680.

125. Guenter Corssen & Edward Domino, *Dissociative Anesthesia: Further Pharmacologic Studies and First Clinical Experience with the Phencyclidine Derivative CI-581*, 45 ANESTHESIA & ANALGESIA 29 (1966).

126. Edward F. Domino et al., *Pharmacologic Effects of CI-581, A New Dissociative Anesthetic, in Man*, 6 CLINICAL PHARMACOLOGY & THERAPEUTICS 279, 319 (1965).

127. Li & Vlisides, *supra* note 122, at 2.

128. *Id.*

129. Domino & Warner, *supra* note 112, at 678.

130. Li & Vlisides, *supra* note 122, at 2–3.

131. Hillhouse & Porter, *supra* note 8, at 12.

minutes of perception distortion, mood and body image changes, and reality dissociation.[132] Its recreational use is limited; an estimated 0.19% of U.S. adults used ketamine in 2019.[133] However, as a result of its increased recreational use, ketamine became a Schedule III non-narcotic substance under the Controlled Substances Act in 1999.[134]

Studies indicate that ketamine can be addictive and can cause severe bladder damage if taken chronically in high doses.[135] Although ketamine (compared to other "club drugs" like MDMA and cocaine) has a relatively mild safety profile, high doses can cause cardiovascular and respiratory toxicity.[136] Likewise, ketamine's dissociative subjective effects can cause those taking the drug to experience physically traumatic events. Death by falls from height, driving accidents, and extended exposure are all major contributors to the drug's death rate.[137]

B. MECHANISM OF ACTION AND SAFETY PROFILE

David Lodge, of the Royal Veterinary College in London, initially proposed a theory for ketamine's mechanism of action in 1982. Lodge used feline models to assert that ketamine caused a selective depression of polysynaptic reflexes via antagonism of NMDA receptors.[138] Further research confirmed that ketamine binds to an ion channel site in the NMDA receptor complex.[139] Interestingly, ketamine has weak binding affinity for dopamine, norepinephrine, and serotonin transporters, which suggests a dramatically different mechanism of action than the monoamine modulators that previously defined the antidepressant landscape.[140]

Ketamine's overall safety profile and relatively low risk of overdose raises the question of why it is not more widely used as an anesthetic, especially

132. DEP'T JUST./DRUG ENFORCEMENT ADMIN., DRUG FACT SHEET KETAMINE (2020), https://www.dea.gov/sites/default/files/2020-06/Ketamine-2020.pdf [hereinafter Ketamine Fact Sheet].

133. R. Andrew Yockey, *Past-Year Ketamine Use: Evidence from a United States Population, 2015–2019*, 55 J. PSYCHOACTIVE DRUGS 134, 136 (2023).

134. Ketamine Fact Sheet, *supra* note 132.

135. Chris Hamby, *A Fraught New Frontier in Telehealth: Ketamine*, N.Y. TIMES (Feb. 20, 2023), https://www.nytimes.com/2023/02/20/us/ketamine-telemedicine.html.

136. John Martin Corkery et al., *Recreational Ketamine-Related Deaths Notified to the National Programme on Substance Abuse Deaths, England 1997–2019*, 35 J. PSYCHOPHARMACOLOGY 1324, 1329 (2021).

137. *Id.*

138. Domino & Warner, *supra* note 112, at 681.

139. Duman & Aghajanian, *supra* note 1, at 233.

140. Mitsuhiro Nishimura et al., *Ketamine Inhibits Monoamine Transporters Expressed in Human Embryonic Kidney 293 Cells*, 88 ANESTHESIOLOGY 768, 773 (1998).

considering the risks of addiction and overdose associated with analgesic and anesthetic opioids use. However, ketamine has a number of physiological side effects, including cystitis and urinary tract degeneration—although these are mostly seen with regular users.[141] More importantly, the psychoactive properties associated with ketamine are likely impeding its widespread adoption as an anesthetic.[142] Even at subanesthetic levels, patients given ketamine may experience unpleasant dissociative symptoms, including feelings of intoxication, somatosensory alteration, depersonalization, delusion, and disorientation.[143] While doctors attempt to mediate these effects with benzodiazepines or α_2-adrenergic receptor agonists (e.g., clonidine), clinicians remain unable to completely remove ketamine's psychotropic side effects.[144] Interestingly, ketamine's psychoactive effects, while undesirable for anesthetic applications, make the drug an interesting candidate for depression treatment.

C. KETAMINE AS AN ANTIDEPRESSANT

Researchers' discovery of ketamine's antidepressant qualities came about amidst frustration in progress towards improving antidepressant therapies. Through diligent follow-up of unexpected clinical results, researchers representing a wide range of public, private, and academic research initiatives helped to ascertain the drug's promise as a revolutionary depression therapy.

1. Discovery of Ketamine's Antidepressant Effects

Spurred by a desire to look beyond the monoamine-targeting drugs of the 20th century, researchers from a collaborative university and government effort began investigating unexpected antidepressant anecdotes from ketamine use in clinical settings. As a glutamate-modulating drug, ketamine proved an excellent target to spur an impressive leap in the field.

a) The Shift to Glutamate-Modulating Drug Targets

As discussed in Part II, *supra*, efficacy improvements for the SSRI, MAOI, and TCA classes of antidepressant therapies began to stall in the 1990s. In response, researchers at Yale School of Medicine, including Robert Berman, John Krystal, and Dennis Charney, hypothesized that pharmaceuticals needed

141. Peggy Sau-Kwan Chu et al., *The Destruction of the Lower Urinary Tract by Ketamine Abuse: A New Syndrome?*, 102 BJU INT'L 1616 (2008); Eric Kutscher & Richard E. Greene, *Ketamine Cystitis: An Underrecognized Cause of Dysuria*, 37 J. GENERAL INTERNAL MED. 1286, 1287 (2022).

142. *See* John H. Krystal et al., *Subanesthetic Effects of the Noncompetitive NMDA Antagonist, Ketamine, in Humans*, 51 ARCHIVES GEN. PSYCHIATRY 199, 200 (1994).

143. Edith Pomarol-Clotet et al., *Psychological Effects of Ketamine in Healthy Volunteers*, 189 BRITISH J. PSYCHIATRY 173, 176–78 (2018).

144. Marieke Niesters et al., *Ketamine for Chronic Pain: Risks and Benefits*, 77 BRIT. J. CLINICAL PHARMACOLOGY 357, 364 (2014).

to shift away from monoamine (e.g., dopamine, serotonin) targets.[145] Based on some promising studies and clinical anecdotes, the Yale researchers hypothesized that glutamate might serve as a catalyst for robust improvements in the fight against depression.[146] Many such drugs existed at the time, and although ketamine is a glutamate-modulating drug, it took a confluence of serendipitous findings and clinical diligence for researchers to hone in on the drug as an antidepressant.[147]

b) Yale Medicine / NIMH Collaboration: Early Antidepressant Findings

The National Institute of Mental Health (NIMH) funded much of glutamate-targeted antidepressant investigative work at Yale.[148] Starting in the 1990s, the NIMH established an Intramural Research Program (IRP) on the NIH campus in Bethesda, Maryland.[149] The IRP worked closely and continued funding the ketamine research work at Yale Medicine; clinicians from both organizations co-published much of their research in the 1990s and 2000s.[150]

At Yale, Berman, Charney, and Krystal recruited Husseini K. Manji and Carlos Zarate for the mood disorders research program with the IRP. Both researchers proved critical to the development of ketamine as an antidepressant.[151] The IRP program ultimately included researchers from several institutions, including clinicians from Mount Sinai Hospital in New York City.[152]

Throughout the 1990s, researchers in the IRP program used very low dose intravenous (IV) injections of ketamine as a potential model of schizophrenia, in order to develop treatments for the condition.[153] Unexpectedly, these subanesthetic doses of ketamine had antidepressant effects on patients with

145. Gordon, *supra* note 22.
146. *Id.*
147. *Id.*
148. *Id.*
149. *Id.*
150. *Id.*
151. *Id.*
152. *Id.*
153. *See* Krystal et al., *supra* note 142; John H. Krystal et al., *Interactive Effects of Subanesthetic Ketamine and Subhypnotic Lorazepam in Humans*, 135 PSYCHOPHARMACOLOGY 213 (1998); John H. Krystal et al., *Dose-Related Ethanol-Like Effects of the NMDA Antagonist, Ketamine, in Recently Detoxified Alcoholics*, 55 ARCHIVES GEN. PSYCHIATRY 354 (1998); John H. Krystal et al., *Interactive Effects of Subanesthetic Ketamine and Haloperidol in Healthy Humans*, 145 PSYCHOPHARMACOLOGY 193 (1999); John H. Krystal et al., *Dissociation of Ketamine Effects on Rule Acquisition and Rule Implementation: Possible Relevance to NMDA Receptor Contributions to Executive Cognitive Functions*, 47 BIOLOGICAL PSYCHIATRY 137 (2000).

depression.[154] Much like in the development of lithium, MAOIs, and TCAs, the observed antidepressant effects prompted further research into the impact that ketamine, an NMDA-receptor antagonist that impacted glutamate concentrations, might have in the treatment of depression.

In 2000, the Yale researchers showed in a small randomized, double-blind study that a single subanesthetic dose of ketamine improved depression in less than twenty-four hours, and in some cases led to a near complete recovery.[155] These results were particularly significant in light of the standard of care for depression—the available antidepressant drugs at that time required four to six weeks for their impacts to be measurable.[156] Importantly, this was also the first clinical study to demonstrate that glutamatergic drugs may be effective for the treatment of depression.[157]

In the wake of the Yale study, several other researchers reported similar antidepressant effects with ketamine administered to patients with depression. One study found an antidepressant impact in the postoperative period for surgical patients who received ketamine as an anesthetic.[158] Another reported promising results from low-dose ketamine infusions in two individuals who suffered from major depressive disorder.[159]

c) Ketamine for Treatment-Resistant Depression: Zarate (2006)

Despite these promising initial findings, skepticism persisted into the mid-2000s about whether ketamine's antidepressant effects could be used on patients suffering from TRD. Through the NIHM IRP collaboration, Zarate, Manji, and Charney planned the first study with ketamine in TRD.[160] The stakes were high—if the drug successfully treated TRD, that constituted a massive breakthrough for the millions of individuals suffering from TRD worldwide.

Zarate, Charney, and Manji conducted a randomized, placebo-controlled, double-blind crossover study from 2004 to 2006 on eighteen patients who previously failed to achieve success following treatment with at least six other

154. Berman et al., *supra* note 99, at 351–54.

155. *Id.*

156. Herbert C. Schulberg et al., *Treating Major Depression in Primary Care Practice: An Update of the Agency for Health Care Policy and Research Practice Guidelines*, 55 ARCHIVES GEN. PSYCHIATRY 1121, 1124 (1998).

157. Hillhouse & Porter, *supra* note 8, at 14.

158. Akira Kudoh et al., *Antidepressant Treatment for Chronic Depressed Patients Should Not Be Discontinued Prior To Anesthesia*, 49 CAN. J. ANESTHESIA 132 (2002).

159. Graeme E. Correll & Graham E. Futter, *Two Case Studies of Patients with Major Depressive Disorder Given Low-Dose (Subanesthetic) Ketamine Infusions*, 7 PAIN MED. 92 (2006).

160. Gordon, *supra* note 19.

antidepressant therapies.[161] The patients received two low-dose IV infusions of either saline (placebo) or ketamine infusions, administered one week apart.[162]

The study results, published in 2006 by Zarate and the other IRP researchers, were jaw-dropping. 71% of the patients experienced antidepressant effects after only one infusion, and 29% achieved full remission of TRD.[163] Adverse effects for patients receiving ketamine were relatively minor.[164] For patients with no otherwise-effective antidepressants available, this was a massive discovery.

d) Post-Zarate (2006) Research

Zarate's 2006 study prompted further research into ketamine's lasting effects on TRD.[165] Since the 2006 study, researchers funded by the NIMH IRP have conducted numerous studies to further understand the mechanisms by which ketamine may produce antidepressant effects. Several studies found that ketamine infusions provided an average of eighteen to nineteen days of relief from depression symptoms in TRD patients, with a number of patients experiencing remission that lasted through the months- or years-long publication of each study.[166] Several post-Zarate (2006) studies of ketamine's antidepressant effects are found in Table 2, *infra.*

161. Carlos A. Zarate Jr, et al., *A Randomized Trial of an N-methyl-D-aspartate Antagonist in Treatment-Resistant Major Depression*, 63 JAMA PSYCHIATRY 856, 858 (2006).

162. *Id.* at 857.

163. *Id.* at 858–60.

164. *Id.* at 861.

165. *Dr. Carlos Zarate Carries the Torch toward FDA Approval of Rapid-Acting Antidepressant*, BRAIN & BEHAVIOR RSCH. FOUND. (Mar. 13, 2014) https://www.bbrfoundation.org/content/dr-carlos-zarate-carries-torch-toward-fda-approval-rapid-acting-antidepressant.

166. Marije aan het Rot et al., *Safety and Efficacy of Repeated-Dose Intravenous Ketamine for Treatment-Resistant Depression*, 69 BIOLOGICAL PSYCHIATRY 139–45 (2010); James W. Murrough et al., *Rapid and Longer-Term Antidepressant Effects of Repeated Ketamine Infusions in Treatment-Resistant Major Depression*, 74 BIOLOGICAL PSYCHIATRY 250, 254 (2013).

Table 2: Notable Studies on Ketamine's Antidepressant Effects, Post-Zarate (2006).

Study	Method of Treatment (Dosage)	Condition Targeted	Results
Matthew et al., 2010	IV Infusion (racemic[167] ketamine 0.5 mg/kg)	Major Depressive Disorder (MDD)	65% of patients experienced remission of depression symptoms within twenty-four hours of ketamine infusion; 50% experienced remission through the seventy-two-hour mark.[168]
Murrough et al., 2013	IV Infusion (racemic ketamine 0.5 mg/kg)	TRD	Antidepressant effect in 70.8% of patients for an average of eighteen days; four participants remained in remission through publication.[169]
Price et al., 2009	IV Infusion (racemic ketamine 0.5 mg/kg)	Suicidal Ideation	Rapid reduction in suicidal ideation/cognition in patients with TRD; reductions were sustained for twelve days by repeated-dose ketamine.[170]
Lally et al., 2014	IV Infusion (racemic ketamine 0.5 mg/kg)	Treatment-Resistant Bipolar Depression	Rapid reduction of depressive symptoms within forty minutes; remission persisted up to fourteen days.[171]
Irwin & Iglewicz, 2010	Oral (racemic ketamine 0.5 mg/kg)	Major Depressive Disorder (MDD)	Single oral dose of low-dose ketamine provided rapid and moderately sustained symptom relief for depressed patients receiving hospice care.[172]

167. "Racemic" refers to a mixture of ketamine with equal parts of the S- and R-enantiomer of the molecule. For a detailed explanation, see Section III.C.3.b *infra*.

168. Sanjay J. Mathew et al., *Riluzole for Relapse Prevention Following Intravenous Ketamine in Treatment-Resistant Depression: A Pilot Randomized, Placebo-Controlled Continuation Trial*, 13 INT'L J. NEUROPSYCHOPHARMACOLOGY 71, 76 (2010).

169. Murrough et al., *supra* note 165, at 254.

170. Rebecca B. Price et al., *Effects of Intravenous Ketamine on Explicit and Implicit Measures of Suicidality in Treatment-Resistant Depression*, 66 BIOLOGICAL PSYCHIATRY 522, 522 (2009).

171. Níall Lally et al., *Anti-Anhedonic Effect of Ketamine and its Neural Correlates in Treatment-Resistant Bipolar Depression*, 14 TRANSLATIONAL PSYCHIATRY 1, 6 (2014)

172. Scott A. Irwin & Alana Iglewicz, *Oral Ketamine for the Rapid Treatment of Depression and Anxiety in Patients Receiving Hospice Care*, 13 J. PALLIATIVE MED. 903, 903 (2010).

Lara et al., 2013	Low-Dose Sublingual (racemic ketamine 10 mg)	Major Depressive Disorder (MDD), Bipolar Disorder	Sublingual (under the tongue) ketamine administration produced rapid, clear and sustained effects on bipolar and depressed patients' mood level and stability, cognition, and sleep quality.[173]
Lapidus et al., 2015	Intranasal (racemic ketamine 50 mg)	Major Depressive Disorder (MDD)	Intranasal ketamine administration showed significant improvements in depressive symptoms for eighteen patients.[174]
Daly et al., 2018	Intranasal (esketamine 28 mg, 56 mg, or 84 mg)	TRD	Patients with TRD experienced significant decreases in depression scores, and results were sustained for several weeks.[175]
Canuso et al., 2018	Intranasal (esketamine 84 mg)	Suicidal Ideation	Significant decrease in depression and suicidal ideation scores for patients receiving intranasal esketamine as compared to a placebo group.[176]

e) Confirming Ketamine's Antidepressant Mechanism of Action

Research published in 2014 confirmed that ketamine is an NMDA receptor antagonist.[177] This helped to explain the drug's antidepressant effects—one of the core pathophysiological changes underlying major depression is the loss of synaptic connectivity, and ketamine is thought to promote synaptogenesis.[178] This growth of new synapses suggests that ketamine may stimulate antidepressant effects that outlast initial drug actions.

173. Diogo R. Lara et al., *Antidepressant, Mood Stabilizing and Procognitive Effects of Very Low Dose Sublingual Ketamine in Refractory Unipolar and Bipolar Depression*, 16 INT'L J. NEUROPSYCHOPHARMACOLOGY 2111, 2111 (2013).

174. Kyle Lapidus et al., *A Randomized Controlled Trial of Intranasal Ketamine in Major Depressive Disorder*, 76 BIOLOGICAL PSYCHIATRY 970, 970 (2015).

175. Ella J. Daly et al., *Efficacy and Safety of Intranasal Esketamine Adjunctive to Oral Antidepressant Therapy in Treatment-Resistant Depression: A Randomized Clinical Trial*, 75 JAMA PSYCHIATRY 139, 146 (2018).

176. Carla M. Canuso et al., Effi*cacy and Safety of Intranasal Esketamine for the Rapid Reduction of Symptoms of Depression and Suicidality in Patients at Imminent Risk for Suicide: Results of a Double-Blind, Randomized, Placebo-Controlled Study*, 175 AM. J. PSYCHIATRY 620, 620–21 (2018).

177. Duman & Aghajanian, *supra* note 1, at 233.

178. *Id.*

Likewise, preclinical studies of ketamine in patients with TRD demonstrate that the antidepressant actions of ketamine are mediated by the induction of synaptic proteins and increased number and function of new spine synapses in the prefrontal cortex.[179] Because of both its rapid antidepressant activity in treatment-resistant patients and potential for long-term therapeutic efficacy, experts hail ketamine as "one of the most significant advances in the field of depression in recent years."[180]

2. Alternative Methods of Administration

Since its first use as an anesthetic, medical professionals traditionally administered ketamine intravenously.[181] Researchers have since developed alternative routes of administration. For example, Stuart L. Weg patented intranasal administration of ketamine for pain management in 1996.[182] Today, ketamine can be safely administered intravenously, intramuscularly, orally, nasally, rectally, subcutaneously, and epidurally.[183]

The efficacy of each method is recorded in "bioavailability," which measures the proportion of the drug that enters the bloodstream when administered, and is therefore physiologically accessible.[184] As shown in Table 3, *infra*, ketamine administered through IV is far more bioavailable than ketamine administered by other treatment methods.

Table 3: Bioavailability of Ketamine by Administration Route.[185]

Route	Bioavailability	Time to Maximum Concentration
IV	100%	three minutes
Intramuscular	93%	five to ten minutes
Oral	17–29%	thirty minutes
Rectal	11–25%	thirty to thirty-five minutes
Intranasal	8–45%	ten to twenty minutes

Although IV or intramuscular (IM) ketamine administration routes result in far higher rates of bioavailability, such methods of treatment require

179. Ronald S. Duman & George K. Aghajanian, *Synaptic Dysfunction in Depression: Potential Therapeutic Targets*, 338 SCI. 68, 73 (2012).

180. *Id.*

181. Li & Vlisides, *supra* note 122, at 23.

182. U.S. Patent No. 5,543,434 (issued Aug. 6, 1996).

183. Li & Vlisides, *supra* note 122, at 2–3.

184. *Id.*

185. *Id.* at 3.

inpatient care and anesthesiologists present.[186] Oral, rectal, and intranasal delivery methods are much less bioavailable than IV delivery but are more amenable to outpatient use.[187]

A shift away from IV or IM administration presents many advantages to patients and medical professionals. IV and IM administration require hospital visits and a more extensive range of medical precautions; this presents a significant barrier to long-term patient compliance.[188] Unlike anesthetic ketamine use, which typically requires only a single large dose of ketamine over the period required for an operation or other medical procedure, antidepressant therapies may call for long-term repeated administration. As such, there are significant incentives for adopting a more seamless and frictionless means of delivery for antidepressant ketamine therapies.

In 2010 and 2012, two papers disclosed that orally administered ketamine effectively relieved depressive symptoms. One showed that a single oral dose of low-dose ketamine provided rapid and moderately sustained symptom relief for depressed patients receiving hospice care.[189] Another study showed that a daily oral ketamine solution created sustained antidepressant and antianxiety effects on a hospice patient with severe anxiety, fear, depression, and chronic pain.[190]

These findings prompted further research into oral administration of ketamine for the treatment of depression. A 2013 NIMH-sponsored study with eight patients found that daily oral ketamine administration alleviated depression symptoms for patients receiving hospice care.[191] Another study found that sublingual administration produced rapid, clear, and sustained effects on bipolar and depressed patients' mood, cognition, and sleep quality.[192] Notably, both the oral and sublingual administrations seemed to minimize some of the more undesirable side effects of ketamine, such as dissociation and psychosis.[193]

186. McElvery, *supra* note 78.

187. Li & Vlisides, *supra* note 122, at 2–3.

188. Gordon, *supra* note 19.

189. Irwin & Iglewicz, *supra* note 172, at 903.

190. Jack P McNulty & Kristian Hahn, *Compounded Oral Ketamine*, 16 INT'L J. PHARM. COMPOUNDING 364, 364 (2012).

191. Scott A. Irwin et al., *Daily Oral Ketamine for the Treatment of Depression and Anxiety in Patients Receiving Hospice Care: A 28-Day Open-Label Proof-Of-Concept Trial*, 16 J. PALLIATIVE MED. 958, 958 (2013).

192. Diogo R. Lara et al., *Antidepressant, Mood Stabilizing and Procognitive Effects of Very Low Dose Sublingual Ketamine in Refractory Unipolar and Bipolar Depression*, 16 INT'L J. NEUROPSYCHOPHARMACOLOGY 2111, 2111 (2013).

193. Lara et al., *supra* note 173, at 2111.

Researchers sought to identify a safe and easy method of delivery that could surpass oral bioavailability, spurring research into intranasal ketamine administration. A 2014 double-blind, crossover clinical study at the Mount Sinai Mood and Anxiety Disorders program provided the first controlled evidence for the antidepressant effects of intranasal ketamine, showing significant improvements in depressive symptoms for twenty patients.[194] A 2018 double-blind, placebo-controlled study showed rapid antidepressant relief for a large group of patients with TRD.[195] Like oral and sublingual methods, intranasal administration of ketamine also produced minimal undesirable side effects.[196] Another 2018 double-blind, placebo-controlled study co-sponsored by Janssen Pharmaceuticals and Yale Medicine showed a significant decrease in depression and suicidal ideation scores for patients receiving an intranasal ketamine enantiomer as compared to a placebo group.[197]

The encouraging results of these oral and intranasal treatments showed promise to researchers interested in using ketamine as an antidepressant therapy. Not only were such treatments effective at treating the symptoms of depression, but they were also safe and avoided the most undesirable dissociative side effects of IV ketamine administration. Most importantly, these methods allowed patients to potentially use ketamine in an outpatient setting, without the more cumbersome and expensive requirements of inpatient care.

3. Development of Spravato

Spravato was the first, and remains the only, FDA-approved ketamine treatment for depression. The development of the drug began with a wide-ranging NIH-backed collaboration but ultimately came to fruition when a researcher from that effort made a jump to the private industry. Spravato showcases how the motivations of patents can push private firms to develop novel, if dubiously beneficial, drug therapies.

a) Motivations and Contributions to the Development of Spravato

Even after the 2006 NIMH studies that found ketamine to be an effective treatment for patients with TRD, the predominantly used IV route of administration meant clinicians expended considerable resources (including

194. Lapidus et al., *supra* note 174, at 970.

195. Ella J. Daly et al., *Efficacy and Safety of Intranasal Esketamine Adjunctive to Oral Antidepressant Therapy in Treatment-Resistant Depression: A Randomized Clinical Trial*, 75 JAMA PSYCHIATRY 139, 147 (2018).

196. Lapidus et al., *supra* note 174, at 970.

197. Canuso et al., *supra* note 176, at 620–21.

inpatient care and an on-site anesthesiologist) while delivering the drug.[198] As such, there were significant incentives for a private pharmaceutical company to develop a patentable, easy-to-deliver ketamine administration formulation. It took a decade of work until Janssen Pharmaceuticals, a Belgium-based subsidiary of Johnson & Johnson, could gain FDA approval for its solution, Spravato, which uses a far less cumbersome—but controversial—method of delivery for ketamine as an antidepressant.

The development of Spravato can be traced to Husseini Manji's arrival at Janssen in 2008. Before working at Janssen, Manji served as director of the Mood and Anxiety Disorders program at the NIMH.[199] At the NIMH, Manji co-authored the first study to replicate Zarate's seminal 2006 study (*see* Table 1, *supra*).[200] Inspired in part by a desire to develop new depression therapies and by similar leaps in cancer treatment spurred through private research, Manji left the NIMH to lead Janssen's Neuroscience Research & Development program in 2008, but continued to co-author ketamine research prodigiously through the 2010s.[201]

Because of this background, Manji understood the antidepressant promise of ketamine, but also the significant hurdles that IV administration created. So, he set about developing a more expedient delivery method for the drug.[202] Manji's team at Janssen worked to develop a nasal spray to deliver racemic ketamine because such a method of delivery did not require an anesthesiologist to be present, and allowed faster delivery to the brain.[203] But because the spray supplied much less of the drug than IV delivery, Manji's team searched for a more potent form of the drug.[204] They found their solution in the S-enantiomer of ketamine.

198. McElvery, *supra* note 78.

199. *Id.*

200. *Id.*; Zarate et al., *supra* note 161.

201. Intravenous ketamine administration requires an anesthesiologist to be present to address safety concerns; intranasal administration does not. Likewise, intranasal administration has a higher upper-range bioavailability than alternatives such as oral and sublingual ketamine. McElvery, *supra* note 89; Li & Vlisides, *supra* note 122, at 2–3.

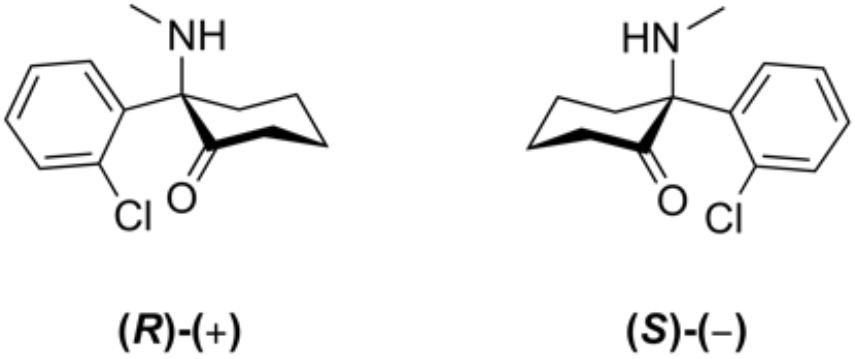
202. Ginny Graves, *The Mind Matters: This Johnson & Johnson Researcher is on a Mission to Change How We Treat Mental Illness*, J&J INNOVATION (May 16, 2017), https://www.jnj.com/innovation/johnson-and-johnson-researcher-on-a-mission-to-change-how-we-treat-mental-illness; Dana Talesnik, *Manji Develops Novel Treatment for Major Depressive Disorder*, NIH RECORD (May 17, 2019), https://nihrecord.nih.gov/2019/05/17/manji-develops-novel-treatment-major-depressive-disorder.

203. McElvery, *supra* note 89.

204. *Id.*

b) Ketamine's Enantiomers and Off-Label Treatment of Depression

Figure 10: Ketamine's R- and S-Enantiomers.[205]



Ketamine exists in two different enantiomer forms: R-ketamine and S-ketamine (often spelled "esketamine").[206] The form of the drug approved by the FDA for anesthetic purposes is equal parts of the R- and S-enantiomers ("racemic" ketamine).[207] Nearly all the influential early ketamine antidepression studies discussed *supra*, including Zarate's in 2006, utilized the racemic form.[208]

However, racemic ketamine is not currently FDA-approved for the treatment of depression. Though there is limited evidence available about the extent of ketamine's off-label use for depression, published records indicate antidepressant use since at least the early 2000s.[209] While in Europe, many countries follow the U.K. National Institute for Health and Care Excellence (NICE) recommendation that clinicians only use ketamine off-label for depression after attempting "all evidence-based antidepressant strategies"

205. *Ketamine*, WIKIPEDIA, https://en.wikipedia.org/wiki/Ketamine (last visited Nov. 1, 2023).

206. *Id.*

207. *Id.*

208. *See* Table 2, *supra*.

209. Gerard Sanacora et al., *A Consensus Statement on the Use of Ketamine in the Treatment of Mood Disorders*, 74 JAMA PSYCHIATRY 399 (2017); Samuel T. Wilkinson et al., *A Survey of the Clinical, Off-Label Use of Ketamine as a Treatment for Psychiatric Disorders*, 174 AM. J. PSYCHIATRY 695, 695–96 (2017).

outlined in clinical guidelines, in the United States, no such restriction exists.[210] Because of this, several startups have sprung up to provide U.S. patients with off-label racemic ketamine for depression, which can include IV, oral, or intranasal administrations of the drug.[211]

Likewise, retrospective studies analyzing clinical data reporting the off-label use of sublingual racemic ketamine found that the drug could be delivered safely at home with significant reductions in patient's depression metric scores.[212] However, alarmed at the extent of off-label use of racemic ketamine, the FDA released a warning to health care professionals in 2022 concerning potential side effects, including sedation, dissociation, and abuse or misuse.[213]

c) Spravato's Use of Esketamine

The clinical team at Janssen argued that the lower bioavailability and metabolism rate that resulted from nasal delivery of the drug (see Table 2) necessitated a more potent version of the ketamine formulation.[214] The patent that would ultimately cover Spravato cited evidence that isolated esketamine has a higher affinity to the binding site on NMDA receptors and is three to four times more potent than R-ketamine.[215] Additionally, research cited by Janssen showed that the esketamine enantiomer is associated with increased cardiac stimulation, decreased spontaneous motor activity, superior analgesia, faster recovery, and fewer psychological side effects.[216]

---

210. Álvaro López-Díaz et al., *Off-Label Use of Ketamine for Treatment-Resistant Depression in Clinical Practice: European Perspective*, 215 BRIT. J. PSYCHIATRY 447, 447 (2019).

211. Rebecca Heilweil, *Startups are Betting on a Psychedelic Gold Rush*, VOX (Oct. 13, 2021), https://www.vox.com/recode/22716491/psychedelics-ketamine-mental-health-research-fda.

212. Kazi Hassan et al., *Safety, Effectiveness and Tolerability of Sublingual Ketamine in Depression and Anxiety: A Retrospective Study of Off-Label, At-Home Use*, 28 FRONTIERS PSYCHIATRY 1, 7 (2022).

213. *FDA Alerts Health Care Professionals of Potential Risks Associated with Compounded Ketamine Nasal Spray*, U.S. FOOD & DRUG ADMIN. (Feb. 16, 2022), https://www.fda.gov/drugs/human-drug-compounding/fda-alerts-health-care-professionals-potential-risks-associated-compounded-ketamine-nasal-spray#:~:text=Ketamine%20hydrochloride%5Ba%5D%20(tradename,and%20maintenance%20of%20general%20anesthesia [hereinafter FDA News Release, Ketamine].

214. McElvery, *supra* note 89.

215. *Id.*; *Orange Book: Approved Drug Products with Therapeutic Equivalence Evaluations, Patent and Exclusivity for: N211243*, U.S. FOOD & DRUG ADMIN., https://www.accessdata.fda.gov/scripts/cder/ob/patent_info.cfm?Product_No=001&Appl_No=211243&Appl_type=N; U.S. Patent No. 8,785,500 (issued Jul. 22, 2014);
Paul F. White et al., *Comparative Pharmacology of the Ketamine Isomers: Studies in Volunteers*, 57 BRIT. J. ANESTHESIA 197 (1985).

216. White et al., *supra* note 215.

Initial trials with esketamine for patients with TRD showed promise, with a single dose offering several days' worth of symptom relief for many patients.[217] So, Manji's team developed a treatment method where patients self-administered the intranasal esketamine formulation twice a week for the first month, then administered the treatments every one to two weeks thereafter (ongoing, or as prescribed by a physician) to maintain the drug's antidepressant effects.[218] Janssen thus moved forward with an intranasal formulation that contains only esketamine—and initiated the FDA approval process of the product that would come to be sold under the brand name "Spravato."[219]

d) FDA Approval

Janssen subsequently conducted a series of clinical trials on over 1,700 patients.[220] The initial success of Janssen's Phase II trials prompted the FDA to grant Janssen a "breakthrough therapy" designation, which allowed the company to "fast track" their Phase III trials.[221] In the approval process for Spravato, Janssen conducted roughly twenty-five different studies. In a pivotal Phase III trial, many patients with TRD saw a reduction in depressive symptoms after twenty-four hours when given Spravato in conjunction with an oral antidepressant.[222] The most common adverse side effects were dissociation, nausea, vertigo, dizziness, and an altered sense of taste.[223] In the clinical trials, many individuals required fewer treatments over time, often only requiring administration once every several weeks.[224] Due to the success of these trials, the FDA approved Janssen's S-ketamine intranasal administration as Spravato in 2019.

Spravato was the first, and remains the only, FDA-approved ketamine-based antidepressant for TRD.[225] It is also the only FDA-approved depression treatment with a glutamate-modulation mechanism of action.[226] In 2020,

217. Talesnik, *supra* note 202.
218. *Id.*
219. McElvery, *supra* note 89.
220. Talesnik, *supra* note 202.
221. Rebecca Bahr et al., *Intranasal Esketamine (Spravato™) for Use in Treatment-Resistant Depression in Conjunction with an Oral Antidepressant*, 44 PHARMACY & THERAPEUTICS 340, 340 (2019).
222. McElvery, *supra* note 89; Vanina Popova et al., *Efficacy and Safety of Flexibly Dose Esketamine Nasal Spray Combined with a Newly Initiated Oral Antidepressant in Treatment-Resistant Depression: A Randomized Double-Blind Active-Controlled Study*, 176 AM. J. PSYCHIATRY 428 (2019).
223. McElvery, *supra* note 89.
224. *Id.*
225. FDA News Release, Ketamine, *supra* note 213.
226. *Id.*

Janssen received FDA approval for use of Spravato for suicidal patients with MDD.[227] In 2021, Janssen implemented the Spravato Pilot Program to expand treatment for adults with suicidal ideation.[228]

e) Limitations and Drawbacks of Intranasal Esketamine

Esketamine, on its own, is not a panacea for depression. The claims of the U.S. patent cited in Spravato's FDA approval letter specify that the drug is to be taken in conjunction with one or more of the traditional antidepressants discussed in Part II (e.g., lithium, tricyclics, MAOIs, SSRIs).[229] Spravato is classified as an "augmentation strategy" to target depression treatment resistance, and so is administered in conjunction with (rather than in lieu of) these widely used pharmaceuticals.[230]

Likewise, despite Spravato's ease of use, the drug still has several downsides compared to other antidepressant therapies. Because of ketamine's potential side effects and abuse potential, Spravato must still be administered in a clinic under a health care professional's supervision.[231] However, much less clinical supervision is required for such ketamine therapies compared to traditional IV administration.[232]

Intranasal Spravato also shares some of the same side effects as IV racemic ketamine, including hallucinations and increased blood pressure.[233] Patients must also remain in the clinic for two or more hours after treatment for monitoring after esketamine administration, and are prohibited from driving for the rest of the day due to the drug's drowsy effects.[234]

With these barriers, Spravato is still far from reaching the accessibility of other antidepressant medications, such as oral SSRIs, which can be taken daily and at home relatively seamlessly. Notably, in the spring of 2020, the FDA waived the requirement that ketamine be administered only at a hospital, clinic, or medical office (due to the SARS-CoV-2 pandemic).[235] As of October 2023,

227. Jon Hamilton, *Nasal Spray Is a New Antidepressant Option for People At High Risk of Suicide*, NPR (Aug. 7, 2020), https://www.npr.org/sections/health-shots/2020/08/07/900272454/nasal-spray-is-a-new-antidepressant-option-for-people-at-high-risk-of-suicide.

228. *Greenbrook TMS Inc. Management's Discussion and Analysis of Financial Conditions and Results of Operation*, at 4, SEC (May 14, 2021), https://www.sec.gov/Archives/edgar/data/1735948/000110465921067010/tm2116020d2_ex99-3.htm.

229. U.S. Patent Application No. 2013/0236573, ¶ 1 (issued Sept. 12, 2013).

230. *Id.*

231. Talesnik, *supra* note 202.

232. Zarate et al., *supra* note 161, at 856–64.

233. Talesnik, *supra* note 202.

234. *Id.*

235. Am. Coll. Obstetricians & Gynecologists v. United States Food & Drug Admin., 472 F. Supp. 3d 183, 194 (D. Md. 2020).

this waiver was extended to at least the end of 2024.[236] This waiver appears to apply only to ketamine, but not Spravato; the former thus can be prescribed off-label via telehealth and taken at home, while the latter must still be taken in a certified treatment center.[237]

f) Criticisms

The FDA approval of Spravato has not been without controversy. In 2020, four Italian researchers working with the World Health Organization (WHO) published a scathing critique of the clinical trial evidence Janssen submitted to the FDA.[238] The researchers noted that, of three randomized trials submitted to the FDA, only one demonstrated the superiority of intranasal esketamine over a placebo.[239] Likewise, even aggregating these finds findings, critics argue the results were so narrowly above the threshold of statistical significance as to have dubious clinical consequence.[240]

Janssen's clinical trials also calculated the efficacy of esketamine against a placebo, instead of against an active and licensed comparator for TRD (such as fluoxetine).[241] Both the FDA and European Medicines Agency (EMA) had only required a placebo-controlled trial for regulatory approval in this case.[242] This brings into question the utility of esketamine, if it potentially did not provide superior results for improving TRD as measured against presently-available therapies.[243] Critics assert that Spravato's efficacy should be measured against existing, readily available, and affordable antidepressants like SSRIs, rather than compared to an inert placebo.[244] However, Spravato is specifically made for TRD patients—those who have *failed* to achieve remission in their depression symptoms with traditional antidepressants, so this specific criticism might be misplaced.[245]

236. Scott Brinks & Miriam E. Delphin-Rittmon, *Second Temporary Extension of COVID-19 Telemedicine Flexibilities for Prescription of Controlled Medications*, FED. REG. (Oct. 10, 2023), https://www.federalregister.gov/documents/2023/10/10/2023-22406/second-temporary-extension-of-covid-19-telemedicine-flexibilities-for-prescription-of-controlled.

237. *Id.*; SPRAVATO® FAQs, SPRAVATO (ESKETAMINE), https://www.spravato.com/patient-education#:~:text=You%20cannot%20take%20SPRAVATO%C2%AE,to%20help%20find%20a%20location (last visited Nov. 22, 2023).

238. Chiara Gastaldon et al., *Esketamine for Treatment Resistant Depression: A Trick of Smoke And Mirrors?*, 29 EPIDEMIOLOGY & PSYCHIATRIC SCIS. 1, 1 (2019).

239. *Id.* at 2.

240. *Id.*

241. *Id.*

242. *Id.*

243. *Id.*

244. *Id.*

245. *See* Hillhouse & Porter, *supra* note 8, at 2.

One of the selling points for the FDA approval of esketamine over the racemic mixture—in addition to its allegedly increased potency[246]—is that the S-enantiomer is supposedly safer than the racemic mixture, but other clinical trials call that assertion into question.[247] At least one analysis of intranasal ketamine treatment for depression argues that there has not been an adequately designed comparator of the esketamine enantiomer and racemic ketamine.[248] Moreover, recent mouse studies using ketamine as an antidepressant have shown the R-ketamine enantiomer to be more potent, with fewer side effects, than the esketamine enantiomer.[249] Another meta-analysis found that intravenously administered racemic ketamine more effectively treated TRD than intranasal esketamine.[250] While none of these results provide a conclusive rebuttal of esketamine's efficacy or safety over the racemic mixture, they nonetheless provide a basis for continued skepticism for the necessity of esketamine in Janssen's drug formulation.

Despite these criticisms, Spravato is proving a lucrative product for Janssen. While initial sales of the drug were somewhat lackluster, Spravato has experienced substantial growth—revenues in the second quarter of 2023 grew almost 100% compared to the same period in 2022, to $169 million worldwide.[251] This strong growth has continued; in the third quarter of 2023, sales increased over 80% compared to the same period in 2022, to $183 million worldwide.[252]

246. *See* White et al., *supra* note 215, at 201.

247. Gastaldon et al., *supra* note 238, at 1; Caroline Caddy et al., *Ketamine and Other Glutamate Receptor Modulators for Depression in Adults*, 9 COCHRANE DATABASE SYSTEMATIC REVS. 1 (2015).

248. Roger S. McIntyre et al., *Synthesizing the Evidence for Ketamine and Esketamine in Treatment-Resistant Depression: An International Expert Opinion on the Available Evidence and Implementation*, 178 AM. J. PSYCHIATRY 383, 386 (2021).

249. Ji-chun Zhang et al., *R (−)-ketamine Shows Greater Potency and Longer Lasting Antidepressant Effects Than S (+)-Ketamine*, 116 PHARMACOLOGY BIOCHEMISTRY & BEHAVIOR 137, 137–38 (2014).

250. Anees Bahji et al., *Comparative Efficacy of Racemic Ketamine and Esketamine for Depression: A Systematic Review and Meta-Analysis*, 278 J. AFFECTIVE DISORDERS 542, 542 (2021).

251. Benjamin A. Smith, *Sales of Johnson & Johnson Esketamine Drug Spravato Rise Nearly 100% Year Over Year*, DALES REP. (July 20, 2023), https://thedalesreport.com/psychedelics/sales-of-johnson-johnson-esketamine-drug-spravato-rise-nearly-100-year-over-year/; *Q2 2023 Results*, JOHNSON & JOHNSON REPS. (July 20, 2023), https://johnsonandjohnson.gcs-web.com/static-files/0d7dfa93-bb82-4fd9-af4d-5ccbd7478495.

252. *Q3 2023 Results*, JOHNSON & JOHNSON REPS. (Oct. 17, 2023), https://www.investor.jnj.com/files/doc_financials/2023/q3/Q3/3Q23-Press-Release_Final_With-Guidance_With-Attachments.pdf.

IV. THE COMPLEX ROLE OF PATENTS, FDA APPROVAL, AND INSURANCE MOTIVATIONS IN THE USE OF KETAMINE FOR DEPRESSION

Ketamine exists within a curious regulatory paradigm that likely impedes its widespread antidepressant use. It is widely available as an anesthetic drug in its racemic form but is only available as an FDA-approved depression therapy in its intranasal esketamine form. Combined with a high potential for abuse and clinical skepticism, ketamine's promise and widespread adoption as an antidepressant is currently falling short of its full potential as a "revolutionary" antidepressant.

A. PATENTS

In the United States, pharmaceutical inventions are patentable, and those that are filed with and granted by the U.S. Patent and Trademark Office (USPTO) are entitled to twenty years of patent protection.[253] Parke-Davis received the original patent for racemic (equal parts R- and S-enantiomer) ketamine in 1966, so that mixture of the drug is now off-patent.[254] Likewise, Stuart L. Weg patented intranasal administration of ketamine for pain management in 1996, and that patent expired in 2014.[255] The USPTO granted a patent for intranasal administration of ketamine to treat depression to Charney et al. in 2014.[256] While that patent is set to expire in 2030, the USPTO granted an additional 596 days for patent term extension associated with the FDA regulatory process of Spravato. On the patent, Mount Sinai School of Medicine, Yale University School of Medicine, and the NIH are named as assignees—these assignees licensed to Janssen for Spravato.[257] The USPTO granted Janssen a patent for their intranasal dosing method to treat suicidal ideation with esketamine on December 22, 2020.[258]

253. 35 U.S.C. § 154(a)(2).
254. *Id.*; Domino & Warner, *supra* note 112, at 679.
255. U.S. Patent No. 5,543,434 (issued Aug. 6, 1996).
256. U.S. Patent No. 8,785,500 (issued July 22, 2014).
257. *Id.*
258. U.S. Patent No. 10,869,844 (issued Dec. 22, 2020).

Table 4: Notable Ketamine Patents

Patent or Patent Application Number	Description	Approval and Expiration Dates	Owners/Assignees
US3254124	First compound ketamine patent; for racemic (equal parts R- and S-enantiomer) ketamine	May 31, 1966–May 31, 1983	Parke-Davis and Co LLC
US5543434	Method of self-administering intranasal ketamine for pain	Aug. 6, 1996–Feb. 25, 2014	Stuart L. Weg
US20070287753	Method of using intranasal ketamine to treat depression	July 22, 2014–Sept. 15, 2030	Yale University, U.S. Dept. of HHS, NIH, Icahn School of Medicine at Mount Sinai, Yale School of Medicine
US8785500	Method of using intranasal ketamine to treat depression in conjunction with an oral antidepressant	July 22, 2014–Sept. 15, 2030	Yale University, U.S. Dept. of HHS, NIH, Icahn School of Medicine at Mount Sinai, Yale School of Medicine
US10869844	Method of using intranasal administration of esketamine to treat depression in patents with TRD and/or suicidal ideation	Dec. 22, 2020–Sept. 14, 2035	Janssen Pharmaceuticals

Some have criticized the patents covering intranasal administration of esketamine for depression as "product-hopping"—a process where drug manufacturers swap subtly modified versions for existing treatments to extend their product monopolies.[259] According to critics, a classic example of "product hopping" occurs when a patent claims only one enantiomer of a

259. I. Glenn Cohen & Mason Marks, *Patents on Psychedelics: The Next Legal Battlefront of Drug Development*, 135 HARV. L. REV. F. 212, 224–226 (2022); Jennifer D. Claytor & Rita F. Redberg, *Product Hopping-An Expensive and Wasteful Practice*, 180 JAMA INTERNAL MED. 1154, 1154 (2021).

molecule that is previously available as a mixture of the right- and left-handed enantiomer of the molecule.[260] This was the case in the patent for treatment of depression using intranasal esketamine, where clinicians long treated depression with off-label racemic ketamine.[261] S-ketamine is present, in equal parts with R-ketamine, in the racemic ketamine formulation frequently used in anesthesia and psychiatry.[262] Critics fear this might reduce incentives for others to enter the market for fear of impeding Janssen's patent, which chills competition and innovation.[263]

Yet, these critiques may overlook the substantial benefits of Spravato's patents. Allowing Janssen to patent Spravato allows for reduced stigmatization through rebranding—which can in turn lead to broader acceptance and increased likelihood of insurance coverage.[264] And Janssen's patent provided the incentives for the considerable expenditures related to Spravato's FDA approval process.[265] Likewise, granting Janssen a patent on Spravato does not necessarily preclude competitors from entering the market with R-ketamine or another novel substance. Moreover, Part V, *infra*, argues that granting a patent to Spravato may, in many ways, *promote* innovation rather than stifle it.[266]

Notably, this patent paradigm shifts when looking to other jurisdictions. In Canada, drugs comprising a medical ingredient of a previously approved drug, such as an enantiomer of the original, constitute a "variation" on the original instead of an independent "innovative drug" worthy of patent-level protection.[267] In fact, the Canadian Federal Court of Appeal held that Spravato is not an "innovative drug" eligible for such protections.[268] Additionally, the United Nations recommends that enantiomers of existing inventions should be presumed unpatentable.[269] The United States does not presume that

260. Michael A. Carrier & Steve D. Shadowen, *Product Hopping: A New Framework*, 92 NOTRE DAME L. REV. 167, 172 (2016).

261. Cohen & Marks, *supra* note 259, at 225.

262. Fernanda S. Correia-Melo et al., *Comparative Study of Esketamine and Racemic Ketamine in Treatment-Resistant Depression: Protocol for a Non-inferiority Clinical Trial*, 97 MED. 1, 1–2 (2018).

263. Cohen & Marks, *supra* note 259, at 226–28.

264. *Id.*

265. *See infra* Section IV.D.

266. *See infra* Section V.C.

267. Takeda Canada Inc. v. Minister of Health (2013) FCA 13, ¶¶ 13–14.

268. Janssen Inc. v. Minister of Health (2021) FCA 137, ¶¶ 2, 37–38.

269. Christopher M. Holman et al., *Patentability Standards for Follow-On Pharmaceutical Innovation*, 37 BIOTECH. L. REP. 131, 132–33 (2018) (describing efforts by the United Nations Development Programme to "protect public health and provide access to medicines" by heightening patentability requirements).

enantiomers of existing inventions are unpatentable, which is how Janssen successfully obtained a patent for a method of treatment using Spravato.[270]

B. FDA APPROVAL PARADIGM

Although clinicians frequently used racemic ketamine off-label for depression treatment before the FDA approval of Spravato, no formulation of the drug was authorized for depression treatment in the United States or any other country.[271] In the FDA approval process for Spravato, Janssen only needed to prove the drug's efficacy for the treatment of TRD over a placebo—a concept known as "absolute efficacy."[272]

Although controversial, clinical trials for antidepressants must only demonstrate efficacy against a placebo for marketing authorization.[273] Researchers have criticized this approval threshold, which is also the regulatory requirement in the European Medicines Agency (EMA), because it fails to compare Spravato's efficacy against other known effective treatments for TRD—utilizing the concept of "added value."[274] This is a disservice, the critics maintain, because it allows the marketing of a new drug that may be less effective, or more harmful, than others already in use.[275]

Despite evidence to support the use of racemic ketamine for the treatment of depression, only Janssen's intranasal esketamine administration is available as an FDA-approved therapy.[276] Additionally, in 2022, the FDA submitted an explicit warning to health care professionals of the risks associated with use of racemic ketamine for depression treatment (including IV, oral, and intranasal administrations).[277] It remains unclear whether these risks differ substantially from those of esketamine; the government likely submitted this warning because, unlike Janssen's safety trials with Spravato, no entity had produced sufficient safety evidence for racemic ketamine's use as an antidepressant.[278]

C. DEA CLASSIFICATION

Unlike other psychedelic drugs, ketamine is listed as a Schedule III drug, which is reserved for substances that have a potential for abuse less than those

270. U.S. Patent No. 10,869,844 (issued Dec. 22, 2020).
271. Gastaldon et al., *supra* note 238, at 1.
272. *Id.* at 2.
273. *Id.*
274. *Id.*
275. *Id.*
276. Olivia Goldhill, *Ketamine's Promise as an Antidepressant is Being Undermined by Its Lack of Profit*, QUARTZ (Aug. 6, 2020), https://qz.com/1889308/why-isnt-ketamine-approved-as-an-antidepressant/.
277. FDA News Release, Ketamine, *supra* note 213.
278. *See id.*

in Schedule I (which contains psychedelics such as LSD and MDMA) and Schedule II.[279] According to both the U.S. Department of Justice and the U.S. Drug Enforcement Administration, this schedule classification is also due to the fact that ketamine is currently approved for sedation, anesthesia, and (in the case of Spravato) TRD.[280]

However, because of its abuse potential and reputation as a "party drug," ketamine likely faces some clinical skepticism and regulatory hesitation for wider adoption. Ketamine's Schedule III classification makes it unique amongst other widely used antidepressants, most of which are either unclassified, or listed under Schedule IV (which is reserved for substances with a low potential for abuse and low risk of dependence).[281]

Table 5: DEA Classification for Common Antidepressants

Drug	Indication	DEA Classification
Lithium	Depression, bipolar disorder	N/A
MAOIs	Depression	N/A
TCAs	Depression, neuropathic pain, migraine, etc.	N/A
Meprobamate	Anxiety	Schedule IV
Benzodiazepines	Anxiety, insomnia, seizures, muscle relaxant, etc.	Schedule IV
Diazepam	Anxiety, sedation, etc.	Schedule IV
Fluoxetine (Prozac) (SSRI)	Depression, OCD, panic attacks, etc.	N/A
Ketamine	Anesthesia, sedation, depression	Schedule III

D. HOW THE PATENT SYSTEM, FDA APPROVAL PROCESS, AND INSURANCE COVERAGE HAVE HAMPERED KETAMINE'S PROMISE AS AN ANTIDEPRESSANT

The controversy surrounding ketamine's accessibility highlights a conflict between the incentives for patents, FDA approval, and insurance coverage in the United States. Currently, Spravato (intranasal esketamine) remains the only FDA-approved ketamine depression therapy. Yet, some speculate that racemic

279. *Controlled Substance Schedules*, DRUG ENF'T ADMIN, https://www.deadiversion.usdoj.gov/schedules/index.html (last visited Nov. 22, 2023).

280. Ketamine Fact Sheet, *supra* note 132.

281. *Id.*; Rick Stassman, *Should We Loosen the Restrictions on Psychedelics?*, SCI. AM. (July 17, 2018), https://blogs.scientificamerican.com/observations/should-we-loosen-the-restrictions-on-psychedelics/.

or R-ketamine is as safe or effective as esketamine. Racemic ketamine is off-patent, so would likely be much less expensive than Spravato. And the introduction of R-ketamine into this space would create an alternative therapy that ostensibly reduces costs through price competition. So, patients could enjoy a more affordable, and potentially equally effective, treatment if either was approved by the FDA as a depression therapy. But because of insufficient financial motivations to pay for clinical trials for either alternative formulation, patients and clinicians remain with a single FDA-approved treatment option in this space. Ideally, an alternate option would exist to decrease costs, but it remains unclear whether the incentive exists for any entity to expend the resources necessary for FDA approval (and, indirectly, insurance coverage) of racemic ketamine as an antidepressant.

1. Patent Monopolies and FDA Approval Incentives

The FDA approval process is extraordinarily expensive. The cost of clinical trials to support FDA approval typically ranges from $12 million to $33 million, with a median cost of $19 million.[282] In exchange for this expense, the FDA typically grants five (and sometimes up to six or seven) years of market exclusivity to applicants for "small molecule" innovator drugs like ketamine.[283] Companies require incentives to undertake such expenses; patents often provide such an incentive.

In the United States, inventors of new drugs receive twenty years of patent protection for their technological advances.[284] This twenty-year period can be extended for a maximum of five years for delays experienced in the FDA approval process.[285] After the patent (including any term extension) expires, the patent holder typically loses their monopoly on the sale of the drug. Companies, through clever "product hopping" or "evergreening" techniques that change formulation, method of treatment, or formulation claims, can continue blocking generics far beyond the original expiration date.[286]

282. Thomas J. Moore et al., *Estimated Costs of Pivotal Trials for Novel Therapeutic Agents Approved by the US Food and Drug Administration, 2015-2016*, 178 JAMA INTERNAL MED. 1451, 1451 (2018).

283. Aaron S. Kesselheim et al., D*eterminants of Market Exclusivity for Prescription Drugs in the United States*, 177 JAMA INTERNAL MED. 1658, 1658–60 (2017).

284. 35 U.S.C. § 154(a)(2).

285. *Id.* § 156 (providing statutory patent term extension).

286. "Product hopping" or "evergreening" involves a patent holder switching the market for a drug to a "reformulated version that has a later-expiring patent" but which offers little or no therapeutic advantage to its predecessor. Companies will spend heavily to convince clinicians and patients to switch to the new formulation, and may even pull the predecessor product from the market to avoid price competition with the newer product. *See, e.g.*, Gregory

Racemic ketamine was originally patented in 1963 and is long expired, even with any term extension.[287] While there are certain cases that provide an effective monopoly through "regulatory exclusivity" (such as for "orphan drugs" used for fewer than 200,000 patients), none of these seem to apply to the use of racemic ketamine for depression therapies.[288]

On the other hand, Janssen has achieved monopolization by cleverly navigating the patent and FDA exclusivity process. The earliest patent on Spravato expires in 2027; this is for the relatively broad "Intranasal administration of ketamine to treat depression" patent (the '207 patent).[289] In addition to two separate regulatory exclusivities, Janssen also acquired several patents that cover more specific dosage requirements, indications, and methods of treatments (such as simultaneous antidepressant therapies)—the latest of which (as of May 2023) expire in 2035.[290]

Janssen could potentially justify the lengthy expenses involved with FDA approval because they held the patent to intranasal delivery of esketamine. The company could conceivably recuperate their expenses through exploitation of their patent-reinforced monopoly on the sale of the drug. No such incentive exists for approval of racemic ketamine for depression treatment. Because racemic ketamine's patent expired in 1983, without a novel application or chemical modification, no company can acquire a patent on the compound. The only monopolization available would be three years of regulatory exclusivity for a "new indication" (here, racemic ketamine for the new indication of depression).[291] Thus, no company could receive the financial windfalls that monopolization from a patented drug confers, and the three years of exclusivity for a company that proves a "new indication" is probably not enough of an incentive to conduct the expensive clinical trials.

So, short of a non-profit or government initiative to assist with the enormous financial resources associated with the FDA approval process, it

H. Jones et al., *Strategies that Delay or Prevent the Timely Availability of Affordable Generic Drugs in the United States*, 127 BLOOD 1398, 1399 (2016).

287. Goldhill, *supra* note 276.

288. *Designing an Orphan Product: Drugs and Biological Products*, U.S. FOOD & DRUG ADMIN. (July 8, 2022), https://www.fda.gov/industry/medical-products-rare-diseases-and-conditions/designating-orphan-product-drugs-and-biological-products.

289. *Orange Book: Approved Drug Products with Therapeutic Equivalence Evaluations, Patent and Exclusivity for: N211243*, U.S. FOOD & DRUG ADMIN., https://www.accessdata.fda.gov/scripts/cder/ob/patent_info.cfm?Product_No=001&Appl_No=211243&Appl_type=N.

290. *Id.*

291. *Frequently Asked Questions on Patents and Exclusivity*, U.S. FOOD & DRUG ADMIN. (Feb. 5, 2020), https://www.fda.gov/drugs/development-approval-process-drugs/frequently-asked-questions-patents-and-exclusivity#:~:text=Patents%20can%20be%20issued%20or,have%20just%20one%20or%20neither.

seems unlikely that racemic ketamine will gain authorization to treat depression anytime soon. Any organization seeking to use their clinical trial data for FDA approval must publish their protocols to ClinicalTrials.gov; as of May 2023, the website lists several trials from nonprofit organizations (such as research hospitals and medical schools) who have run clinical trials for racemic ketamine use in depression. However, the majority of these have terminated, and the remainder are far from the multi-stage trial threshold required for FDA approval.[292]

2. FDA Approval and Insurance Coverage

Insurance coverage is often linked to FDA approval.[293] Medicaid must cover essentially all FDA-approved drugs (that are prescribed for a Medicaid patient by their physician), and Medicare has limited ability to decline to cover FDA-approved drugs.[294] Private insurance companies, similarly, are only ever *required* to cover a drug if it has FDA approval. And, if insurance companies do not have the FDA's stamp of approval that a drug works, they are more reluctant to pay for it.[295]

Without FDA approval, medical professionals can still prescribe racemic ketamine as an antidepressant, but this is considered "off-label" use of the drug, meaning it is for a clinical outcome not specified in the drug's FDA-approved indication(s).[296] Because the use of racemic ketamine to treat depression is an "off-label" application, it is less likely to be covered as an antidepressant by insurance than the patented Spravato, which is FDA approved as a depression therapy.[297]

Such off-label usage of a drug is difficult to reimburse through insurance, so patients and medical professionals are incentivized to favor the esketamine

292. *See Search Results*, CLINICALTRIALS.GOV, https://clinicaltrials.gov/ct2/results?cond=depression&term=ketamine&cntry=&state=&city=&dist= (last visited Dec. 2, 2022) (providing a list of trials for ketamine use in depression treatment). While termination does not necessarily indicate that any issues occurred during the clinical trials, a terminated study will not lead to clinically relevant evidence to support an FDA application.

293. Rachel Sachs, *Your Weekly Reminder That FDA Approval and Insurance Coverage Are Often Linked*, HARV. L. PETRIE-FLOM CTR. BILL HEALTH BLOG (Nov. 30, 2016), https://blog.petrieflom.law.harvard.edu/2016/11/30/your-weekly-reminder-that-fda-approval-and-insurance-coverage-are-often-linked/.

294. *Id.*

295. *See, e.g.*, AETNA BETTER HEALTH, OFF-LABEL USE OF FDA-APPROVED DRUGS POLICY (2016).

296. *Understanding Unapproved Use of Approved Drugs "Off Label"*, U.S. FOOD & DRUG ADMIN. (Feb. 2, 2018), https://www.fda.gov/patients/learn-about-expanded-access-and-other-treatment-options/understanding-unapproved-use-approved-drugs-label.

297. Steve Levine, *Ketamine: A Cautionary Tale*, PSYCH. TODAY (Nov. 30, 2021), https://www.psychologytoday.com/ca/blog/pathways-progress/202111/ketamine-cautionary-tale.

intranasal application of Spravato, despite the cheaper cost of racemic ketamine.[298] This can be a substantial expense—infusions of racemic ketamine for depression cost roughly $5–$15 per week for the drug alone, whereas Spravato costs $1,000–$1,600 per week.[299] Add that to the fact that, in 2022, the FDA submitted an explicit warning to health care professionals of the risks associated with use of racemic ketamine for depression treatment, and a rapid expansion of racemic ketamine antidepressant therapies in the near future grows unlikely.[300] Critics argue that this is deeply regrettable, given the affordability of racemic ketamine and the promise that the drug shows in treating depression.[301]

V. INNOVATIVE RESPONSES TO KETAMINE'S RESTRICTIVE REGULATORY LANDSCAPE

Given the current regulatory and public perception paradigm, ketamine faces an uphill battle towards increased widespread adoption. There are two promising avenues that might lead to more substantial use of the drug for depression therapies.

First is the budding psychedelic therapy space, which embraces drugs in spite of, and perhaps *because of*, their complex regulatory restrictions. Expansion in this space seems likely, especially given ketamine's promising initial antidepressant results and relatively safe use profile. Second, ketamine represents the immense untapped potential of glutamatergic/NMDA-reception modulating antidepressant therapies. Ketamine's ability to treat those who struggle to achieve depression remission on monoamine-targeting drugs will likely prompt significantly more research into the mechanistic understanding of the glutamatergic/NMDA-reception pathway. These insights may lead to novel drug therapies that avoid some of the obstacles facing ketamine.

Counterintuitively, constraints imposed by the existing regulatory landscape drive innovation in these spaces. In response to conditions that make the widespread antidepressant adoption of ketamine unlikely in its current distribution channels, both psychedelic therapy entrepreneurs and glutamatergic/NMDA-modulating drug researchers show that limitations can lead to *increased* innovation.

298. *Id.*

299. CADTH COMMON DRUG REVIEW, PHARMACOECONOMIC REPORT ESKETAMINE HYDROCHLORIDE (SPRAVATO) (2021) (providing cost information in Appendix 1, Cost Comparison Table) [hereinafter PHARMACOECONOMIC REPORT, SPRAVATO].

300. FDA News Release, Ketamine, *supra* note 213.

301. *See* Cohen & Marks, *supra* note 259, at 226–28.

A. PSYCHEDELIC THERAPY AND PSYCHEDELIC STARTUPS

Psychedelics have long been subject to draconian restrictions—scaring off researchers from investigating these drugs and their components.[302] As a result, little is known about these drugs' potential, but studies of drugs like MDMA, psilocybin, and ketamine suggest they could provide novel approaches to difficult psychiatric conditions.[303] Because of this untapped potential, entrepreneurs see immense upside despite the risks associated with this space.

More than a dozen psychedelic therapy start-ups have emerged in the past decade.[304] Notably, Field Trip Health, a Canadian company that operates high-end ketamine clinics, raised over $150 million to finance their expansion into the antidepressant therapy field.[305] Field Trip clinics offer ninety-minute ketamine "trips" with therapist-guided "integration sessions" to help patients process these experiences.[306]

Many companies like Field Trip are exploring more enduring therapies to treat MDD, TRD, and PTSD, using drugs such as psilocybin or MDMA. However, ketamine is primarily used in such facilities because it is legally available to patients outside a clinical study.[307] Despite this, those in the psychedelic therapy space are beginning to leverage the knowledge gained in ketamine depression studies to inform other unconventional depression treatments, such as those using psilocybin.[308] Spravato's success has even spurred other large pharmaceutical companies to invest in research using other psychedelics and their derivatives as antidepressants.[309]

These therapy channels, while auspicious, are also fraught with concerns about safety and oversight. During the pandemic, the Trump administration relaxed telehealth restrictions, and the Biden administration maintained this

302. Andrew Jacobs, *The Psychedelic Revolution Is Coming. Psychiatry May Never Be the Same*, N.Y. TIMES (Nov. 11, 2021), https://www.nytimes.com/2021/05/09/health/psychedelics-mdma-psilocybin-molly-mental-health.html.

303. *See, e.g.*, Jennifer M. Mitchell et al., *MDMA-Assisted Therapy for Severe PTSD: A Randomized, Double-Blind, Placebo-Controlled Phase 3 Study*, 27 NATURE MED. 1025 (2021); Roland R. Griffiths et al., *Psilocybin Produces Substantial and Sustained Decreases in Depression and Anxiety In Patients with Life-Threatening Cancer: A Randomized Double-Blind Trial*, 30 PSYCHOPHARMACOLOGY 1181 (2016).

304. Jacobs, *supra* note 302, at 2.

305. *Id.* at 2–4.

306. *Id.* at 3.

307. *Id.*

308. McElvery, *supra* note 89.

309. Christoph Kraus et al., *The Influence of Ketamine on Drug Discovery in Depression*, 24 DRUG DISCOVERY TODAY 2033 (2019).

policy.[310] Telehealth increases access to off-label uses of racemic ketamine for depression but raises substantial concerns about a lack of clinical supervision. For example, Joyous, a ketamine telehealth startup, provides prescriptions of the drug in as short as a thirty-minute video call.[311] This shift away from clinics and towards at-home frequent use of ketamine alarms many public health officials because TRD patients, given their condition, are a particularly vulnerable population.[312] Additionally, telehealth channels might discourage patients from revealing adverse effects from ketamine, for fear that such disclosure inevitably results in (often prohibitively expensive) in-person care.[313]

This situation might be the reckoning of access issues caused by the very regulation that many public health officials advocate for. Because Spravato is the only FDA-approved antidepressant use of ketamine and insurance carriers are only likely to reimburse approved therapies, Janssen essentially has a monopoly on authorized ketamine depression treatments in the United States, which has led to exclusionary pricing of the drug.[314]

Many patients report that ketamine is "life changing" and "the only drug that ever relieved their crushing symptoms," but this paradigm means access to approved antidepressant administration of the drug is expensive and out of reach for many.[315] Thus, psychedelic therapy and telehealth startups are one promising alternative avenue to ketamine access for patients with depression, against the backdrop of an overly restrictive regulatory state.

B. MECHANISM OF ACTION: KETAMINE DERIVATIVES AND ALTERNATIVE GLUTAMATERGIC/NMDA-RECEPTION MODULATING DRUGS FOR DEPRESSION TREATMENT

Researchers remain unsure what precise mechanism of action causes ketamine's antidepressant effect, but discoveries into the method could prompt further breakthroughs in ketamine or ketamine-derived depression treatments. Recent proposals suggest that activation of α-amino-3-hydroxy-5-methyl-4- isoxazole propionic acid (AMPA) receptors by hydroxynorketamine, a ketamine metabolite, causes the rapid antidepressant-like properties observed with the drug.[316] Ketamine also acutely increases hippocampal brain-derived neurotropic factor, which some propose might cause antidepressant

310. Hamby, *supra* note 135.
311. *Id.*
312. *Id.*
313. *Id.*
314. *See* PHARMACOECONOMIC REPORT, SPRAVATO, *supra* note 299, at 20.
315. Hamby, *supra* note 123.
316. Panos Zanos et al., *NMDAR Inhibition-Independent Antidepressant Actions of Ketamine Metabolites*, 533 NATURE 481, 481 (2016).

effects.[317] Still others have postulated that ketamine may affect brain regions through epigenetic mechanisms. [318] Researchers continue investigating ketamine's impact on neural interconnectivity; one recent development suggests that subanesthetic ketamine administration (at a level used in depression treatment) disrupts functional connectivity between the subgenual anterior cingulate cortex (which is involved with mood modulation) and the thalamus, hippocampus, and retrosplenial cortex.[319]

A detailed mechanistic understanding of ketamine's antidepressant impact, at the very least, illuminates other potential drugs and targets in this pathway. Although much of the research around ketamine and depression pertains to increasing or prolonging ketamine's antidepressant effects, some researchers are working to manipulate the chemical composition of ketamine to reduce the drug's abuse potential.[320] Carlos Zarate, who was fundamental to the initial research into ketamine's antidepressant effects, is studying hydroxynorketamines (HNKs), ketamine metabolites which can offer rapid, sustained antidepressant effects without many of the drug's side effects.[321]

Recent efforts also focus on developing novel oral and sublingual formulations for ketamine, with an eye towards low-dose antidepressant use of the drug in an outpatient setting.[322] Death by ketamine overdose, in any delivery form, is rare and usually involves other intoxicants or physical trauma from accidents while under the influence of the drug.[323]

In a 2000 study on ketamine's antidepressant effects, Berman et al. suggested that other glutamatergic and NMDA receptor-modulating drugs might prove useful for patients with depression.[324] Many such drugs exist, and several are currently undergoing clinical trials as antidepressants.

317. Lêda S.B. Garcia et al., *Acute Administration of Ketamine Induces Antidepressant-Like Effects in the Forced Swimming Test and Increases BDNF Levels in the Rat Hippocampus*, 32 PROGRESS NEURO-PSYCHOPHARMACOLOGY & BIOLOGICAL PSYCHIATRY 140, 140–41 (2008).

318. Miyeon Choi et al., *Ketamine Produces Antidepressant-Like Effects Through Phosphorylation-Dependent Nuclear Export of Histone Deacetylase 5 (HDAC5) in Rats*, 112 PROCS. NAT'L ACAD. SCIS. 15755, 15755–56 (Nov. 2015).

319. Jing J. Wong et al., *Ketamine Modulates Subgenual Cingulate Connectivity with the Memory-Related Neural Circuit—A Mechanism of Relevance to Resistant Depression?*, 4 PEERJ 1710 (2016).

320. Jaclyn N. Highland et al., *Hydroxynorketamines: Pharmacology and Potential Therapeutic Applications*, 73 PHARMACOL. REV. 763, 765 (2021).

321. *Id.*

322. Chui Chong et al., *Development of a Sublingual/Oral Formulation of Ketamine for Use in Neuropathic Pain*, 29 CLINICAL DRUG INVESTIGATION 317 (2009).

323. Brendon R. Lalonde & H. Rachelle Wallage, *Postmortem Blood Ketamine Distribution in Two Fatalities*, 28 J. ANALYTICAL TOXICOLOGY 71, 71 (2004).

324. Berman et al., *supra* note 99, at 351.

For example, the NMDA-receptor antagonist drug memantine displayed promising results as an antidepressant for patients who also suffered from alcoholism.[325] Lanicemine, an NMDA receptor open-channel blocker, also showed significant antidepressant effects with minimal side effects in a randomized, double blind, placebo-controlled study.[326] And D-cycloserine, an NMDA receptor agonist, worked to decrease depressive symptoms and suicidal ideation when used in conjunction with ketamine treatment.[327]

Manji, at Janssen, expressed a strong interest in the AMPA receptors as a promising regulatory pathway for future mental health therapeutics.[328] The AMPA receptors, which are ionotropic glutamate receptor subunits, exist throughout the brain and regulate excitability.[329] Manji hopes that the ubiquity of the AMPA receptors and the relatively few existing therapeutics in the field that target the pathway, might present opportunities for novel ways to treat mental illness conditions.

C. CONSTRAINTS AS A SOURCE OF CREATIVITY: REGULATORY RESTRICTIONS, PATENTS, AND CLINICAL SKEPTICISM AS INNOVATION DRIVERS

In 2015, Joseph P. Fishman published *Creating Around Copyright* in the Harvard Law Review, arguing that the *constraints* created by copyright law were themselves major sources of creativity.[330] Fishman's paper begins with the story of a filmmaker who devised a *Flash Gordon* remake. Unable to secure a license, the filmmaker cleverly worked around the *Flash Gordon* copyright, distilling visual thematic aspects of that story to construct a new universe of characters and settings. That filmmaker was George Lucas, and the galaxy far, far away eventually became the *Star Wars* universe.[331]

325. Leea H. Muhonen et al., *Double-Blind, Randomized Comparison of Memantine and Escitalopram for the Treatment of Major Depressive Disorder Comorbid with Alcohol Dependence*, 69 J. CLINICAL PSYCHIATRY 392, 392 (2008).

326. Gerard Sanacora et al., *Lanicemine: A Low-Trapping NMDA Channel Blocker Produces Sustained Antidepressant Efficacy with Minimal Psychotomimetic Adverse Effects*, 19 MOLECULAR PSYCHIATRY 978, 978 (2014).

327. Mu-Hong Chen et al., *Maintenance of Antidepressant and Antisuicidal Effects by D-Cycloserine Among Patients with Treatment-Resistant Depression who Responded to Low-Dose Ketamine Infusion: A Double-Blind Randomized Placebo-Control Study*, 44 NEUROPSYCHOPHARMACOLOGY 2112, 2112 (2019).

328. Talesnik, *supra* note 202.

329. *Id.*

330. Joseph P. Fishman, *Creating Around Copyright*, 128 HARV. L. REV. 1333 (2015).

331. *Id.* at 1336; J.W. RINZLER, THE MAKING OF STAR WARS 4 (2007).

Fishman's article describes how fears of copyright infringement can, paradoxically, result in imaginative creations.[332] Fishman and others note that this phenomenon occurs throughout the intellectual property landscape; constraints also promote innovation in the realm of patents and useful innovations.[333]

Impediments created by patent monopolies force inventors to look beyond the "default" and towards disparate applications and processes that might not initially appear promising.[334] A patentee's right to exclude triggers competitors to develop innovative creations that compete with and improve upon the patented invention.[335]

Ketamine provides a lucid illustration of this phenomena. The drug faces a litany of obstructions to widespread adoption as an antidepressant, from restrictive drug classifications to a misaligned patent and regulatory approval motivation paradigm. Although these conditions doubtlessly discourage many from entering the space, they also force those who wish to operate in this space to do so creatively.

1. *Psychedelic Therapy Startups and Telehealth: Creative Solutions to Restrictive Ketamine Access*

Psychedelic therapy startups rebelled against one framework by creating a new one, building a product that delivered treatment despite a restrictive regulatory landscape.[336] Companies such as Field Trip Health responded to clinical skepticism around ketamine's use as an antidepressant by creating a novel medical model for psychedelics. This creates a blueprint for others providing access to drugs, such as psilocybin and MDMA, that provide immense potential upside to patients facing difficult-to-treat conditions (such as TRD and PTSD), despite restrictive access issues.[337]

Likewise, those operating in the telehealth space are unquestionably serving as the type of "disruptors" that drive progress in ossified systems.[338] Access to pharmaceuticals, especially those that are not FDA-approved or used "off-label," can be incredibly cumbersome. Clinicians are skeptical about

332. Fishman, *supra* note 330, at 1336.

333. *Id.* at 1351.

334. *Id.*

335. *Id.* at 1339.

336. *Id.* at 1337; Philip N. Johnson-Laird, *Freedom and Constraint in Creativity*, *in* THE NATURE OF CREATIVITY 202, 212–13 (Robert J. Sternberg ed., 1988).

337. This is already happening. Companies are taking notice of ketamine's rollout in these psychedelic therapy startups and applying those learnings to increase access to other drugs and methods of treatment. *See, e.g.*, Jacobs, *supra* note 302.

338. Hamby, *supra* note 135.

prescribing such drugs, insurance companies seldom reimburse patients for them, and for those who have access, costs are often astronomical. Telehealth companies like Joyous provide relatively inexpensive access to drugs like ketamine cheaply, quickly, and to patients throughout the United States, regardless of their geographic proximity to clinics.[339]

There are certainly downsides to these approaches, discussed at length in Section IV.D, *supra*.[340] Nevertheless, these pathways are doubtlessly *innovative* in their approach to increasing access to novel therapies. In the oft-stagnate field of pharmaceutical access, this is the type of change that might inevitably prove immensely valuable to patients.

2. *Innovating Around Patents: Spravato and Novel Glutamate-Modulating Drugs*

Policy justifications for intellectual property protections in the United States typically focus on rewards for resource-consuming efforts while developing new inventions.[341] With the motivation of a government-sanctioned temporary monopoly, creators expend time and money designing products that benefit the public. This is a frequently discussed motivation for inventors; less examined is the impact that such monopolies have on *other* innovators.

Yet, courts and commentators recognize that "inventing around" patents creates a generative source of creativity.[342] For example, in *James P Marsh Corp. v. U.S. Gauge Co.*, Seventh Circuit Judge Evans noted that the patent system spurs competitors to "put forth their best effort to produce a product as good, yet different from the patentee's."[343] Others observe that innovation is improved through the patent system's "mandatory differentiation

339. *Id.*

340. *See id.*

341. *See, e.g.*, Fishman, *supra* note 330, at 1345; WILLIAM M. LANDES & RICHARD A. POSNER, THE ECONOMIC STRUCTURE OF INTELLECTUAL PROPERTY LAW 69 (2003).

342. Fishman, *supra* note 330, at 1351.

343. 129 F.2d 161, 164 (7th Cir. 1942); *see also* Chicago Steel Foundry Co. v. Burnside Steel Foundry Co., 132 F.2d 812 (7th Cir. 1943). In *Chicago Steel Foundry*, Judge Evans again made a justification for the existence of the patent system, noting "instead of displaying monopolistic traits, the patent fosters competition among inventors and begets new and better products at lesser costs." *Chicago Steel Foundry*, 132 F.2d at 816.

mechanism."[344] In several decisions, the Federal Circuit cited "inventing around" as a major positive outcome of the patent system.[345]

Spravato is an example of the rewards that such diversified search routes promote. In attempting to "invent around" the existing ketamine landscape, Janssen developed a unique drug formulation and method of treatment. The USPTO granted Janssen a patent for their efforts in developing Spravato; in return, the public gained access to a novel drug therapy. Because Janssen's patent provided sufficient motivation to pay for the process, the company largely funded the otherwise prohibitively expensive FDA approval process for Spravato. So, when Janssen's patents ultimately expire, generic manufacturers will be able to provide a cheaply accessible *and* FDA-approved antidepression treatment.[346]

There is good reason to believe that similar motivations will drive novel glutamatergic/NMDA-receptor modulating drug therapies. With Spravato's existing patents and racemic ketamine's long-expired protections, companies might find that their best route to profitability in this space will be to develop completely new formulations of drugs. As discussed *supra*, this is already happening—several pioneers who established ketamine's antidepressant efficacy are now developing alternate drug formulations that modulate the glutamate/NMDA pathway, hoping to provide an alternative or improvement to ketamine.[347]

Antidepressant therapies are ripe for this type of divergent thinking. Depression treatments exist in a field where the optimal solution is not necessarily known ex ante—clinicians often must try numerous classes of drugs before a patient achieves remission.[348] A diverse set of solutions available in this space increases the chances of successful treatment.[349]

Research into this class of drugs might even open the floodgates to an entire new class of antidepressants. Scientists may soon develop drugs that harness ketamine's antidepressant power without its undesirable dissociative

344. *See, e.g.*, F. SCOTT KIEFF ET AL., PRINCIPLES OF PATENT LAW 70–71 (4th ed. 2008); Matthew J. Conigliaro et al., *Foreseeability in Patent Law*, 16 BERKELEY TECH. L.J. 1045, 1050 n.17 (2001).

345. *See, e.g.*, TiVo Inc. v. EchoStar Corp., 646 F.3d 869, 883 (Fed. Cir. 2011) (en banc); Hilton Davis Chem. Co. v. Warner-Jenkinson Co., 62 F.3d 1512, 1520 (Fed. Cir. 1995)

346. *See* Gastaldon et al., *supra* note 238.

347. *See, e.g.*, Berman et al., *supra* note 99, at 351–54; Muhonen et al., *supra* note 325; Sanacora et al., *supra* note 326; Chen et al., *supra* note 327.

348. Philip Royce & Cassandra Ma, *Choosing an Antidepressant*, 44 AUS. PRESCRIBER 12, 12–15 (2021); Richard R. Nelson, *Uncertainty, Learning, and the Economics of Parallel Research and Development Efforts*, 43 REV. ECON. & STAT. 351, 352 (1961).

349. *See* Fishman, *supra* note 330, at 1353; Nelson, *supra* note 348.

side effects. This might even lead to a class of drugs that, like SSRIs, patients can take daily with minimal adverse effects. Forced to explore realms outside of the current pharmaceutical mainstream, clinicians might develop a drug that becomes as powerful and as popular as Prozac was in the 1980s.

VI. CONCLUSION

The development story of ketamine follows the same track as many early antidepressant drugs (e.g., MAOIs, TCAs): researchers, using a drug for one therapeutic purpose, observe an unexpected side effect and follow through with clinical diligence to identify another useful purpose of the drug. Ketamine (and, potentially, its derivatives) holds immense promise for advances in antidepressant therapies. However, the current regulatory paradigm for ketamine in the United States also showcases a tension between the patent incentive system, the FDA approval process, and insurance carriers that might be limiting the otherwise breakthrough potential of ketamine as a depression treatment. For ketamine to truly achieve its prospect as "one of the most significant advances in the field of depression in recent years," regulators may need to rethink how novel uses of previously approved drug therapies can gain FDA approval for new indications and methods of treatment. Without such intervention, millions of individuals suffering from depression may not receive access to a potentially consequential intervention.

THE CAR-T CELL THERAPY INNOVATION DRIVERS: A YESCARTA CASE STUDY

Christine R. O'Brien Laramy[†]

TABLE OF CONTENTS

DOI: https://doi.org/10.15779/Z38CZ32610

† Ph.D., Northwestern University, Department of Chemical and Biological Engineering, 2018; J.D. Candidate, University of California, Berkeley School of Law, Class of 2024. This Article benefitted from guidance, support, and feedback from Prof. Peter Menell and Allison Schmitt as well as other students in the 2022–23 Life Sciences & Innovation Workshop.

> Cancer randomly attacks people of all ages and forces its victims and their families to watch impotently as it grows and spreads. Cancer murders innocents. It is a holocaust.
>
> —Steven A. Rosenberg, National Cancer Institute[1]

I. INTRODUCTION

A highly effective treatment for cancer lies within our own bodies: our immune system. Chimeric antigen receptor (CAR)-T cell therapy harnesses patients' own immune cells to treat cancer. This Article explores the innovation drivers that spurred CAR-T cell therapy development.

From its inception, the United States sought to incentivize scientific innovation through various schemes. First, the Constitution drafters empowered Congress to create intellectual property rights for inventors—for example, patent protection.[2] Congress implemented these rights in several intellectual property schemes, including patent rights.[3] Later, the U.S. government developed additional innovation incentives: it created government research agencies (e.g., the National Cancer Institute), provided grants to researchers through its agencies (e.g., National Institutes of Health grants), and offered regulatory exclusivity to drug manufactures who successfully demonstrate innovative, safe, and efficacious drugs (e.g., biologic exclusivity).[4] This Article outlines the role of these and other innovation incentives in the successful development of CAR-T cells as cancer therapeutics.

1. Steven A. Rosenberg, *Immersion in the Search for Effective Cancer Immunotherapies*, 27 MOL. MED. 63, 2 (2021).

2. U.S. CONST. art. I, § 8, cl. 8.

3. *See, e.g.*, 35 U.S.C. §§ 1-390; Defend Trade Secrets Act, 18 U.S.C. § 1836.

4. *See, e.g.*, NATIONAL RESEARCH COUNCIL COMMITTEE ON ASSESSING THE VALUE OF RESEARCH IN ADVANCING NATIONAL GOALS, FURTHERING AMERICA'S RESEARCH ENTERPRISE 20–33 (Richard F. Celeste, Ann Griswold & Miron L. Straf eds., 2014).

Doctors have treated cancer, with varying degrees of success, for hundreds of years.[5] First, doctors attempted to remove cancer cells surgically.[6] Next, following X-ray technology development, doctors treated patients with radiation. Chemical warfare developed during World War II provided foundational research for the first chemotherapeutics.[7] More recent cancer therapeutics derive from advances in genetic engineering and understanding of the immune system. These recent therapeutics include anti-cancer monoclonal antibodies (i.e., engineered versions of natural proteins designed to bind to molecules associated with cancer cells), small molecules targeted to bind to proteins associated with cancer-causing genetic mutations, and CAR-T cells. Unlike earlier therapeutics, CAR-T cells are "living" therapeutics comprising engineered versions of patients' natural immune cells designed to target and kill cancer cells.[8]

CAR-T cell therapy innovation began with individual researchers driven by intrinsic and extrinsic motivations.[9] Researchers sought treatments with better results and reduced side effects relative to surgery and traditional chemotherapies. Because of rare but repeated reports of spontaneous cancer remission in patients with an activated immune system (e.g., due to an infection), the immune system seemed to hold the answer. Tenacity, curiosity, and grant funding fueled individual researchers' investigations into the immune system and its anti-cancer activity. New technology enabled researchers to understand immune system components, like B cells and T cells. Genetic engineering techniques allowed researchers to engineer B and T cells to perform new or modified functions.[10] CAR-T cell therapy involves engineering a patient's own T cells to produce a CAR protein, causing the T cell to attack the patient's cancer cells.

Researchers' efforts combined with pharmaceutical company investment and manufacturing expertise led to FDA approval of six CAR-T cell therapies starting in 2017.[11] In some instances, CAR-T cell therapies offer advantages over traditional chemotherapies including reduced treatment time (months vs. years), shorter-term and lesser side effects, and longer-lasting efficacy.[12] As of

5. *See, e.g.*, *Milestones in Cancer Research and Discovery*, NAT'L CANCER INST. (Aug. 31, 2020), https://www.cancer.gov/research/progress/250-years-milestones.

6. *See* discussion *infra* Sections II.A–II.C.

7. *See* discussion *infra* Section II.C.

8. *See* discussion *infra* Sections II.D–II.F.

9. *See* discussion *infra* Section IV.A.

10. *See* discussion *infra* Sections II.D–II.F, III.A.

11. *See* discussion *infra* Sections III.B–III.C.

12. *See, e.g.*, Zoom Interview with Dario Campana, Professor, Nat'l Univ. of Sing., Dep't of Paediatrics (Apr. 11, 2023) [hereinafter Campana Interview].

April 2024, all six FDA-approved therapies treat blood cancers, but researchers hope to expand CAR-T cell therapies to treat solid tumors in the future.[13]

This Article explores the innovation drivers that incentivized individuals and companies to advance CAR-T cells therapeutics from the bench to the bedside. First, this Article will explain the scientific background for CAR-T cell therapy development. Next, the Article will discuss the CAR-T cell therapy development from the researcher brainstorming phase through commercialization. Finally, the Article will identify individual researcher and corporate innovation drivers, including individual intrinsic motivations like curiosity and altruism and external incentives like patent rights, trade secret protection, and regulatory exclusivity.

II. BACKGROUND

Today, researchers understand the immune system as a complex system including two important cell types (B cells and T cells) that distinguish between the body's natural cells and materials and foreign materials. B cells secrete antibodies, specialized proteins designed to specifically bind to other, foreign proteins circulating in the body.[14] B cells' genetic material encodes the information required for the cells to create their proteins, including antibodies.[15] T cells recognize foreign materials differently. Instead of secreting antibodies, T cells have receptors on their cell surfaces designed to specifically bind foreign proteins.[16] T cell receptors (TCRs) are also proteins, encoded by T cells' genetic material. The portion of the TCR responsible for binding to the foreign protein is structurally similarly to the corresponding portion of an antibody.[17] However, unlike antibodies which bind to foreign proteins free in circulation, TCRs bind to foreign proteins displayed on the surface of other cells by a surface protein called the major histocompatibility complex (MHC).[18] Prior to the 1960s, scientists suspected the immune system's role in cancer suppression, but lacked this foundational understanding of B and T cell functioning.

13. *See* discussion *infra* Sections II.F, III.C.

14. Alex D. Waldman et al., *A Guide to Cancer Immunotherapy: From T Cell Basic Science to Clinical Practice*, 20 NATURE REVS. IMMUNOLOGY 651, 652 (2020).

15. *See, e.g.*, Caressa N. Tsai, *The Invention of Next-Generation Sequencing*, 39 BERKELEY TECH. L.J. 613, II.A (2024) (providing additional information on the translation of genetic information).

16. *Id.*

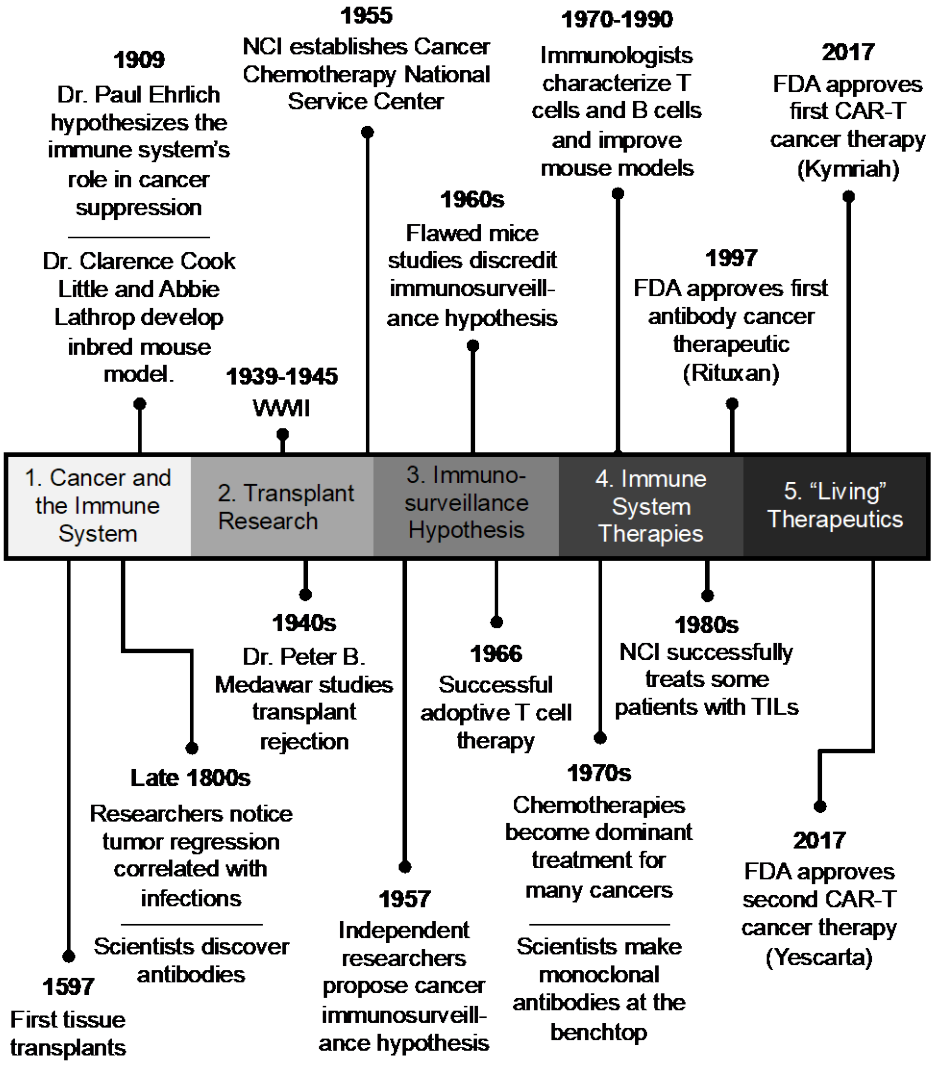
17. *See infra* Section III.A.

18. *Id.*

Yescarta harnesses a patient's own immune cells to treat their cancer.[19] The development of CAR-T cell therapies, like Yescarta, required advances in transplantation research (Section II.B), immune system and cancer biology understanding (Sections II.A, II.C–II.D), and genetic sequencing and editing techniques (Section II.E). This Section traces these scientific developments over the last century to provide context for the innovation of CAR-T cell therapy (Figure 1).

19. *CAR T Cells: Engineering Patients' Immune Cells to Treat Their Cancers*, NAT'L CANCER INST. (Mar. 10, 2022), https://www.cancer.gov/about-cancer/treatment/research/car-t-cells (Mar. 10, 2022) [hereinafter NCI 2022].

Figure 1: Timeline of key events leading to the first CAR-T cancer therapeutics.



A. CANCER AND THE IMMUNE SYSTEM

Researchers have long suspected that the immune system naturally suppresses or mitigates cancer. In the late 1800s, Wilhelm Busch and Friedrich Fehleisen noticed tumor regression in human patients who had also developed a skin infection.[20] A few years later, New York physician William Coley injected his cancer patients with bacteria to spur an immune response.[21]

20. Waldman et al., *supra* note 14, at 651.
21. *Id.*

In 1909, one year after winning the Nobel Prize in Physiology or Medicine, German chemist and immunologist Paul Ehrlich hypothesized that the immune system might play a role in tumor suppression.[22] He observed that cancer occurred in families, but typically developed later in adulthood.[23] Therefore, he hypothesized, parents can pass on cancer to their children but the body has some defenses to suppress tumors for years.[24] However, without animal cancer models, scientists could not test this hypothesis.[25] Thus, in the early 20th century, most doctors treated cancer with surgery and localized radiation, even though both treatments frequently failed to eradicate all of the cancer cells.[26]

B. TRANSPLANTATION RESEARCH ELUCIDATES IMMUNE PROCESSES

Evidence from surgical transplantation research further supported Ehrlich's hypothesis that some bodily defenses could recognize harmful or foreign cells.[27] As early as 1597, surgeon Gaspare Tagliacozzi of Bologna noticed most successful tissue transplants (mostly skin grafts) occurred when the tissue came from the patient and not from a donor.[28] His work and that of other transplantation surgeons led tumor biologists to graft tumors into mice to study cancer and graft rejection.[29] However, mouse immune cells appeared to recognize the graft cells as foreign and reject them.[30] As both surgeons and tumor biologists continued to face non-self-transplant rejection, this research stalled.[31]

The need to treat burn victims from World War II renewed interest in transplant research. Many patients' injuries were too severe for them to act as their own tissue donors.[32] The British Medical Research Counsel assigned zoologist Peter B. Medawar to research transplantation in the 1940s.[33] By

22. Paul Ehrlich, *Ueber Den Jetzigen Stand Der Karzinomforschung*, 5 NED.TIJDSCHR. GENEESKD 273, 289–90 (1909); Stefan H. E. Kaufmann, *Immunology's Coming of Age*, 10 FRONTIERS IMMUNOLOGY 684, 685 (2019); Waldman et al., *supra* note 14, at 651.

23. Ehrlich, *supra* note 22, at 288–90.

24. *Id.*

25. *See* Gavin P. Dunn et al., *Cancer Immunoediting: From Immunosurveillance to Tumor Escape*, 2 NATURE IMMUNOLOGY 991, 991 (2002).

26. Vincent T. DeVita, Jr. & Edward Chu, *A History of Cancer Chemotherapy*, 68 CANCER RSCH. 8643, 8643 (2008).

27. *See* Dunn, *supra* note 25, at 991.

28. *See* Arthur M. Silverstein, *Transplantation and Immunogenetics*, *in* HISTORY OF IMMUNOLOGY 275, 276–78 (1989).

29. *See id.* at 279–83.

30. *Id.* at 278–82.

31. *Id.* at 283–85.

32. *Id.* at 285–91.

33. *Id.*

studying human patients with skin grafts, and later, transplant rejection in laboratory animals, Medawar and others confirmed that immune cells caused transplant rejection.[34] Their work caught the attention of the growing immunology field.[35]

C. THE CANCER IMMUNOSURVEILLANCE HYPOTHESIS

Medawar's work and the creation of reliable mouse models re-ignited research into the connection between cancer and the immune system. At the same time Ehrlich proposed his immune system cancer hypothesis, scientist Clarence Cook Little and mouse breeder Abbie Lathrop created the first inbred mouse model.[36] Inbred mouse models allow multiple generations of mice to have nearly identical genetic makeups.[37] The genetic similarity permitted tumor transplantation from one inbred mouse to another—an early animal cancer model. Further, in support of Ehrlich's hypothesis, researchers discovered they could train an inbred mouse's immune system to recognize a transplant from a genetically similar mouse as foreign.[38] This training involved inducing tumor formation (e.g., through exposure to a carcinogen), removing the tumor, and, after a period of time, re-transplanting the tumor back into the mouse.[39] This training research led scientists to hypothesize that the immune system recognized markers on the surface of tumor cells (i.e., "tumor-specific antigens").[40]

By 1957, two researchers had independently proposed the "cancer immunosurveillance" hypothesis.[41] The hypothesis is as follows: when cancer cells develop, either from inherited cancer-causing genes or from a cancer-causing genetic mutation, the cancer cells lose their "self" antigens or develop foreign antigens, and then provoke "an effective immunological reaction with regression of the tumor and no clinical hint of its existence."[42]

---

34. *Id.*

35. *Id.*

36. Tom Clarke, *Mice Make Medical History*, NATURE (Dec. 5, 2002), https://www.nature.com/articles/news021202-10; *see also* Leila McNeill, *The History of Breeding Mice for Science Begins with a Woman in a Barn*, SMITHSONIAN MAG. (Mar. 20, 2018), https://www.smithsonianmag.com/science-nature/history-breeding-mice-science-leads-back-woman-barn-180968441/.

37. Clarke, *supra* note 36.

38. Lloyd J. Old & Edward A. Boyse, *Immunology of Experimental Tumors*, 15 ANN. REV. MED. 167, 173 (1964).

39. *Id.*

40. Dunn, *supra* note 25, at 991; *see also* Old & Boyse, *supra* note 38, at 167–69.

41. *See* Macfarlane Burnet, *Cancer – A Biological Approach*, 1 BRIT. MED. J. 841, 846 (1957); *see also* Dunn, *supra* note 25, at 991–92.

42. Burnet, *supra* note 41, at 846.

Nude mouse models, another advance in animal models, initially threw cold water on the cancer immunosurveillance hypothesis.[43] Nude mice have severely impaired immune systems, with different levels and types of impairment depending on the method scientists use to induce impairment.[44] In the 1960s, researchers developed an athymic nude mouse model, a genetically immunocompromised model lacking a thymus and most T cells.[45] Despite the severe immune impairment, the athymic mice showed no significant difference in spontaneous tumor formation compared to immunocompetent mice.[46] The cancer immunosurveillance hypothesis, and research on the immune system's role in suppressing cancer, thus fell into temporary disfavor.[47]

In addition to the initial nude mice experiment results, another class of cancer therapeutics distracted from cancer immunotherapy research. World War II kicked off intense research into the chemical components of poison gases called nitrogen mustards as cancer "chemotherapeutics."[48] These efforts eventually led Congress to provide $5 million to the National Cancer Institute to establish the Cancer Chemotherapy National Service Center.[49] After initial skepticism related to severe adverse reactions, improved chemotherapeutics became the dominant treatment for many blood cancers (including large B-cell lymphoma) by the 1970s.[50] Still in use today, these treatments prolong life expectancy, but often fail to cure patients and cause severe adverse reactions.[51]

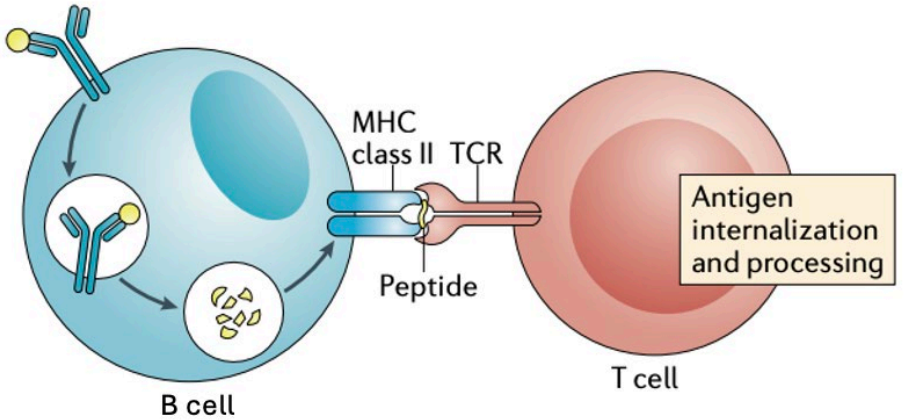
D. THE IMMUNE SYSTEM AS A THERAPEUTIC TOOL

Advances in immunology renewed focus on the cancer immunosurveillance hypothesis.[52] By the 1960s, immunologists identified the thymus and bone marrow as key tissues where immune cells arise.[53] Cells arising from the thymus became known as T cells; those arising from bone marrow became known as B cells.[54] During the 1970s and 1980s,

43. Dunn, *supra* note 25, at 992.
44. *Id.*
45. *Id.*
46. *Id.*
47. *Id.*; *see also* discussion *supra* Section II.D.
48. DeVita, Jr. & Chu, *supra* note 26, at 8643–47.
49. *Id.*
50. *Id.* at 8647–49.
51. *Id.* at 8647–52.
52. Kaufmann, *supra* note 22, at 7–8; Dunn, *supra* note 25, at 992–94.
53. Jacques F. A. P. Miller, *The Golden Anniversary of the Thymus*, 11 NATURE REVS. IMMUNOLOGY 489, 490 (2011).
54. *Id.* at 491.

immunologists learned that T cells and B cells work collaboratively.[55] A subclass of T cells ("helper T cells") help B cells to make antibodies.[56] T cells and B cells both possess surface receptors that bind to antigens (e.g., proteins) (Figure 2).[57] TCRs bind only to antigens displayed on cell surfaces by the MHC, an issue that would become relevant to early CAR-T cell designs.[58]

Figure 2: B cell receptors bind to free antigens (shown as a yellow circle) while TCRs bind to antigen fragments displayed by an MHC protein on another cell's surface, such as a B cell (edited from original source).[59]



The discovery of T cell and B cell receptors and their role in immune regulation revealed that earlier nude mice were not as immunodeficient as previously believed.[60] Studies with nude mice modified for additional immunosuppression supported the cancer surveillance hypothesis.[61] Nude mice with certain immunosuppressive modifications were more susceptible to tumors (induced and spontaneously generated) than unmodified nude mice.[62] The cancer surveillance hypothesis also appeared to hold up in humans.

55. *Id.*
56. *Id.*
57. *Id.* at 491–92; Yoshihisa Kuwana et al., *Expression of Chimeric Receptor Composed of Immunoglobulin-derived V Regions and T-Cell Receptor-Derived C Regions*, 149 BIOCHEMICAL & BIOPHYSICAL RSCH. COMMC'NS 960 (1987).
58. *See* sources cited *supra* note 57.
59. Munir Akkaya et al., *B Cell Memory: Building Two Walls of Protection Against Pathogens*, 20 NATURE REVS. IMMUNOLOGY 229, 233 (2020) (showing a portion of Figure 2).
60. Dunn, *supra* note 25, at 992–93.
61. *Id.*
62. *Id.*

Correlational data suggests immunosuppression correlates with increased cancer risk in humans.[63]

One of the first treatments developed from improved immunology knowledge was adoptive T cell therapy (ACT), a process where doctors infuse cancer patients with T cells (either their own or from a donor).[64] Doctors first saw promising results with ACT in 1966, when they noticed tumor regression in patients treated with a mixture of their own tumor cells and leukocytes (i.e., white blood cells, including T cells and B cells).[65] The National Cancer Institute built on these advances in the 1980s by treating patients with lymphocytes (i.e., a subset of leukocytes that includes T cells and B cells) isolated from their own tumor biopsies (tumor-infiltrating lymphocytes, TILs).[66] Patient response to ACT improved dramatically when patients underwent lymphodepletion, a process where doctors reduce patients' T cells, prior to treatment with TILs.[67] However, many patients' tumors lacked enough TILs for effective ACT.[68]

At the same time, scientists explored another strategy to harness the immune system to treat cancer: infusing patients with antibodies designed to target cancer cell antigens.[69] Scientists discovered antibodies in the 1890s.[70] By the 1970s, scientists understood the role of antibodies in the immune system and established a robust method to produce monoclonal antibodies (i.e., antibodies designed to target a single antigen).[71] Identification of a protein called CD20 on the surfaces of cancerous B cells associated with non-Hodgkin's lymphoma led to approval of rituximab, the first FDA-approved antibody to treat cancer.[72] Today, scientists continue to advance antibody

63. *Id.* at 994–95.

64. Waldman et al., *supra* note 14, at 658; M. Teresa Villanueva, *Engineering Armed T Cells for the Fight*, NATURE CANCER MILESTONES (Dec. 10, 2020), https://www.nature.com/articles/d42859-020-00077-6.

65. Chester M. Southam et al., *Effect of Leukocytes on Transplantability of Human Cancer*, 19 CANCER 1743 (1966); Waldman et al., *supra* note 14, at 658.

66. Waldman et al., *supra* note 14, at 658; Villanueva, *supra* note 64.

67. Waldman et al., *supra* note 14, at 658; *see also* Steven A. Rosenberg et al., *Durable Complete Responses in Heavily Pretreated Patients with Metastatic Melanoma Using T-Cell Transfer Immunotherapy*, 17 CLINICAL CANCER RSCH. 4550, 4556 (2011) (explaining several hypotheses for lymphodepletion's beneficial effects, including less competition with other T cells for the resources which promote T cell growth).

68. *See* sources cited *supra* note 67.

69. Paula Dobosz & Tomasz Dzieciątkowski, *The Intriguing History of Cancer Immunotherapy*, 10 FRONT. IMMUNOL. 2965, 3–4 (2019).

70. *Id.*

71. *Id.*

72. *Id.*

cancer therapeutics with positive clinical results.[73] For patients with cancer cells that display identifiable and targetable antigens, treatment with antibodies often enables better outcomes and reduced adverse reactions relative to chemotherapeutics.[74] However, some patients fail to respond or show minimal responses to antibody therapeutics.[75]

E. ENGINEERING T CELLS AS A "LIVING" THERAPEUTIC

By the 1990s, researchers hypothesized that T cells engineered to specifically target cancer antigens would combine the benefits of ACT, a "living" therapeutic, with the specificity and MHC-independence of antibody-based therapeutics.[76]

Substantial evidence now shows tumor cells persist because they evade the body's natural immune response.[77] Most proteins on the surface of tumor cells do not elicit a strong immune response because they appear on non-tumor cells as well (i.e., self antigens).[78] Even when one or more of a tumor cell's antigens can trigger an immune response, tumor cells may evade T cell detection by producing less of the antigen and/or MHC proteins and creating an immunosuppressive microenvironment.[79]

---

73. *Id.* at 3–5.

74. Andrew M. Scott et al., *Antibody Therapy of Cancer*, 12 NATURE REVS. CANCER 278, 278, 281, 284 (2012); *see also* Ruei-Min Lu et al., *Development of Therapeutic Antibodies for the Treatment of Diseases*, 27 J. BIOMED. SCI. 1, 2–5 (2020) (listing in Table 1, FDA-approved monoclonal antibodies to-date as well as their target antigens).

75. *See, e.g.*, Esteban Cruz & Veysel Kayser, *Monoclonal Antibody Therapy of Solid Tumors: Clinical Limitations and Novel Strategies to Enhance Treatment Efficacy*, 13 BIOLOGICS: TARGETS & THERAPY 33, 33–34 (2019).

76. Lærke J. B. Brandt et al., *Emerging Approaches for Regulation and Control of CAR T Cells: A Mini Review*, 11 FRONTIERS IMMUNOLOGY 326, 1 (2020); Waldman et al., *supra* note 14, at 659; Helene M. Finney et al., *Activation of Resting Human Primary T Cells with Chimeric Receptors: Costimulation from CD28, Inducible Costimulator, CD134, and CD137 in Series with Signals from the TCRζ Chain*, 172 J. IMMUNOLOGY 104 (2004); Gideon Gross & Zelig Eshhar, *Endowing T Cells with Antibody Specificity Using Chimeric T Cell Receptors*, 6 FASEB J. 3370 (1992); Villanueva, *supra* note 64; Michel Sadelain et al., *The Promise and Potential Pitfalls of Chimeric Antigen Receptors*, 21 CURRENT OPINION IMMUNOLOGY 215 (2009); Kuwana, *supra* note 57, at 965–67.

77. U.S. Patent No. 7,446,190, at [1:17-19] (filed May 28, 2003) [hereinafter '190 patent]; *see also* Anat Globerson Levin et al., *CAR T Cells: Building on the CD19 Paradigm*, 51 EUR. J. IMMUNOLOGY 2151 (2021).

78. '190 patent, *supra* note 77, at [1:19-21]; *see also* Sadelain, *supra* note 76, at 217; John Maher et al., *Human T-lymphocyte Cytotoxicity and Proliferation Directed by a Single Chimeric TCRζ/CD28 Receptor*, 20 NATURE BIOTECHNOLOGY 70, 70 (2002).

79. '190 patent, *supra* note 77, at [1:21-29]; *see also* Levin, *supra* note 77, at 2151; Maher, *supra* note 78, at 70; Waldman et al., *supra* note 14, at 658–60; Federico Garrido et al., *The Urgent Need to Recover MHC Class I in Cancers for Effective Immunotherapy*, 39 CURRENT OPIN. IMMUNOLOGY 44, 48 (2016); Soldano Ferrone et al., *How Much Longer Will Tumour Cells Fool the Immune System?* 21 IMMUNOLOGY TODAY 70, 70–71 (2000).

CAR-T cell therapies avoid some tumor cell defenses by modifying the native TCR to act more like an antibody.[80] As explained *supra*, antibodies bind to antigens that are not displayed by MHC proteins on cell surfaces (e.g., circulating antigens or antigens displayed directly on cell surfaces without MHC proteins).[81] Despite this binding difference, antibodies and TCRs share many structural similarities.[82] With advances in DNA sequencing and gene editing technology, scientists leveraged TCRs' structural similarity with antibodies to modify the binding region of patients' native TCRs with a single chain version of an antibody binding domain ("scFv") targeting a particular cancer antigen.[83] Scientists dubbed these engineered T cells chimeric antigen receptor (CAR) T cells or CAR-T cells.[84] A chimera is a hybrid creature from Greek mythology (part lion, part goat, and part serpent); a CAR is a hybrid protein that contains part of an antibody binding region attached to part of a TCR (the intracellular portion)[85] (Figure 5). However, "first-generation" CAR-T cells failed to live up to their promise.[86] The CAR-T cells neither proliferated nor mounted a strong immune response to their target tumor antigen.[87]

F. CARs WITH CO-STIMULATORY DOMAINS ACHIEVE CLINICAL SUCCESS

The key insight that transformed CAR-T cells from benchtop hope to clinical success was that natural T cells require two binding events to activate an immune response: T cells must bind to both (1) the target antigen and (2) a "co-stimulatory" molecule, such as another protein on the cell surface like CD28.[88] Upon receiving signals from both binding events, the TCR intracellular portion (CD3ζ) signals the cell to multiply to create an army of T cells and to release chemical signals to recruit other immune cells to destroy

80. *See infra* Section III.A.

81. Maher, *supra* note 78, at 70.

82. *See infra* Secion III.A, Figure 5.

83. Gross & Eshhar, *supra* note 76, at 3372–73; Levin, *supra* note 77, at 2151; *see also* Waldman et al., *supra* note 14, at 659; Villanueva, *supra* note 64; Sadelain, *supra* note 76, at 215, 217–18.

84. Vicki Brower, *The CAR T-Cell Race*, SCIENTIST (Apr. 1, 2015), https://www.the-scientist.com/bio-business/the-car-t-cell-race-35701 (Fig. 2 illustrating first-, second-, and third-generation CAR technology differing primarily in the intracellular signaling domain)).

85. *See infra* Section III.A.

86. *Id.*

87. *Id.*

88. Ronald H. Schwartz, *T Cell Anergy*, SCI. AM. 62, 68 (1993); Maher, *supra* note 78, at 70, 74; Waldman et al., *supra* note 14, at 652, 659; Finney et al., *supra* note 76, at 104; Sadelain, *supra* note 76, at 215, 217–18; Kuwana, *supra* note 57, at 965; Villanueva, *supra* note 64.

target antigen-bearing cells.[89] When a T cell receives only one signal from binding to the target antigen, the T cell may fail to replicate and even initiate a programmed cell death pathway.[90]

"Second generation" CARs supplemented the native TCR intracellular signaling domain (CD3ζ) with a second, "costimulatory" signaling domain (e.g., CD28 or 4-1BB signaling domains).[91] The "costimulatory" domain causes the T cell to mount an immune response upon binding to *only* the target antigen (Figure 2).[92] With this modification, the first CAR-T cell therapies showed dramatic success in treating blood cancers.[93] The innovation underlying Yescarta's success is a second-generation CAR with an intracellular signaling domain comprising CD3ζ and portions of the CD28 signaling element (SEQ ID NO:6 in U.S. Pat. No. 7,446,190 ("the '190 patent"); Figure 3).[94]

89. Schwartz, *supra* note 88, at 62; Sadelain, *supra* note 76, at 217; Maher, *supra* note 78, at 70.

90. '190 patent, *supra* note 77, at [1:49-67]; *see also* Schwartz, *supra* note 88, at 66, 68; Sadelain, *supra* note 76, at 217; Maher, *supra* note 78, at 70–71, 74.

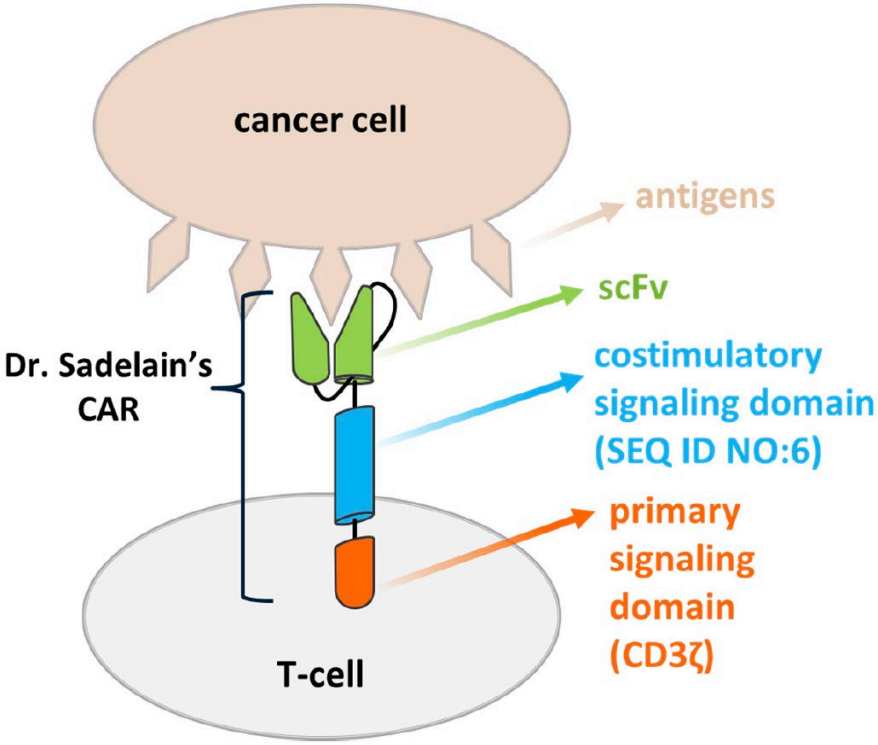
91. Petition for Writ of Certiorari, at 2–3, 10–11, Juno Therapeutics, Inc. v. Kite Pharma, Inc., 143 S. Ct. 402, *reh'g denied*, 143 S. Ct. 631 (2023); *see also* Donald B. Kohn et al., *CARS on Track in the Clinic*, 19 MOLECULAR THERAPEUTICS 432, 432, 434 (2011).

92. *See* sources cited *supra* note 91.

93. Waldman et al., *supra* note 14, at 660.

94. Maher, *supra* note 78, at 70, 74; Juno Therapeutics, Inc. v. Kite Pharma, Inc. (*Juno v. Kite I*), No. 2:17-cv-07639 SJO-KS, 2020 WL 10460622, at *9 (C.D. Cal. Mar. 24, 2020) ("Plaintiffs presented evidence and testimony that Defendant knew that Dr. Rosenberg from National Cancer Institute ("NCI") copied Dr. Sadelain's backbone, as demonstrated by Defendant's attempting to be the first to license and to invalidate the '190 [p]atent. Plaintiff's fact witness Dr. Dash testified that Dr. Belldegrun was so desperate to pursue a license to the '190 [p]atent that he appeared at her office, despite not having a meeting. Dr. Jakobovitz similarly testified that Dr. Belldegrun met with Plaintiffs in an attempt to license the '190 [p]atent."), *rev'd*, 10 F.4th 1330 (Fed. Cir. 2021) (appealing only on invalidity arguments (not non-infringement)); *see also* Petition for Writ of Certiorari, *Juno v. Kite*, *supra* note 91, at 14 ("Kite stipulated that Yescarta literally infringes the ['190] patent" with only one independent claim reciting SEQ ID NO:6).

Figure 3: The Yescarta co-stimulatory domain comprises CD3ζ and portions of CD28 (including '190 patent SEQ ID NO: 6).[95]



Blood cancers made for a promising first target for CAR-T cell therapies because scientists had already identified antigens to target on blood cancer cells (e.g., rituximab targeted the CD20 marker on B cells), doctors can easily monitor cell counts, and T cells easily access the location of these cancers (e.g., blood, bone marrow, and lymph nodes); now the field aims to expand to solid tumors.[96]

CAR-T cell therapeutics differ from off-the-shelf small-molecule therapeutics; the cells are highly personalized, engineered versions of each patient's own T cells (i.e., "autologous" T cells).[97] To make a CAR-T cell

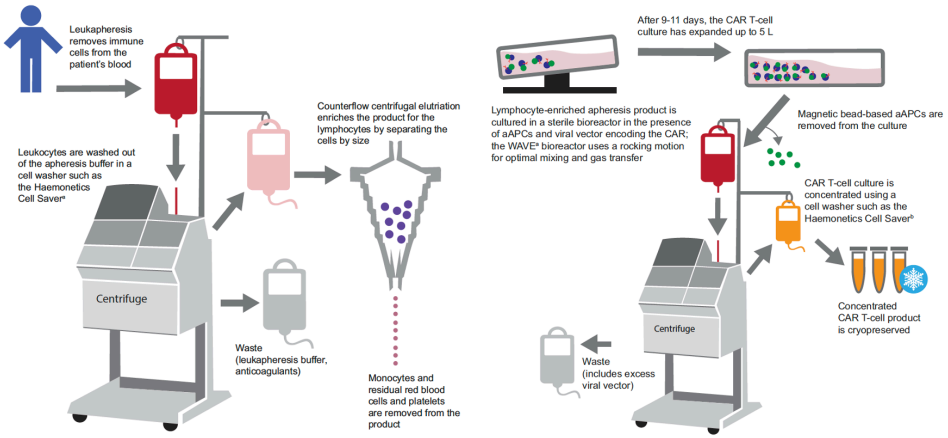
95. Petition for Writ of Certiorari, *Juno v. Kite*, *supra* note 91, at 12.

96. *See* Marcela V. Maus et al., *Antibody-Modified T Cells: CARs Take the Front Seat for Hematologic Malignancies*, 123 BLOOD 2625 (2014); NCI 2022, *supra* note 19; Waldman et al., *supra* note 14, at 660.

97. *See* Daniel Hollyman et al., *Manufacturing Validation of Biologically Functional T Cells Targeted to CD19 Antigen for Autologous Adoptive Cell Therapy*, 32 J. IMMUNOTHERAPY 169, 169–70 (2009).

therapy for a single patient, researchers withdraw the patient's blood, separate T cells from red blood cells and other white blood cells, introduce genetic material encoding the CAR gene, and multiply the engineered T cells to a sufficient quantity to achieve therapeutic effect (Figure 4).[98]

Figure 4: Patient-specific CAR-T cell manufacturing process.[99]



III. DEVELOPMENT HISTORY OF INVENTION

Yescarta and other CAR-T cell therapy development occurred in three phases. First, researchers identified effective co-stimulatory domains.[100] Next, hospitals with research facilities developed small-scale manufacturing techniques to transform patients' own T cells into cancer-fighting CAR-T cells in small, Phase I clinical studies.[101] Finally, both start-up and established

98. Bruce L. Levine et al., *Global Manufacturing of CAR T Cell Therapy*, 4 MOLECULAR THERAPY – METHODS & CLINICAL DEV. 92, 92–93 (2017); *see also* Hollyman, *supra* note 97, at 170–72.

99. One complexity of CAR-T cell therapy manufacturing is that each patient requires their own unique dose. The process starts when doctors withdraw a patient's own T cells. Then, scientists engineer these cells to express a CAR targeted to a particular antigen. Eventually, doctors administer the engineered cells back to the patient. Levine, *supra* note 98, at 93–94 (Figures 2 and 3). This is an open access article under the CC BY-NC-ND license (http://creativecommons.org/licenses/by-nc-nd/4.0/). Figure reproduced from Levine, *supra* note 98, at 93-94.

100. *See infra* Section III.A.

101. *See infra* Section III.B.

pharmaceutical companies provided funding and expertise to expand CAR-T cell manufacturing for Phase II and III clinical studies.[102]

A. FINDING THE RIGHT CAR CONSTRUCT

Researchers hypothesized that substitution of the TCR binding domain for the antibody binding domain would permit TCRs to bind to antigens without also binding to MHC proteins, as discussed in Section II.E, *supra*.[103] Antibodies and TCRs share many functional and structural features.[104] Functionally, antibodies and TCRs include a region capable of binding specifically to an antigen.[105] Structurally, the binding regions of both proteins comprise two peptide chains covalently bound together (Figure 5).[106] One key difference is that antibodies bind to free antigens, while TCRs bind to antigens attached to MHC proteins on cells' surfaces.[107] Early efforts by Zelig Eshhar's team at the Weizmann Institute of Science, and others, struggled to test this hypothesis due to low yields of this chimeric protein.[108] One reason for the low yields related to the antibody binding domain structure.[109] Natively, two peptide chains must bind to form each arm of the antibody binding domain.[110] In 1990, Eshhar took a one-year sabbatical to collaborate with Steven Rosenberg at NIH's National Cancer Institute (NCI) on CAR-T cells targeted to human melanoma.[111]

By 1993, Eshhar's team overcame the two peptide chain challenge by implementing a "single chain" antibody binding domain, called a single chain variable region (scFv).[112] A scFv includes a "linker" to connect the two

102. *See infra* Section III.C.

103. *See, e.g.*, Nicholas R. J. Gascoigne et al., *Secretion of a Chimeric T-Cell Receptor-Immunoglobulin Protein*, 84 PROC. NAT'L. ACAD. SCIS. 2936 (1987); Kuwana, *supra* note 57, at 960–61; Peter Braendstrup et al., *The Long Road to the First FDA-Approved Gene Therapy: Chimeric Antigen Receptor T Cells Targeting CD19*, 22 CYTOTHERAPY 57, 58–59 (2020); Gideon Gross et al., *Expression of Immunoglobulin-T-Cell Receptor Chimeric Molecules as Functional Receptors with Antibody-Type Specificity*, 86 PROC. NAT'L ACAD. SCIS. 10024 (1989).

104. Gross, *supra* note 103, at 10024.

105. *Id.*

106. *Id.*

107. *Id.*

108. Kuwana, *supra* note 57, at 966–67; Zelig Eshhar et al., *Specific Activation and Targeting of Cytotoxic Lymphocytes Through Chimeric Single Chains Consisting of Antibody-Binding Domains and the γ or ζ Subunits of the Immunoglobulin and T-Cell Receptors*, 90 PROC. NAT'L ACAD. SCIS. 720, 720–21 (1993).

109. *See* sources cited *supra* note 108.

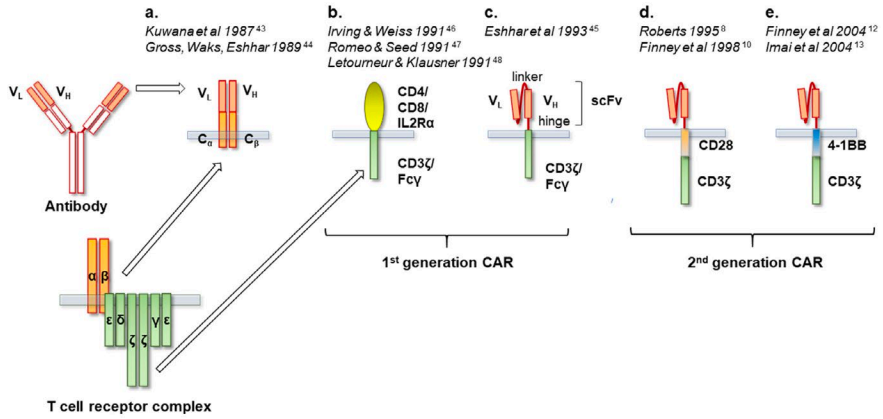
110. *Id.*

111. Brower, *supra* note 84.

112. Eshhar, *supra* note 108, at 723; Brower, *supra* note 84; Braendstrup, *supra* note 103, at 58; Villanueva, *supra* note 64; Sadelain, *supra* note 76, at 215.

antibody binding domain peptide chains (Figure 5(a) shows an antibody binding domain with two, unconnected peptide chains (V_L and V_H); Figure 5(c) shows an antibody binding domain (orange) with peptide chains chemically connected with a "linker" (red)).[113] Eshhar created the "first-generation" CAR when his team connected this scFv to TCR's native, intracellular signaling domain, CD3ζ (Figure 5(c)).[114]

Figure 5: Structural evolution of CARs from dual peptide (a) to single peptide (b–e) and from first-generation (b–c) to second-generation (d–e).[115]



In 1988, following the excitement around recent, successful biotech IPOs (e.g., Genentech, Amgen), medical researchers and entrepreneurs founded Cell Genesys to develop therapies based on gene editing, specifically cancer therapeutics and vaccines.[116] Stephen Sherwin served as Cell Genesys's first CEO following his work at Genentech (1983–1990) and NCI (pre-1983).[117] Margo Roberts, principal scientist and director of Immune and Cell Therapy at Cell Genesys, and her collaborators created a "first-generation" CAR targeting HIV antigens.[118] Their research led to the first CAR-T cell clinical

113. *See* sources cited *supra* note 112.

114. *Id.*

115. Braendstrup, *supra* note 103, at 59 (Figure 2).

116. Bernadette Tansey, *Drug Trial Halted; Cell Genesys Shares Plummet*, SFGATE (Aug. 28, 2008), https://www.sfgate.com/business/article/Drug-trial-halted-Cell-Genesys-shares-plummet-3198009.php; Cell Genesys, Inc., Annual Report (Form 10-K), at 3 (Mar. 31, 2001).

117. *Stephen A. Sherwin, MD*, PARKER INST. CANCER IMMUNOTHERAPY, https://www.parkerici.org/person/stephen-a-sherwin-md/ (last visited Sept. 24, 2023).

118. Margo R. Roberts et al., *Targeting of Human Immunodeficiency Virus-Infected Cells by CD8+ T Lymphocytes Armed with Universal T-Cell Receptors*, 84 BLOOD 2878 (1994); *Margo Roberts, PhD*,

trials in 1994 in collaboration with Carl June at the University of Pennsylvania (who was already investigating cell-based therapies).[119] When these clinical studies showed only limited efficacy and HIV antiviral treatments proved effective, Cell Genesys shifted focus to cancer vaccines and prostate cancer.[120] Despite limited clinical efficacy, these studies progressed CAR-T cell manufacturing techniques and evidenced the importance of "co-stimulation" to trigger robust CAR-T cell activation.[121] T cells naturally require "co-stimulation" to activate.[122]

In February 1995, Roberts solved the co-stimulation problem by adding a "co-stimulatory" domain to the first-generation CAR, inventing a "second-generation" CAR (Figure 5(d); Figure 6).[123] This second-generation CAR's signaling domain included portions of two native, T cell stimulating receptors: the TCR CD3ζ signaling domain and the CD28 signaling domain. Cell Genesys patented the invention in U.S. Patent No. 5,712,149 ("the '149 patent"). As late as 2002, Cell Genesys continued to protect their chimeric receptor intellectual property, pursing interference or opposition proceedings to ensure patent rights.[124] However, in 2005, Cell Genesys restructured to focus resources on their "most advanced and most promising development

UNITY BIOTECHNOLOGY, https://unitybiotechnology.com/team/margo-roberts/ (last visited Sept. 24, 2023) [hereinafter Roberts Bio].

119. *Cells Genesys Gains NIAID AIDS Researcher Hoth*, PINK SHEET (July 5, 1993), https://pink.pharmaintelligence.informa.com/PS022870/CELLS-GENESYS-GAINS-NIAID-AIDS-RESEARCHER-HOTH; Steven G. Deeks et al., *A Phase II Randomized Study of HIV-Specific T-Cell Gene Therapy in Subjects with Undetectable Plasma Viremia on Combination Antiretroviral Therapy*, 5 MOLECULAR THERAPY 788, 796 (2002) (using CD28 stimulation); Ronald T. Mitsuyasu et al., *Prolonged Survival and Tissue Trafficking Following Adoptive Transfer of CD4ζ Gene-Modified Autologous CD4+ and CD8+ T Cells in Human Immunodeficiency Virus-Infected Subjects*, 96 BLOOD 785 (2000); Robert E. Walker et al., *Long-Term In Vivo Survival of Receptor-Modified Syngenic T Cells in Patients with Human Immunodeficiency Virus Infection*, 96 BLOOD 467 (2000); Braendstrup, *supra* note 103, at 59; J. L. Macpherson & J. E. J. Rasko, *Clinical Potential of Gene Therapy: Towards Meeting the Demand*, 44 INTERNAL MED. J. 224, 229–30 (2014).

120. Gloria B. Kim et al., *CAR Talk: How Cancer-Specific CAR T Cells Can Instruct How to Build CAR T Cells to Cure HIV*, 10 FRONTIERS IMMUNOLOGY 2310, 2310–12 (2019); Braendstrup, *supra* note 103, at 59; Macpherson & Rasko, *supra* note 119, at 229–30; Ron Leuty, *Inside a Big Pharma Cancer Drug Approval with Roots in a Small Bay Area Biotech*, SAN FRANCISCO BUS. TIMES (June 1, 2021), https://www.bizjournals.com/sanfrancisco/news/2021/06/01/bristol-myers-squibb-car-t-abecma-multiple-myeloma.html.

121. Kim, *supra* note 120, at 2310–12; Braendstrup, *supra* note 103, at 59; Macpherson & Rasko, *supra* note 119, at 229–30.

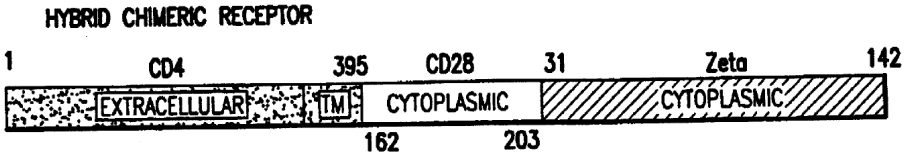
122. *See supra* Section II.F.

123. U.S. Patent No. 5,712,149 at [4:60-5:50] (filed Feb. 3, 1995) [hereinafter '149 patent]; Braendstrup, *supra* note 103, at 60.

124. Cell Genesys, Inc., Annual Report (Form 10-K), at 10, 21 (Mar. 31, 2001); Cell Genesys, Inc., Annual Report (Form 10-K), at 11, 23 (Mar. 31, 2002); Cell Genesys, Inc., Annual Report (Form 10-K), at 10, 23 (Mar. 31, 2003).

programs," primarily their cancer vaccines and not CAR-T cell therapies.[125] Cell Genesys merged with another pharmaceutical company after terminating their vaccine clinical studies due to safety issues in 2008.[126] Later, Kite Pharma, Inc. ("Kite"), the company that makes Yescarta, acquired Cell Genesys's CAR patents.[127]

Figure 6: One of Roberts's second-generation CARs including CD3ζ and CD28 costimulatory domains.[128]



To compete with the U.S. biotechnology industry, the British government funded biotechnology initiatives which led to the founding of Celltech Group Limited in 1980 to develop antibody-derived drugs.[129] Helene Finney and colleagues at Celltech also created a CD28-based second-generation CAR and filed a patent application on December 23, 1996.[130] Faced with repeated rejections over the '149 patent (and other prior art), Celltech abandoned their U.S. application.[131] In 2001, Finney (and, later, independent researchers at St. Jude Children's Research Hospital) invented a different second-generation CAR with the 4-1BB signaling domain in place of the CD28 domain (4-1BB-

125. Cell Genesys, Inc., Annual Report (Form 10-K), at 6 (Mar. 13, 2006).

126. Cell Genesys, Inc., Annual Report (Form 10-K), at 6–7 (Mar. 9, 2009); *BioSante, Cell Genesys Merge in $38M Deals*, FIERCE BIOTECH (June 30, 2009), https://www.fiercebiotech.com/biotech/biosante-cell-genesys-merge-38m-deals.

127. Kite Pharma, Inc., Registration Statement (Form S-1), at 79 (May 19, 2014).

128. '149 patent, *supra* note 123, at Fig. 1D.

129. Celltech Group PLC, Annual Report (Form 20-F), at 11 (June 30, 2003); *see also* Tim Harris, *A British Biotech Biopedia: Early Days in the U.K.*, GENETIC ENG'G & BIOTECHNOLOGY NEWS (Oct. 4, 2021), https://www.genengnews.com/commentary/a-british-biotech-biopedia-early-days-in-the-u-k/ (explaining the National Enterprise Board, among others, provided initial Series A funding for Celltech).

130. Helene M. Finney et al., *Chimeric Receptors Providing Both Primary and Costimulatory Signaling in T Cells from a Single Gene Product*, 161 J. IMMUNOLOGY 2791, 2791–92 (1998); Braendstrup, *supra* note 103, at 60.

131. Braendstrup, *supra* note 103, at 60; *see* Mar. 21, 2000 Office Action, File History of U.S. Patent Application No. 2003/0077249, at 15 [hereinafter '249 application]; Feb. 27, 2003 Office Action, File History of '249 application, at 3–8; July 9, 2004 Abandonment, File History of '294 application.

CD3ζ)(Figure 5(d–e)).[132] Celltech continued to develop antibody-derived and small-molecule therapeutics until 2004, when they were acquired by UCB S.A., but never focused on cell-based therapies.[133]

Michel Sadelain and colleagues at Memorial Sloan Kettering Cancer Center (MSKCC) improved early second-generation CD28-based CARs by implementing a longer CD28 co-stimulatory domain in 2002.[134] Their second-generation CAR-T cells not only killed cancer cells, but also underwent "multiple rounds of expansion and continue[d] to specifically kill tumor cells, even after withdrawal and re-exposure to the target antigen."[135] The longer CD28 domain included a thirty-nine amino acid portion of CD28's *extracellular* domain (in addition to earlier second-generation CARs use of CD28 intracellular and transmembrane domains).[136] Although they did not yet know the mechanism, Sadelain and colleagues were the first to recognize that extracellular portions of CD28 acted not merely as inert spacers, but as CAR functionality modulators.[137]

In addition to an effective signaling portion, researchers sought an extracellular binding region specific to therapeutically relevant targets. By the early 2000s, researchers identified the CD19 protein as an attractive target for CAR-T cells.[138] First, the CD19 protein specifically exists on the surface of a

132. WO 2002/033101 (filed Oct. 16, 2001); Finney et al., *supra* note 76, at 104–6; Chihaya Imai et al., *Chimeric Receptors with 4-1BB Signaling Capacity Provoke Potent Cytotoxicity Against Acute Lymphoblastic Leukemia*, 18 LEUKEMIA 676 (2004) (Figure 2 showing second generation CAR constructs incorporate a co-stimulatory domain, often CD28 or 4-1BB).

133. *See* Celltech Group PLC, Annual Report (Form 20-F), at 11–24 (June 25, 2004).

134. Maher, *supra* note 78, at 70; '190 patent, *supra* note 77; Villanueva, *supra* note 64; Sadelain, *supra* note 76, at 215; Juno Therapeutics, Inc. v. Kite Pharma (*Juno v. Kite IPR Appeal*), No. 17-cv-07639 SJO-RAO, 2018 WL 1470594, at *1 (C.D. Cal. Mar. 8, 2018); Petition for Writ of Certiorari, *Juno v. Kite*, *supra* note 91, at 12.

135. Patent Owner Response, at 1, Kite Pharma, Inc. v. Sloan Kettering Inst. for Cancer Research, IPR2015-01719 (P.T.A.B. Dec. 16, 2016) [hereinafter Patent Owner Response].

136. *Id.* at 1–2; Maher, *supra* note 78, at 70; Brower, *supra* note 84 ("'Ultimately, we needed 20 years to learn how to supercharge these cells to deliver anticancer activity,' says Arie Belldegrun, president and CEO of Kite Pharma in Santa Monica, California, which is assessing CAR T cells in six trials for B cell leukemia and lymphomas, and glioblastoma.").

137. Patent Owner Response, *supra* note 135, at 1–2; *see also* Maher, *supra* note 78, at 73 (proposing several hypotheses for improved CAR-T cell functionality due to CD28 region); Yangbing Zhao et al., *A Herceptin-Based Chimeric Antigen Receptor with Modified Signalling Domains Leads to Enhanced Survival of Transduced T Lymphocytes and Antitumor Activity*, 183 J. IMMUNOL. 5563, 5563–64 (2009) (describing a collaboration of Drs. Sadelain, Eshhar, and Rosenberg, citing Maher, *supra* note 78, for creating effective second-generation CAR with CD28-CD3ζ co-stimulatory domain).

138. Braendstrup, *supra* note 103, at 60; Juno Therapeutics, Inc., Registration Statement (Form S-1), at 99 (Nov. 17, 2014); Michel Sadelain et al., *The Basic Principles of Chimeric Antigen*

particular subset of cells found in the blood, B cells, and is not present on other cell types.[139] Second, most types of B cell cancers express the CD19 antigen.[140] Third, patients tolerate loss of healthy B cells (i.e., an off-target effect of CD19-targeting CAR-T cell therapy).[141] And, as discussed in Section II.E *supra*, blood cancer therapeutics benefit from the relative ease of reaching tumor cells.

These advances resulted in the CAR protein key to Yescarta's clinical success.[142] The primary funding for this foundational CAR research came from government grants, charitable organizations, and private investment (Table 1).

Receptor Design 3 CANCER DISCOV. 388, 393 (2013); Junru Lu & Guan Jiang, *The Journey of CAR-T Therapy in Hematological Malignancies*, 21 MOL. CANCER 194, 4 (2022).

139. Sadelain, *supra* note 138, at 393; *see also* Pier Luigi Zinzani & Giorgio Minotti, *Anti-CD19 Monoclonal Antibodies for the Treatment of Relapsed or Refractory B-Cell Malignancies: A Narrative Review with Focus on Diffuse Large B-Cell Lymphoma* 148 J. CANCER RSCH & CLINICAL ONCOLOGY 177, 178 (2021); Hollyman, *supra* note 97, at 169.

140. Sadelain, *supra* note 138, at 393; *see also* Zinzani, *supra* note 139, at 178.

141. James N. Kochenderfer et al., *Construction and Preclinical Evaluation of an Anti-CD19 Chimeric Antigen Receptor*, 32 J. IMMUNOTHERAPY 689, 689–90 (2009).

142. *See* '190 patent, *supra* note 77, at [1:13-2:36]; *see also Juno v. Kite I*, *supra* note 94, at *9 ("Plaintiffs presented evidence and testimony that Defendant knew that Dr. Rosenberg from National Cancer Institute ("NCI") copied Dr. Sadelain's backbone, as demonstrated by Defendant's attempting to be the first to license and to invalidate the '190 [p]atent. Plaintiff's fact witness Dr. Dash testified that Dr. Belldegrun was so desperate to pursue a license to the '190 [p]atent that he appeared at her office, despite not having a meeting. Dr. Jakobovitz similarly testified that Dr. Belldegrun met with Plaintiffs in an attempt to license the '190 Patent."); Petition for Writ of Certiorari, *Juno v. Kite*, *supra* note 91, at 14 ("Kite stipulated that Yescarta literally infringes the ['190] [p]atent" with only one independent claim reciting SEQ ID NO:6).

Table 1: Government, charitable funds, and corporate collaborations funded early CAR construct invention (selected).

Inventor	CAR Construct	Funding
Zelig Eshhar (Weizmann Institute of Science)[143]	CD3ζ	Charitable Funds (Crown Endowment Fund for Immunological Research)
Margo Roberts (Cell Genesys, Inc.)[144]	CD28-CD3ζ	Corporate (Cell Genesys, Inc.)
Helene Finney and collaborators (Celltech Therapeutics Ltd.)[145]	CD28-CD3ζ 4-1BB- CD3ζ	Corporate (Celltech Therapeutics Ltd.)
Michel Sadelain[146] (MSKCC)	CD28-CD3ζ	Government grants (NIH) Charitable Funds (CaP CURE Association, Cure for Lymphoma Foundation) Individual investigator grants (Jean Shanks Clinical Research Fellowship)
Dario Campana, Chihaya Imai (St. Jude Children's Research Hospital)[147]	4-1BB- CD3ζ	Government grants (NCI, Center of Excellence grant from the State of Tennessee) Charitable Funds (American Lebanese Syrian Associated Charities) Individual investigator grants (FM Kirby Clinical Research Professor of the American Cancer Society)

B. EARLY, SINGLE-CENTER CLINICAL STUDIES

Manufacturing challenges posed the next major barrier to commercializing CAR-T cell therapies. By the early 2000s, researchers could make small numbers of CAR-T cells at the benchtop, but clinical trials required significantly more cells.[148]

Research institutions with a hospital arm like MSKCC, NCI, and the University of Pennsylvania harnessed their combined clinical and research capabilities to bring CAR-T cells from the benchtop to the bedside. In

143. Eshhar, *supra* note 108, at 724.
144. '149 patent, *supra* note 123.
145. Finney, *supra* note 130, at 2791; Finney et al., *supra* note 76, at 104.
146. Maher, *supra* note 78, at 75.
147. Imai, *supra* note 132, at 683.
148. Hollyman, *supra* note 97, at 169–70, 173, 179; Levine, *supra* note 98, at 93–99.

collaboration with NCI, MSKCC initiated the first clinical study of a second-generation (CD28-CD3ζ) CAR-T cell therapy in 2007.[149] This Phase I study evaluated CAR-T safety in eight patients with relapsed purine analog-refractory chronic lymphocytic leukemia (CLL) at a single center, MSKCC.[150] MSKCC and NCI soon initiated a second Phase I study in two patients with $CD19^+$ B-cell acute lymphoblastic leukemia (B-ALL).[151] MSKCC relied on their research facilities to rapidly (within two to three weeks) engineer and scale-up personalized CAR-T cells for each patient in their trials.[152] Soon after, NCI (led by Rosenberg) developed their own manufacturing methods for CAR-T cells based on a different co-stimulatory design (4-1BB-CD3ζ) and initiated another Phase I clinical trial.[153] Carl June at the University of Pennsylvania tested a similar co-stimulatory design (4-1BB-CD3ζ) in another small Phase I clinical study.[154] The 4-1BB-CD3ζ design ultimately became the

149. *Treatment of Relapsed or Chemotherapy Refractory Chronic Lymphocytic Leukemia or Indolent B Cell Lymphoma Using Autologous T Cells Genetically Targeted to the B Cell Specific Antigen CD19*, CLINICALTRIALS.GOV, https://clinicaltrials.gov/ct2/show/NCT00466531?id=NCT00466531&draw=2&rank=1 (last visited Sept. 24, 2023); Renier J. Brentjens et al., *Safety and Persistence of Adoptively Transferred Autologous CD19-Targeted T Cells in Patients with Relapsed or Chemotherapy Refractory B-Cell Leukemias*, 118 BLOOD 4817 (2011); Levin, *supra* note 77, at 2152; Braendstrup, *supra* note 103, at 60; James N. Kochenderfer et al., *Eradication of B-Lineage Cells and Regression of Lymphoma in a Patient Treated with Autologous T Cells Genetically Engineered to Recognize CD19*, 116 BLOOD 4099 (2010) (reporting study results).

150. Brentjens, *supra* note 149, at 4817; *see also* Levin, *supra* note 77, at 2152; Braendstrup, *supra* note 103, at 60; Kochenderfer, *supra* note 149, at 4099. Relapsed CLL patients received but did not respond well to earlier "purine analog" treatment.

151. *Precursor B Cell Acute Lymphoblastic Leukemia (B-ALL) Treated With Autologous T Cells Genetically Targeted to the B Cell Specific Antigen CD19*, CLINICALTRIALS.GOV, https://clinicaltrials.gov/ct2/show/NCT01044069?id=NCT01044069&draw=2&rank=1 (last visited Sept. 24, 2023); Brentjens, *supra* note 149, at 4817–18; Renier J. Brentjens et al., *CD19-Targeted T Cells Rapidly Induce Molecular Remissions in Adults with Chemotherapy-Refractory Acute Lymphoblastic Leukemia*, 5 SCI. TRANSLATIONAL MED. 177ra38, 1–2 (2013).

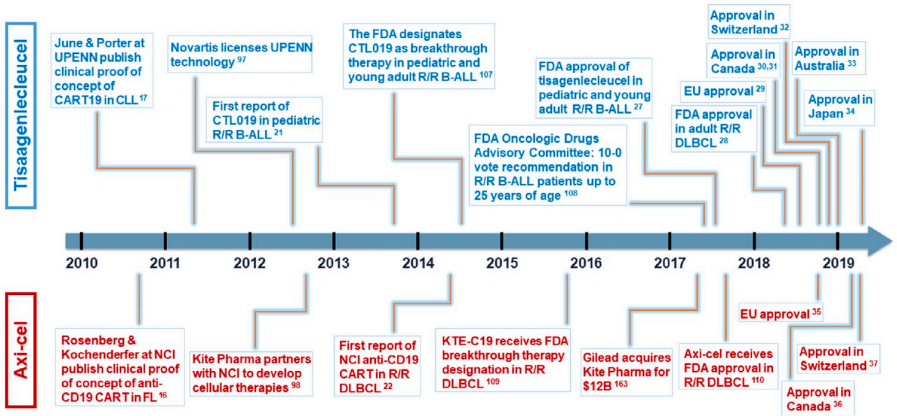
152. Brentjens, *supra* note 149, at 4818; Hollyman, *supra* note 97, at 169–70, 173, 179.

153. *CAR T Cell Receptor Immunotherapy for Patients With B-cell Lymphoma*, CLINICALTRIALS.GOV, https://clinicaltrials.gov/ct2/show/NCT00924326?id=NCT00924326&draw=2&rank=1 (last visited Sept. 24, 2023); Kochenderfer, *supra* note 141, at 689–90.

154. *CART19 to Treat B-Cell Leukemia or Lymphoma That Are Resistant or Refractory to Chemotherapy*, CLINICALTRIALS.GOV, https://clinicaltrials.gov/ct2/show/NCT01029366?id=NCT01029366&draw=2&rank=1 (last visited Sept. 24, 2023); Stephan A. Grupp et al., *Chimeric Antigen Receptor-Modified T Cells for Acute Lymphoid Leukemia*, 368 NEW ENGLAND J. MED. 1509, 1509–10 (2013); Shannon L. Maude et al., *Chimeric Antigen Receptor T Cells for Sustained Remissions in Leukemia*, 371 NEW ENGLAND J. MED. 1507, 1507–8 (2014); David L. Porter et al., *Chimeric Antigen Receptor-Modified T Cells in Chronic Lymphoid Leukemia*, 365 NEW ENGLAND J. MED. 725, 731, 733 (2011); Michael Kalos et al., *T Cells with Chimeric Antigen Receptors Have Potent Antitumor Effects and Can Establish Memory in Patients with Advanced Leukemia*, 3 SCI. TRANSLATIONAL MED. 95ra73, 1–2 (2011).

first CAR-T therapeutic approved by the FDA (Kymriah, tisagenlecleucel; Figure 7).[155]

Figure 7: Timeline showing key events leading to regulatory approval of first two CAR-T cancer therapeutics.[156]



In addition to reporting promising results, these studies established the feasibility of small-scale clinical CAR-T cell manufacturing.[157] Other institutions with research and hospital arms followed suit.[158]

Funding of these studies relied primarily on government and charitable foundation grants (Table 2).

155. Braendstrup, *supra* note 103, at 60–61; Brower, *supra* note 84.

156. Braendstrup, *supra* note 103, at 58 (Figure 1).

157. Brentjens, *supra* note 149, at 4818; Hollyman, *supra* note 97, at 169–70, 173, 179; Kochenderfer, *supra* note 141, at 689–90; James N. Kochenderfer et al., *B-Cell Depletion and Remissions of Malignancy Along with Cytokine-Associated Toxicity in a Clinical Trial of Anti-CD19 Chimeric-Antigen-Receptor-Transduced T Cells*, 119 BLOOD 2709 (2012); Brentjens, *supra* note 151, at 1–2; Kalos et al., *supra* note 154, at 2.

158. Kohn, *supra* note 91, at 433; James N. Kochenderfer & Steven A. Rosenberg, *Treating B-Cell Cancer with T Cells Expressing Anti-CD19 Chimeric Antigen Receptors*, 10 NAT'L REV. CLINICAL ONCOLOGY 267, 269–74 (2013) (Tables 1 and 3 showing multiple combined hospitals and research sites initiated early, single-site clinical studies of second-generation CAR-T cell therapies (as of publication on April 2, 2013)).

Table 2: Government, charitable funds, and corporate collaborations funded early CAR-T clinical studies (selected) (continued on the next page).

Study Details	Funding
Institution MSKCC (with NCI) CAR Construct CD28-CD3ζ Clinical Study NCT00466531[159] Initiation Date 4/27/2007	**Government grants** (NIH, NCI, National Center for Advancing Translational Sciences) **Charitable Funds** (e.g., The Annual Terry Fox Run for Cancer Research, Lymphoma Research Foundation) **Individual investigator grants** (e.g., ASCO Conquer Cancer Foundation Young Investigator Award, American Society of Hematology Scholar Clinical Fellow Award, Leukemia and Lymphoma Society Career Development Grant)
Institution MSKCC (with NCI) CAR Construct CD28-CD3ζ Clinical Study NCT01044069[160] Initiation Date 1/7/2010	**Government grants** (NIH, NCI, National Center for Advancing Translational Sciences) **Charitable Funds** (e.g., The Annual Terry Fox Run for Cancer Research, Lymphoma Research Foundation, Carson Family Charitable Trust) **Individual investigator grants** (e.g., ASCO Conquer Cancer Foundation Young Investigator Award, American Society of Hematology Scholar Clinical Fellow Award, Leukemia and Lymphoma Society Career Development Grant)

159. Brentjens, *supra* note 149, at 4817, 4827; Mark B. Geyer et al., *Safety and Tolerability of Conditioning Chemotherapy Followed by CD19-Targeted CAR T Cells for Relapsed/Refractory CLL*, 4 JCI INSIGHT e122627 1, 15 (2019).

160. Brentjens, *supra* note 149, at 4817, 4827; Brentjens, *supra* note 151, at 7, 9.

Institution NCI CAR Construct 4-1BB- CD3ζ Clinical Study NCT00924326[161] NCT01087294[162] Initiation Date 6/18/2009 3/16/2010	**Government grants** (NCI, NIH) **Corporate collaboration** (Kite Pharma, Inc.)
Institution University of Pennsylvania CAR Construct 4-1BB- CD3ζ Clinical Study NCT01029366[163] Initiation Date 12/10/2009	**Government grants** (NIH, Pennsylvania Department of Health) **Charitable Funds** (e.g., Leukemia and Lymphoma Society, Jeffrey Jay Weinberg Memorial Foundation, Alliance for Cancer Gene Therapy) **Individual investigator grants** (e.g., St. Baldrick's Foundation Scholar Award, Research Scholar Grant from the American Cancer Society) **Corporate collaboration** (Novartis)

As of 2012, the biggest challenge facing CAR-T cell therapeutics was a lack of financial investment and expertise to scale CAR-T cell manufacturing sufficiently to progress the candidates from small-scale single-center clinical

161. James N. Kochenderfer et al., *Lymphoma Remissions Caused by Anti-CD19 Chimeric Antigen Receptor T Cells Are Associated with High Serum Interleukin-15 Levels*, 35 J. CLINICAL ONCOLOGY 1803, 1803–13 (2017).

162. James N. Kochenderfer et al., *Donor-Derived CD19-Targeted T Cells Cause Regression of Malignancy Persisting After Allogeneic Hematopoietic Stem Cell Transplantation*, 122 BLOOD 4129, 4129–38 (2013).

163. Maude et al., *supra* note 154, at 1507, 1516; Porter et al., *supra* note 154, at 726, 733; Kalos et al., *supra* note 154 at 9, 11.

studies to large-scale multi-center studies and, eventually, to commercialize successful candidates.[164]

C. INDUSTRY GETS INVOLVED

Institutions with successful results from early clinical studies partnered with companies to fund larger clinical studies (Figure 8). The initial CAR-T cell therapeutics targeted CD19, but recent approvals target a B cell maturation antigen (BCMA) (Table 3). As of April 2024, the FDA has approved six CAR-T cell therapies.[165]

The University of Pennsylvania partnered with Novartis in August 2012 resulting in FDA approval of Kymriah (tisagenlecleucel) in 2017 (Table 3).[166] The partnership followed a publication that detailed promising results from a single patient enrolled in a three-patient Phase I clinical study.[167]

Arie Belldegrun, a surgeon and former mentee of Rosenberg at NCI, founded Kite in 2009 to develop cancer immunotherapies.[168] NCI partnered with Kite and Gilead in 2012 (Gilead later acquired Kite in 2019 for $11.9B) resulting in FDA approval of Yescarta (axicabtagene ciloleucel) on October 18, 2017.[169] Roberts, formerly with Cell Genesys (discussed *supra*), led Kite's

164. Carl June et al., *T-Cell Therapy at the Threshold*, 30 NAT'L BIOTECHNOLOGY 611, 614 (2012); Kohn, *supra* note 91, at 432; Brower, *supra* note 84; Braendstrup, *supra* note 103, at 60; Deborah Bach, *Three Cancer Research Powerhouses Form Immunotherapy Startup*, FRED HUTCH CANCER CTR. (Dec. 3, 2013), https://www.fredhutch.org/en/news/center-news/2013/11/cancer-research-powerhouses-form-juno-therapeutics.html.

165. NCI 2022, *supra* note 19.

166. *University of Pennsylvania and Novartis Form Alliance to Expand Use of Personalized T Cell Therapy for Cancer Patients*, PENN MED. NEWS (Aug. 6, 2012), https://www.pennmedicine.org/news/news-releases/2012/august/university-of-pennsylvania-and; *University of Pennsylvania and Novartis Form Alliance to Expand Use of Personalized T Cell Therapy for Cancer Patients*, FIERCE PHARMA (Aug. 6, 2012), https://www.fiercepharma.com/pharma/university-of-pennsylvania-and-novartis-form-alliance-to-expand-use-of-personalized-t-cell; Braendstrup, *supra* note 103, at 60–61; Brower, *supra* note 84; Novartis 2014 Complaint at ¶ 11, *Tr. of the Univ. of Pennsylvania v. St. Jude Child.'s Research Hosp.*, No. 2:13-cv-01502 SD, 2014 WL 12610149 (2014).

167. Porter, *supra* note 154, at 725–26.

168. *Aya Jakobovits, Ph.D., Named President and CEO of Kite Pharma, Inc.*, GILEAD (Sept. 16, 2010), https://www.gilead.com/news-and-press/press-room/press-releases/2010/9/aya-jakobovits-phd-named-president-and-ceo-of-kite-pharma-inc; *Eight Lessons from Arie Belldegrun (Kite/Allogene)*, AXIAL (Feb. 7, 2021), https://medium.com/@axialxyz/eight-lessons-from-arie-belldegrun-kite-allogene-7bf09c504f19.

169. Braendstrup, *supra* note 103, at 60–61; Brower, *supra* note 84; Kite Pharma, Inc., Registration Statement (Form S-1) at 12 (May 19, 2014); Petition for Writ of Certiorari, *Juno v. Kite*, *supra* note 91, at 14; *Gilead Sciences to Acquire Kite Pharma for $11.9 Billion*, BUSINESSWIRE (Aug. 28, 2017), https://www.businesswire.com/news/home/20170828005415/en/;

Yescarta team as Kite's Chief Scientific Officer from 2013 to 2014.[170] Yescarta received regulatory approval in the European Union in 2018, in Canada and Switzerland in 2019, and in Australia and Japan in 2021 for various blood cancers.[171]

MSKCC inventors together with other researchers founded Juno Therapeutics ("Juno") to commercialize their CAR-T technology.[172] Celgene partnered with Juno to develop CAR-T cell therapies, and then acquired Juno in 2018.[173] Bristol-Myers Squibb (BMS) acquired Celgene in 2019, largely for their CAR-T cell portfolio.[174] Juno (within BMS) received approval for their first CAR-T cell therapeutic, Breyanzi, in 2021.[175]

YESCARTA (axicabtagene ciloleuce), U.S. FOOD & DRUG ADMIN. (Oct. 18, 2017), https://www.fda.gov/vaccines-blood-biologics/cellular-gene-therapy-products/yescarta-axicabtagene-ciloleucel.

170. Roberts Bio, *supra* note 118; *Kite Pharma Expands Leadership Team and Announces Senior Management Promotions*, GILEAD (Apr. 14, 2014), https://www.gilead.com/news-and-press/press-room/press-releases/2014/4/kite-pharma-expands-leadership-team-and-announces-senior-management-promotions.

171. Braendstrup, *supra* note 103, at 61; *Kite's Yescarta® (Axicabtagene Ciloleucel) CAR T-Cell Therapy Now Widely Available and Publicly Funded For Patients in Australia with Four Types of Aggressive Non-Hodgkin Lymphoma*, KITE THERAPEUTICS (Aug. 5, 2021), https://www.kitepharma.com/news/company-statements/kite-yescarta-axicabtagene-ciloleucel-car-t-cell-therapy-now-widely-available-and-publicly-funded-for-patients-in-australia-with-four-types-of-aggressive-non-hodgkin-lymphoma; *Daiichi Sankyo Authorizes the First YESCARTA® (Axicabtagene Ciloleucel) CAR T-cell Therapy Treatment Site in Japan*, GILEAD (Dec. 16, 2021), https://www.gilead.com/news-and-press/press-room/press-releases/2021/12/daiichi-sankyo-authorizes-the-first-yescarta-axicabtagene-ciloleucel-car-tcell-therapy-treatment-site-in-japan.

172. Christina Pernambuco-Holsten, *New Biotech Startup Will Pit the Immune System Against Cancer*, MEMORIAL SLOAN KETTERING CANCER CTR. (Dec. 6, 2013); Bach, *supra* note 164.

173. *Celgene Corporation to Acquire Juno Therapeutics, Inc.*, CELGENE (Jan. 22, 2018), https://www.celgene.com/newsroom/cellular-immunotherapies/celgene-corporation-to-acquire-juno-therapeutics-inc/#:~:text=About%20the%20Juno%2DCelgene%20Collaboration,CAR%20T%20and%20TCR%20technologies.

174. *Bristol-Myers Drives into CAR-T Therapies*, ECONOMIST INTELLIGENCE UNIT (Feb. 18, 2019), https://www.eiu.com/industry/article/817665265/bristol-myers-drives-into-car-t-therapies/2019-02-18. *But see* Carl H. June et al., *CAR T Cell Immunotherapy for Human Cancer*, 359 SCI. 1361, 1364 (2018) (noting that Juno terminated clinical development of JCAR015 in Mar 2017 because of five deaths related to cerebral edema using "the CD19 CAR originally developed by Brentjens and colleagues").

175. Steve Brachmann, *Supreme Court's Denial of Juno Therapeutics is Another Blow to the Life Science Patent Industry*, IPWATCHDOG (Nov. 8, 2022), https://ipwatchdog.com/2022/11/08/supreme-courts-denial-juno-therapeutics-another-blow-life-science-patent-industry/id=152655/.

Figure 8: Corporate investment in CAR-T cell therapy commercialization occurred through start-ups and partnerships with established pharmaceutical companies.[176]

CAR-T Cell Company IPOs		
Company	**Date**	**Value**
Kite Pharma	2014	$134.1M
Bellicum Pharmaceuticals	2014	$160M
Juno Therapeutics	2014	$264.6M
Cellectis	2015	$228M

CAR-T Cell Corporate Deals		
Institution/Company	**Partner**	**Date**
University of Pennsylvania	Novartis	2012
Celgene	Bluebird Bio, Baylor College of Medicine	2013
Cellectis	Pfizer	2014
Cellectis	Ohio State University	2015
Kite Pharma	Amgen	2015
MD Anderson Cancer Center	Ziopharm, Intrexon	2015

Table 3: As of April 2024, the FDA has approved six CAR-T cell therapies; most target CD19, but the two most recently approved therapies target BCMA; and most use the 4-1BB construct, but Kite uses the CD28 construct.

Product	**Sponsor**	**First Approval Date**	**First Approved Indication**
Kymriah[177] (tisagenlecleucel) Target CD19 Co-Stimulation Domain 4-1BB	Novartis Pharmaceuticals, Inc.	Aug. 30, 2017	Patients up to 25 years of age with B-cell precursor acute lymphoblastic leukemia (ALL) that is refractory or in second or later relapse

176. Brower, *supra* note 84.

177. *Package Insert – KYMRIAH*, U.S. FOOD & DRUG ADMIN. 1, 22, 29 (May 2022), https://www.fda.gov/vaccines-blood-biologics/cellular-gene-therapy-products/kymriah-tisagenlecleucel; *Approval Letter – KYMRIAH*, U.S. FOOD & DRUG ADMIN. 1 (Aug. 30, 2017), https://www.fda.gov/vaccines-blood-biologics/cellular-gene-therapy-products/kymriah-tisagenlecleucel.

Yescarta[178] (axicabtagene ciloleucel) Target CD19 Co-Stimulation Domain CD28	Kite Pharma, Inc.	Oct. 18, 2017	Adult patients with relapsed or refractory large B-cell lymphoma after two or more lines of systemic therapy
Tecartus[179] (brexucabtagene autoleucel) Target CD19 Co-Stimulation Domain CD28	Kite Pharma, Inc.	July 24, 2020	Adult patients with relapsed/refractory mantle cell lymphoma
Breyanzi[180] (lisocabtagene maraleucel) Target CD19 Co-Stimulation Domain 4-1BB	Juno Therapeutics, a Bristol-Myers Squibb Company	Feb. 5, 2021	Adult patients with relapsed or refractory large B-cell lymphoma after two or more lines of systemic therapy

178. *Package Insert – YESCARTA*, U.S. FOOD & DRUG ADMIN. 2, 22, 32 (Mar. 2024), https://www.fda.gov/vaccines-blood-biologics/cellular-gene-therapy-products/yescarta-axicabtagene-ciloleucel; *Approval Letter – YESCARTA*, U.S. FOOD & DRUG ADMIN. 1 (Oct. 18, 2017), https://www.fda.gov/vaccines-blood-biologics/cellular-gene-therapy-products/yescarta-axicabtagene-ciloleucel.

179. *Package Insert – TECARTUS*, U.S. FOOD & DRUG ADMIN. 2, 21, 30 (Oct. 2021), https://www.fda.gov/vaccines-blood-biologics/cellular-gene-therapy-products/tecartus-brexucabtagene-autoleucel; *Approval Letter – TECARTUS*, U.S. FOOD & DRUG ADMIN. 1 (July 24, 2020), https://www.fda.gov/vaccines-blood-biologics/cellular-gene-therapy-products/tecartus-brexucabtagene-autoleucel.

180. *Package Insert – BREYANZI*, U.S. FOOD & DRUG ADMIN. 29, 38 (June 2022), https://www.fda.gov/vaccines-blood-biologics/cellular-gene-therapy-products/breyanzi-lisocabtagene-maraleucel; *Approval Letter – BREYANZI*, U.S. FOOD & DRUG ADMIN. 1 (Feb. 5, 2021), https://www.fda.gov/vaccines-blood-biologics/cellular-gene-therapy-products/breyanzi-lisocabtagene-maraleucel.

Abecma[181] (idecabtagene vicleucel) Target BCMA Co-Stimulation Domain 4-1BB	Celgene Corporation, a Bristol-Myers Squibb Company	Mar. 26, 2021	Adult patients with relapsed or refractory multiple myeloma after four or more prior lines of therapy including an immunomodulatory agent, a proteasome inhibitor, and an anti-CD38 monoclonal antibody
Carvykti[182] (ciltacabtagene autoleucel) Target BCMA Co-Stimulation Domain 4-1BB	Janssen Biotech, Inc.	Feb. 28, 2022	Adult patients with relapsed or refractory multiple myeloma after four or more prior lines of therapy, including a proteasome inhibitor, an immunomodulatory agent, and an anti-CD38 monoclonal antibody

IV. ANALYSIS OF INNOVATION DRIVERS

CAR-T cell therapy development followed a familiar pharmaceutical development pattern. Researchers at academic institutions and pharmaceutical companies conceived of the CAR constructs and conducted the early clinical studies to show their therapeutic promise.[183] These researchers were driven by financial rewards (e.g., compensation, grants, commercialization), professional recognition (e.g., papers, awards), and intrinsic motivations (e.g., curiosity, altruism). For inventions to reach patients, clinical study data must show they

181. *Package Insert – ABECMA*, U.S. FOOD & DRUG ADMIN. 2, 23, 34 (Mar. 2021), https://www.fda.gov/vaccines-blood-biologics/abecma-idecabtagene-vicleucel; *Approval Letter – ABECMA*, U.S. FOOD & DRUG ADMIN. 1 (Mar. 26, 2021), https://www.fda.gov/vaccines-blood-biologics/abecma-idecabtagene-vicleucel.

182. *Package Insert – CARVYKTI*, U.S. FOOD & DRUG ADMIN. 1, 24, 33 (Feb. 2023), https://www.fda.gov/vaccines-blood-biologics/carvykti; *Approval Letter – CARVYKTI*, U.S. FOOD & DRUG ADMIN. 1 (Feb. 28, 2022), https://www.fda.gov/vaccines-blood-biologics/carvykti.

183. *See infra* Section IV.A.

are safe and effective.[184] Grants and charitable donations provided sufficient funding to perform early, single-site clinical studies, but not the large, multi-site clinical studies necessary for regulatory approval.[185] Promising results from early studies enticed private sector funding for the large, multi-center clinical studies.[186] These actors were driven primarily by profit maximization, often via market exclusivity—in the form of patent protection, trade secret protection, and regulatory exclusivity.[187] CAR-T cell therapy is now one of the most promising cancer therapy research areas with academic and industry projects in the pipeline.[188] Intellectual property and regulatory exclusivity continue to play a prominent and growing role in CAR-T cell therapy development.[189]

A. CURIOSITY, SERENDIPITY, TENACITY, ALTRUISM, AND PATENT RIGHTS

Individual researchers, like the early CAR-T cell therapy inventors, often pursue research for personal and professional reasons.[190] Eshhar's, Sadelain's, Rosenberg's, Campana's, and June's experiences illustrate these innovation

184. *See The FDA's Drug Review Process: Ensuring Drugs are Safe and Effective*, U.S. FOOD & DRUG ADMIN. (Nov. 24, 2017), https://www.fda.gov/drugs/information-consumers-and-patients-drugs/fdas-drug-review-process-ensuring-drugs-are-safe-and-effective.

185. *See supra* Section III.A, III.B; *see also* Bach, *supra* note 164 ("In an era of shrinking federal funding, the Hutch's president and director reasoned, the center needed a bold new strategy – one that would allow it to freely pursue innovation without being slowed down by a grants process that, while useful in providing pilot data, would not be large enough to enroll and follow the number of patients required to develop an adequate clinical profile for a novel cancer therapy.").

186. *See supra* Section III.B–III.C; *infra* Section IV.B–IV.C.

187. *See* sources cited, *supra* note 186; Olga Gurgula, *Strategic Patenting by Pharmaceutical Companies – Should Competition Law Intervene?*, 51 IIC INT'L REV. INDUS. PROP. COPYRIGHT LAW 1062, 1066 (2020); *see also* William T. Allen et al., *Commentaries and Cases on the Law of Business Organization* 311 (Rachel E. Barkow et al. eds., 6th ed. 2021) (explaining that U.S. corporations act under the shareholder primacy norm where maximizing profits for shareholders motivates business decisions).

188. *See supra* Section III.C.

189. *See Price Declines After Branded Medicines Lose Exclusivity in the U.S.*, IMS INST. FOR HEALTHCARE INFORMATICS 2, 4 (2016), https://www.iqvia.com/-/media/iqvia/pdfs/institute-reports/price-declines-after-branded-medicines-lose-exclusivity-in-the-us.pdf; Sam F. Halabi, *The Drug Repurposing Ecosystem: Intellectual Property Incentives, Market Exclusivity, and the Future of New Medicines*, 20 YALE L.J. & TECH. 1, 6–23 (2018); Matthew J. Higgins et al., *The Role of Assets in Place: Loss of Market Exclusivity and Investment*, Nat'l Bureau of Econ. Rsch. Working Paper No. 27588 25–27 (2020); Gurgula, *supra* note 187, at 1066.

190. *See* Alice Lam, *What Motivates Academic Scientists to Engage in Research Commercialization: 'Gold', 'Ribbon' or 'Puzzle'?*, 40 RSCH. POL'Y 1354 (2011).

drivers for CAR-T cell therapies.[191] For Eshhar—who routinely lacked grant funding—curiosity, tenacity, and revenues from patent royalties represent the primary innovation drivers. For Rosenberg, Sadelain, and Campana, who received adequate funding through grants and institutional support, curiosity and altruism represent the primary innovation drivers. For June, altruism and personal tragedy represent primary innovation drivers. For all five, the timing of their early professional lives serendipitously coincided with renewed interest in cancer immunotherapies.

1. Eshhar

Curiosity, serendipity, professional awards, tenacity, a flash of genius, altruism, and patent rights drove Eshhar's CAR-T cell therapy innovations.

Eshhar's scientific story begins with curiosity. While serving in the Israeli military, Eshhar saw a presentation by researchers from Weismann Institute of Science on molecular biology.[192] In his words: "My jaw dropped. Immediately I wanted to translate all the wonders I'd come to know into molecules."[193]

Serendipity and professional prizes also drove Eshhar's innovation. He chose TCRs as the subject for his doctoral research in the 1960s, just as interest in the cancer immunosurveillance hypothesis renewed.[194] Eshhar chose to work with a series of renowned researchers who went on to receive top scientific awards shortly after mentoring Eshhar.[195] At the time, he viewed TCR research as "totally basic science" and he had "no concept or pretention that a day would come when that knowledge would serve [him] in devising a treatment for cancer."[196] His research resulted in identifying the native TCR structure and amino acid code.[197] When Eshhar decided to pursue post-doctoral research, his advisor dissuaded him from a school in New York and, "on the spot", called a friend at Harvard to secure Eshhar a place in more

191. Finney declined an interview for this research. Roberts, Sadelain, and June did not respond to an interview request. Information about Eshhar's, Rosenberg's, Sadelain's, and June's experiences comes from publicly available interviews and articles. Information about Campana's experience comes from an interview with the author.

192. *See* Smadar Reisfeld, *The Story Behind an Israeli Immunologist's Cancer-Fighting Breakthrough*, HAARETZ (Nov. 10, 2017), https://www.haaretz.com/science-and-health/2017-11-10/ty-article-magazine/.premium/the-scientist-who-paved-the-way-for-a-chimeric-cancer-therapy/0000017f-e6e1-da9b-a1ff-eeefeac70000.

193. *Id.*

194. *See id.*

195. *See id.* (explaining Eshhar selected advisors "simply because they were the best in the field").

196. *See id.*

197. *See id.*

family-friendly Boston.[198] Eshhar's post-doctoral advisor, Baruj Benacerraf, received the Nobel Prize in Physiology or Medicine in 1980 for his T cell research, just four years after Eshhar left.[199] Benacerraf directed Eshhar to engineer T cells to target "a distinctive molecule that characterizes the cancerous cells" Benacerraf recently discovered.[200] In 1976, his last year at Harvard, Eshhar heard a lecture about a method to produce antibodies by fusing a B cell with a cancer cell.[201]

Tenacity and a flash of genius drove Eshhar to combine his serendipitous knowledge of TCRs and antibodies into a cancer-fighting CAR-T cell therapy. After the 1976 antibody lecture, Eshhar showed up, unannounced, to work in the inventor's lab—the Milstein lab in Cambridge, England.[202] According to Eshhar's recollection, Milstein rejected Eshhar, asking why he failed to contact the lab before showing up.[203] Eshhar replied: "I was impassioned, and I was certain we would work something out."[204] When Milstein did not relent, Eshhar sought out a different inventor, Georges Kohler in Switzerland, to learn the antibody manufacturing method.[205] While implementing the method in his own lab at the Weismann Institute, Eshhar thought:

> Why not take the best of both worlds? In principle, a T cell is capable of eradicating a cancerous cell, thanks to its killer mechanism, but it's not good at identifying the target. An antibody, in contrast, is an expert in identifying targets but it has no killer mechanism. What if the capabilities are combined? We'll create a hybrid, a chimera – the monster in Greek mythology that had the head of a lion, the body of a goat and the tail of a dragon or snake. On the one hand, it will have the antibody's excellent binding ability, and on the other, the T cell's killer ability. We named the chimera the "T-body," a kind of verbal hybrid of antibody and T cell.[206]

Eshhar conceived of this idea with his graduate students, including Gideon Gross.[207] Shortly after, in 1990, Eshhar spent a year on sabbatical with Rosenberg at the NIH and initiated his first clinical study with human cancer

198. *See id.* (explaining Eshhar had three children at the time and his advisor believed Boston would be a better city to raise his family).
199. *See id.*
200. *See id.*
201. *See id.*
202. *See id.*
203. *See id.*
204. *See id.*
205. *See id.*
206. *See id.*
207. *See id.*

patients.[208] The NIH results failed to show clinical efficacy and Eshhar returned home.[209]

Because Eshhar failed to receive sufficient grants to fund his research, he "constantly registered patents in order to use the money from the royalties."[210] For example, when Eshhar learned of a United Nations initiative offering large grants to prevent drug abuse, he pitched an idea to a Swedish company to develop an antibody-based opium sensor.[211] The company licensed Eshhar's patented idea.[212] He similarly patented his CAR technology.[213] When the Weismann Institute, the original assignee, refused to continue maintenance payments, Eshhar and his co-inventors bought the patent rights from the Institute.[214] When Kite eventually licensed Eshhar's patent, Eshhar and his co-inventors personally received royalties from their invention.[215]

In addition to other innovation drivers, Eshhar's motivation is also altruistic—he receives great satisfaction when he "happen[s] to meet someone whose life was saved by the treatment."[216] According to him, "there's nothing greater than that."[217]

2. Sadelain

Serendipity, tenacity, curiosity, and altruism drove Sadelain's innovations.

Serendipity placed Sadelain at the start of his career in the 1980s when ACT and other immune-based approaches began to show clinical promise for cancer therapy.[218] Like Eshhar, Sadelain's doctoral research focused on T cells.[219] Sadelain selected the Massachusetts Institute of Technology for his post-doctoral research because it was one of "only a handful of institutions in the world" beginning to insert foreign genes into cells.[220] To his new colleagues' surprise, he selected an "esoteric purpose" for genetic engineering—modifying T cells.[221] In fact, his "official" project focused on

208. *See id.*
209. *See* Rosenberg, *supra* note 1, at 15.
210. *See* Reisfeld, *supra* note 192.
211. *See id.*
212. *See id.*
213. *See id.*
214. *See id.*
215. *See id.*
216. *See id.*
217. *See id.*
218. *See* Jennifer E. Adair, *An Interview with Michel Sadelain, MD, PhD*, 29 HUM. GENE THERAPY 530 (2018).
219. *See id.* at 531.
220. *See id.*
221. *See id.*

genetically engineering different cells.[222] After two to three years of failed experiments, Sadelain genetically modified a T cell to express a foreign gene in 1992.[223] He presented the result at the World Congress of Immunology where "it elicited absolutely zero interest."[224] Serendipitously, Eshhar published his first CAR-T cell paper just one year later.[225]

Curiosity and altruism drove Sadelain to persist. He applied to permanent positions at institutions which "understood clinical trials and getting treatments to patients."[226] Sadelain joined MSKCC because it ranked highly in Investigational New Drug holdings.[227] There, Sadelain engineered T cells to target blood cancers (particularly directed to cell surface markers CD19, CD20, and CD22) because of MSKCC colleagues' experience with bone marrow transplants.[228] Serendipity struck again when Sadelain identified a CAR construction with improved co-stimulatory properties through an unknown mechanism.[229] Sadelain, with his collaborator Isabelle Rivière, set out to "pave the way" for CAR-T cell therapies to reach patients.[230] Over a decade, Sadelain's team developed capacity to manufacture and test CAR-T cell therapies on MSKCC patients. To spur adoption of new CAR-T cell therapies, Sadelain coordinated with NCI and the University of Pennsylvania to publish the "provocative data" from the first clinical studies.[231]

Commercialization did not initially drive Sadelain's research. Because CAR-T cell therapy was "both a cell therapy and a genetic therapy," Sadelain knew his work "was not the kind of thing [he] could take to a company for clinical development."[232] Instead he and Rivière leveraged MSKCC's resources to develop a facility following Good Manufacturing Practices in-house.[233] With just three rooms, Sadelain and Rivière treated over 250 patients with more than

222. *See id.*

223. *See* Katrina Altersitz, *'A Moment of Marvel' in Manhattan Brings a Revolution in CAR T-Cell Therapy*, HEALIO (May 24, 2019), https://www.healio.com/news/hematology-oncology/20190522/a-moment-of-marvel-in-manhattan-brings-a-revolution-in-car-tcell-therapy.

224. *See id.*

225. *See* Eshhar, *supra* note 108.

226. *See* Altersitz, *supra* note 223.

227. *See id.*

228. *See id.*

229. *See* Maher, *supra* note 78, at 73 (proposing several hypotheses for improved CAR-T cell functionality due to CD28 region).

230. *See* Altersitz, *supra* note 223.

231. *See id.*

232. *See id.*

233. *See id.*

350 different CAR-T cell products.[234] Positive results from this work enabled them to expand to thirteen rooms.[235]

While grants and charitable donations provided sufficient funds for initial, small-scale clinical studies, these resources could not fund the large-scale clinical studies required for CAR-T cell therapies to receive FDA approval and reach patients more broadly.[236] Sadelain and his collaborators founded Juno to accelerate widespread access to CAR-T therapies through collaboration and private sector funding.[237]

3. Rosenberg

Rosenberg's cancer immunotherapy innovations arose from altruism, curiosity, and stubbornness as well as serendipity; to him, commercialization represented only a pathway to bring his breakthroughs to more patients.

As early as high school, Rosenberg recognized that "[c]ancer randomly attacks people of all ages and forces its victims and their families to watch impotently as it grows and spreads" and decided he wanted to "stop everyone's suffering."[238] In addition to altruistic motivations, Rosenberg found cell biology "thrill[ing]."[239] Rosenberg's experiences as a surgical resident piqued his curiosity about the immune system's regulation of cancer.[240] He encountered a patient who experienced "one of the rarest events in medicine," a stomach cancer diagnosis which underwent complete, spontaneous remission.[241] His interests piqued at just the right time—Rosenberg initiated research into cancer immunotherapies in the late 1960s and early 1970s at the NIH, just as interest in the cancer immunosurveillance hypothesis re-ignited.[242]

Pursuing cancer immunotherapy research required Rosenberg to persevere through skepticism as many researchers feared "there was no such thing as an immune response to spontaneous cancers in humans."[243] A serendipitous 1976 research article detailing a method to permit scientists to grow human T cells

234. *See id.*

235. *See id.*

236. *See* Andrew Pollack, *Setting the Body's 'Serial Killers' Loose on Cancer*, N.Y. TIMES (Aug. 1, 2016), https://www.nytimes.com/2016/08/02/health/cancer-cell-therapy-immune-system.html; *see also* Bach, *supra* note 164.

237. *See Fred Hutchinson, Memorial Sloan-Kettering Team Up to Launch Juno Therapeutics*, CENTERWATCH (Dec. 5, 2013), https://cms.centerwatch.com/articles/18926; *see also* Bach, *supra* note 164.

238. *See* Rosenberg, *supra* note 1, at 2–3.

239. *See id.* at 2.

240. *See id.*

241. *See id.*

242. *See id.* at 2; *see also supra* Section II.E.

243. *See* Rosenberg, *supra* note 1, at 3.

in the laboratory through exposure to a T cell growth factor called interleukin-2 (IL-2) enabled Rosenberg to make crucial progress in ACT.[244] "Intuitively," Rosenberg selected lymphocytes harvested from within the tumor (i.e., TILs) as the "most likely site to find T-cells reactive against" the tumor and found some tumor-killing ability *in vitro*.[245] Despite these successes in the late 1970s, Rosenberg's innovation required more stubborn determination to prevail. In the first seventy-six patients Rosenberg treated with various immunotherapies, none showed anti-tumor effects.[246] His first clinical successes came from treating patients directly with IL-2.[247] Rosenberg published these results in a 1985 study with data on "the first patients to develop reproducible tumor shrinkages from any immunotherapy."[248] Shortly after, Rosenberg published results showing successful clinical outcomes for patients treated with TILs; these studies were enabled, in part, by IL-2's ability to grow large numbers of TILs.[249]

Motivated by curiosity and altruism to improve TILs' cancer-targeting abilities, Rosenberg pursued strategies to modify TIL receptors in the late 1980s. Regulatory and ethical concerns about treating patients with cells engineered to express "foreign genes" represented a hurdle to his research.[250] However, after a year negotiating with various NIH review bodies, the NIH approved a study and, in 1990, Rosenberg demonstrated treatment with genetically-modified human cells could be safe.[251] In the early 1990s, Rosenberg learned of Eshhar's CAR work and "quickly invited" him to collaborate.[252] By 2010, Rosenberg's group demonstrated clinical success with anti-CD19 CAR-T cell therapy.[253]

Commercialization and profit did not drive Rosenberg's experimentation and discovery. In the 1980s, when Rosenberg sought IL-2 in large quantities from corporate suppliers for his experiments, he attended a conference by IL-2 manufacturer Cetus.[254] Rather than agree to keep conference research confidential, Rosenberg "sat in a side room unable to hear their discussion" because he found "secrecy in medicine" to be "unseemly when one was trying

244. *See id.*
245. *See id.* at 4.
246. *See id.* at 5–6.
247. *See id.* at 6–7.
248. *See id.* at 6.
249. *See id.* at 9.
250. *See id.* at 9–11.
251. *See id.* at 11.
252. *See id.* at 15.
253. *See id.* at 17.
254. *See id.* at 5.

to develop treatments for desperate cancer patients."[255] When Rosenberg achieved clinical success with a CAR-T cell therapy, Belldegrun, one of Rosenberg's former colleagues and, at the time, a UCLA urology professor, contacted him.[256] Belldegrun wanted to commercialize the CAR-T cell therapy through a new company, Kite.[257] NCI transferred the CAR-T cell therapy technology to Kite under a Cooperative Research and Development Agreement.[258]

4. Campana

Campana's innovations arose from serendipity, professional achievement, altruism, stubbornness, and curiosity.

Serendipity and professional achievement led Campana to specialize in hematology, especially in children.[259] After medical school, students chose a specialty department.[260] Campana meant to choose clinical medicine, but, by chance, "showed up in the wrong department."[261] He bumped into a professor, Federico Caligaris-Cappio, who encouraged Campana to pursue hematology.[262] This chance encounter and curiosity led Campana to a career in hematology, a field that permitted him to pursue both research and clinical work.[263] After graduation, Campana accepted a position in England first as a visiting researcher and then as a professor in immunology.[264] Campana moved to St. Jude Children's Research Hospital because he knew of its strong clinical and research reputation.[265] This position drew Campana to childhood oncology, St. Jude's focus, and to the most common childhood cancer—acute lymphocytic leukemia (ALL).[266]

Altruism and curiosity motivated Campana to research improved cancer treatments.[267] From the beginning of his medical education, Campana focused on translational, rather than basic, research.[268] He quickly realized current drugs had reached a plateau in treatment efficacy, especially for children, at

255. *See id.*
256. *See id.* at 17–18.
257. *See id.*
258. *See id.*
259. Campana Interview, *supra* note 12.
260. *See id.*
261. *See id.*
262. *See id.*
263. *See id.*
264. *See id.*
265. *See id.*
266. *See id.*
267. *See id.*
268. *See id.*

about 90% efficacy.[269] Although highly effective, the treatments pose significant time and quality of life challenges for patients—the drugs produce toxic side effects, require years of treatment, and often leave long term side effects.[270] Doctors could not increase patients' doses due to drug toxicity.[271] At St. Jude's, Campana researched the interaction between leukemia cells and the bone marrow microenvironment and sensitive methods to detect leukemia cells.[272] He leveraged this expertise to develop new blood cancer treatments.[273] In the late 1990s, Campana attended a presentation by Shimon Slavin about a technique called donor lymphocyte infusion showing one child with leukemia in remission due to the treatment.[274] Although some patients, like this child, responded well to donor lymphocyte infusion, the treatment was not effective for many children.[275] Campana sought methods to increase the treatment's success rate and implement it to treat ALL.[276] Around this time, Campana and his post-doctoral researcher, Chihaya Imai, learned about Eshhar's CAR research.[277] They hypothesized a CD19-targeting antibody would target ALL.[278] Heddy Zola provided a CD19-targeting antibody scFv.[279] Imai used the CD19-targeting scFv to create a CAR with the CD3ζ domain.[280] Imai and Campana knew about the co-stimulation issue with first-generation CARs and learned of Sadelain's work with the CD28 co-stimulatory region.[281] They also knew, from St. Jude's ALL database, that few cancer cells naturally expressed co-stimulatory proteins.[282] This challenge motivated them to screen CAR constructs with CD28 and other co-stimulatory regions in different configurations (e.g., CD3ζ followed by 4-1BB vs. 4-1BB followed by CD3ζ) against ALL cells.[283] Their most promising results stemmed from a 4-1BB co-stimulatory domain.[284] Campana and Imai were "amazed": "You could see your target cells just dying in front of you. You sit at the microscope and it's kind of mesmerizing. You just don't want to leave. You just watch the action

269. *See id.*
270. *See id.*
271. *See id.*
272. *See id.*
273. *See id.*
274. *See id.*
275. *See id.*
276. *See id.*
277. *See id.*
278. *See id.*
279. *See id.*
280. *See id.*
281. *See id.*
282. *See id.*
283. *See id.*
284. *See id.*

happening in front of your eyes." Despite their excitement about the results, their publication initially received rejections "almost everywhere" and the community had "no interest at all" in their technology.[285]

Stubbornness and altruism fueled the next stages of Campana's CAR-T cell therapy development. In addition to facing publication rejection, the team also faced challenges getting their new CAR-T cell treatment to patients.[286] Only a few "visionary" physicians would attempt to treat patients with the untested therapy.[287] The 90% efficacy rate with current treatments further disincentivized physicians from trying new therapies.[288] Campana also expected pharmaceutical companies would not be interested without clinical data, especially for a therapy more complex and "far-fetched" than traditional small-molecule drugs.[289] Despite these challenges, Campana and Imai sought to patent their invention because it was "an invention worth protecting."[290] The breakthrough came when Imai presented the results from their publication at the American Society of Hematology (ASH) meeting in the early 2000s to a session attended by only ten to fifteen people.[291] Luckily, June was one of those who attended Imai's presentation.[292] Campana and Imai provided their construct to June.[293] June treated patients and found promising results.[294] After June published results, the community and pharmaceutical companies started to pay attention to CAR-T cell therapies.[295]

Campana's experience with CAR-T cell therapies changed his view of commercialization.[296] While previously uninterested, he realized commercialization could provide the funds and resources required to bring a therapeutic candidate from proof-of-concept to the clinic.[297] Now, he sees commercialization as the route "to reach as many patients as possible."[298]

---

285. *See id.*; *see also* Imai, *supra* note 132.
286. *See* Campana Interview, *supra* note 259.
287. *See id.*
288. *See id.*
289. *See id.*
290. *See id.* ("St. Jude is not very commercially-oriented so we were working there, we were not really that interested in starting companies, neither me nor my colleagues . . . and also St. Jude itself is . . . entirely dependent on . . . philanthropy so it is not really that kind of institute that wants to generate a lot of revenues from patents.").
291. *See id.* ("Although you know ASH is attended by typically 20,000 hematologists . . . it just shows you how little interest there was in that kind of technology at that time.").
292. *See id.*
293. *See id.*
294. *See id.*
295. *See id.*; *see also infra* Section IV.A.5.
296. *See* Campana Interview, *supra* note 259.
297. *See id.*
298. *See id.*

5. June

Serendipity, altruism, and tenacity drove June's CAR-T cell therapy innovations.

Serendipitously, June's research career began with the Navy in the 1970s, a time when the Navy sought treatments for patients exposed to radiation.[299] June researched one such treatment, bone marrow transplantation, during his last year of medical school at the World Health Organization.[300] In 1983, the Navy sent June to continue his bone marrow transplantation research at Fred Hutchinson Cancer Center.[301] June arrived at Fred Hutchinson just as his mentors realized bone marrow transplantation did more than replace immune cells following cancer treatment.[302] They discovered transplanted cells contributed to an immune response against cancer cells and laid the foundation for ACT.[303] By the mid-1980s, June had focused his research on methods to grow T cells in a lab.[304] This T cell research led to a collaboration with Cell Genesys to develop a therapy for HIV.[305]

Altruism and personal tragedy re-directed June's research to focus on T cell-based cancer therapies. In 2001, June's wife passed away from ovarian cancer, despite treatment with June's own "primitive immune therapies."[306] Motivated by a desire to advance cell therapies to cancer patients, June transitioned from treating patients to a full-time researcher position at the University of Pennsylvania.[307] Two years after his wife's passing, June attended a presentation on CAR-T cell therapy by Campana.[308] June requested a sample of Campana's CAR, implemented the CAR design into T cells, and secured one of the first grants from the Alliance for Cancer Gene Therapy, a non-profit, to fund a three-person clinical study to treat leukemia with the CAR-T

299. *See* Pollack, *supra* note 236.

300. *See* Mary Engel, *Dr. Carl June Weaves Together HIV and Cancer Research to Advance Cures for Both*, FRED HUTCH CANCER CTR. NEWS STORIES (Aug. 17, 2017), https://www.fredhutch.org/en/news/center-news/2017/08/carl-june-weaves-together-hiv-and-cancer-research-to-advance-cures-for-both.html.

301. *See id.*

302. *See id.*

303. *See id.*

304. *See* Pollack, *supra* note 236.

305. *See id.*

306. *See id.*

307. *See id.*

308. *See id.*

cell therapy.[309] Two of his three patients went into complete remission.[310] But, June's grant money ran out after this small clinical trial completed.[311] June decided to publish the study results to spur interest in CAR-T cell therapies.[312] The publication drew interest from patients with similar diagnoses, as well as large pharmaceutical companies and start-up investors interested in commercializing a treatment.[313] June's team selected Novartis as their commercialization partner because they believed a large pharmaceutical company could advance the therapy faster than the alternatives.[314] According to June, working with Novartis

> was an ethical decision. Speed to market was important because it was not a question of whether it would work, which it often is. By going to a pharma, there was no delay in building bricks and mortar and hiring people. They had a salesforce in place. We just had to teach their people to manufacture a cell therapy.[315]

Interestingly, for June's subsequent therapeutic candidates, he pivoted to start-up partners.[316] In his view, "[i]f you have a company that's singularly focused, it can be more nimble, and that's what I learned from the Kite versus Novartis experiments. Novartis has this huge portfolio and decision makers in Switzerland and Massachusetts. It just can't keep up with a highly focused team."[317]

B. INTELLECTUAL PROPERTY EXCLUSIVITY

The Yescarta manufacturer (Kite) and other CAR-T cell therapy manufacturers rely primarily on patents and trade secrets for intellectual property exclusivity. Historically, pharmaceutical companies have relied on patent exclusivity to ensure recovery of their substantial research and development (R&D) and clinical investment.[318] CAR-T cell therapy developers similarly relied on patents, even in the early CAR construct development

309. *See id.*; *see also* Antonio Regalado, *T-Cell Pioneer Carl June Acknowledges Key Ingredient Wasn't His*, MIT TECH. REV. (Mar. 14, 2016), https://www.technologyreview.com/2016/03/14/161592/t-cell-pioneer-carl-june-acknowledges-key-ingredient-wasnt-his/.

310. *See* Pollack, *supra* note 236.

311. *See* Ben Fidler, *CAR-T Pioneer Carl June on Founding Startups and Cell Therapy's Next Act*, BIOPHARMA DIVE (Oct. 18, 2022), https://www.biopharmadive.com/news/carl-june-in-vivo-car-t-capstan-tmunity/633980/.

312. *See id.*

313. *Id.*

314. *Id.*

315. *Id.*

316. *Id.*

317. *Id.*

318. *See* Halabi, *supra* note 189, at 6.

stage.[319] However, recent patent litigation created uncertainty on the validity of a particular class of patent claims important to therapeutics manufacturers: composition claims.[320]

Trade secret protection affords additional exclusivity protection for CAR-T cell manufacturers. Because CAR-T cell therapeutics require a complex manufacturing process, manufacturing conditions are critical to therapeutic success, and competitors cannot easily (if at all) determine important know-how (like cell culture conditions) based on the product alone, CAR-T cell manufacturing processes are strong candidates for trade secret protection.[321]

1. Patents

Patent claims to compositions of matter tend to afford the strongest protection for pharmaceutical products because they typically withstand validity challenges.[322] The next strongest claims for pharmaceutical products include methods of manufacturing and methods of treatment (e.g., covering new dosing regimens or indications).[323] Pharmaceutical companies often rely on one or more of these types of patent claims to maintain exclusivity for their products.[324]

a) CAR-T Cell Therapy Composition Patent Landscape

Early CAR-T cell therapy innovators sought patent protection (Table 4). Eshhar acquired multiple patents covering first-generation CAR constructions, including U.S. Pat. No. 7,741,465 ("the '465 patent") claiming "chimeric DNA" encoding an antibody-derived binding region connected to an "endogenous" signaling protein, including CD3.[325] Finney and Roberts, and their respective employers, also sought patent protection for their second-generation CAR constructs.[326] Sadelain acquired patent claims covering the

319. *See*, *e.g.*, '149 patent, *supra* note 123; '249 application, *supra* note 131; U.S. Patent No. 7,741,465 (filed July 2, 1993) [hereinafter '465 patent]; '190 patent, *supra* note 77.

320. *See* Juno Therapeutics, Inc. v. Kite Pharma, Inc. (*Juno v. Kite II*), 10 F.4th 1330, 1335–41 (Fed. Cir. 2021), *cert. denied*, Juno Therapeutics, Inc. v. Kite Pharma, Inc. (*Juno v. Kite III*), 143 S. Ct. 402, (2022), *reh'g denied*, 143 S. Ct. 631, (2023).

321. *See* Joyce Wing Yan Tam, *Biologics Revolution: The Intersection of Biotechnology, Patent Law, and Pharmaceutical Regulation*, 98 GEO. L.J. 535, 545–47 (2010).

322. *See* N. Nicole Stakleff, *A Drug Life: The Chemistry of Patent and Regulatory Exclusivity for Pharmceuticals*, 16 FLA. COASTAL L. REV. 27, 53–54, 61–62 (2014); Gurgula, *supra* note 187, at 1067–68.

323. *See* sources cited, *supra* note 322.

324. *See id.*

325. *See* Kite Pharma, Inc., Registration Statement (Form S-1) at Ex. 10.17 (License Agreement with Cabaret Biotech Ltd. on December 12, 2013); '465 patent, *supra* note 319, claims 1, 6.

326. *See, e.g.*, '249 application, *supra* note 131; '149 patent, *supra* note 123.

sequence of his improved second-generation CAR in U.S. Pat. No. 7,446,190, including a sequence used in the Yescarta CAR.[327] Eshhar and Sadelain licensed their patents to start-up companies Kite and Juno, respectively, which leveraged the patent assets to attract investors to fund additional clinical studies.[328]

Patent exclusivity was key to Kite's business strategy from the outset. Kite's registration statement identified patents as important to competing in the market.[329] One of Kite's first corporate acts was to license Eshhar's CAR patents (including the '465 patent) from his licensing company, Cabaret Biotech Ltd.[330] Kite also licensed Cell Genesys patents.[331] Kite's '465 patent family includes applications filed in Europe, Canada, Japan, and Australia.[332] Kite applied Yescarta's patent term extension to the '465 patent.[333] Further, Kite invested in a re-examination proceeding at the U.S. Patent and Trademark Office (USPTO) for the '465 patent and acquired new claims in 2016.[334] With

327. *See Juno v. Kite I*, at *9–10 ("Plaintiffs presented evidence and testimony that Defendant knew that Dr. Rosenberg from National Cancer Institute ("NCI") copied Dr. Sadelain's backbone, as demonstrated by Defendant's attempting to be the first to license and to invalidate the '190 [p]atent. Plaintiff's fact witness Dr. Dash testified that Dr. Belldegrun was so desperate to pursue a license to the '190 [p]atent that he appeared at her office, despite not having a meeting. Dr. Jakobovitz similarly testified that Dr. Belldegrun met with Plaintiffs in an attempt to license the '190 [p]atent."); Petition for Writ of Certiorari, *Juno v. Kite*, *supra* note 91, at 14 ("Kite stipulated that Yescarta literally infringes the ['190] patent" with only one independent claim reciting SEQ ID NO:6).

328. *See* CLAUDE BARFIELD & JOHN E. CALFEE, TECHNOLOGY AND THE PATENT SYSTEM: BALANCING INNOVATION AND PROPERTY RIGHTS 27 (2007) (explaining that patents are typically "crucial" for startup biotechnology companies because they serve as stable assets to attract investment); *see also* Kite Pharma, Inc., Registration Statement (Form S-1), *supra* note 138, at Ex. 10.17 (License Agreement with Cabaret Biotech Ltd. on December 12, 2013); Bach, *supra* note 164; Brendan Doherty, *Cell Genesys Transforms Patents Into Gold Mines*, S.F. BUS TIMES (June 16, 2002), https://www.bizjournals.com/sanfrancisco/stories/2002/06/17/newscolumn1.html.

329. Kite Pharma, Inc., Registration Statement (Form S-1), *supra* note 138, at 31.

330. *Id.* at 86 (indicating that Cabaret patents and not NCI patents cover KTE-C19); *see also id.* at 2–5, 30–31, Ex. 10.17 (License Agreement with Cabaret Biotech Ltd. on December 12, 2013); Complaint at ¶¶ 23–24, Cabaret Biotech Ltd. v. Kite Pharma, Inc., No. 1:19-cv-01732 LPS, 2020 WL 8265236 (2019) [hereinafter Cabaret Complaint].

331. Kite Pharma, Inc., Registration Statement (Form S-1) at 79 (May 19, 2014).

332. *See* WO 93/19163; AU668156; EP0638119; CA2132349; JP3643590.

333. Cabaret Complaint, *supra* note 330 at ¶¶ 32–36; *Applications for Patent Term Extension And Patent Terms Extended Under 35 U.S.C. § 156*, U.S.P.T.O., https://www.uspto.gov/patents/laws/patent-term-extension/patent-terms-extended-under-35-usc-156 (last accessed Nov. 11, 2022).

334. Reexamination Request 90/013,790.

the exception of a 2019 dispute, Kite (and later Gilead) continuously paid and continues to pay royalties on Eshhar's patents.[335]

Like Kite, Juno similarly relied on patent rights. Researchers affiliated with Fred Hutchinson Cancer Research Center, MSKCC, and Seattle Children's Research Institute founded Juno to commercialize cancer immunotherapies including the technology claimed in Sadelain's '190 patent.[336] Juno's registration statement also identifies patents as key to its ability to compete in the market.[337] Several of Juno's first corporate actions involved licensing agreements with various research organizations, including MSKCC, Fred Hutchinson Cancer Research Center, Seattle Children's Research Institute, and St. Jude Children's Research Hospital.[338] In 2014, Juno sued the University of Pennsylvania and Novartis to enforce patent rights over the CD3ζ-4-1BB CAR design (voluntarily settled in 2015).[339]

335. Cabaret Complaint, *supra* note 330, at ¶ 31 (Kite paid licensing fees to Cabaret from December 2013 to October 2018); *Id.* at ¶¶ 31, 37–40 (Gilead pushed back and eventually stopped paying licensing fees from 2017 to 2019); *Id.* at ¶ 61 (Cabaret sued Kite/Gilead for declaratory judgment that '465 patent valid and Yescarta® infringes in 2019); Joint Claim Construction Brief, Cabaret Biotech Ltd. v. Kite Pharma, Inc., No. 1:19-cv-01732 LPS, 2020 WL 8265236 (2019) (filed July 13, 2020); Stipulation of Dismissal, Cabaret Biotech Ltd. v. Kite Pharma, Inc., No. 1:19-cv-01732 LPS, 2020 WL 8265236 (2019) (parties settled in December 2020).

336. *See* Bach, *supra* note 164. Strikingly, the '190 patent lacks international counterparts.

337. Juno Therapeutics, Inc., Registration Statement (Form S-1) at 108 (Nov. 17, 2014).

338. *See id.* at 71, 110–16.

339. *See* Trustees of the Univ. of Pennsylvania v. St. Jude Children's Rsch. Hosp., 2014 WL 12610149 (E.D. Pa. Mar. 13, 2014) (voluntarily dismissed); *see also* Juno Therapeutics, Inc., Registration Statement (Form S-1), *supra* note 138, at 53 (Nov. 17, 2014).

Table 4: CAR-T inventors sought patent protection for two key signaling constructs (exemplary patents).

U.S. Patent No. / Appl. No.	CAR Construct	Earliest Priority Year	Inventor	Initial Assignee	Current Assignee
7,741,465	CD3ζ	1993	Eshhar & others	Yeda Research and Development Co. Ltd.	Eshhar (Licensed to Kite)[340]
5,712,149	CD28-CD3ζ	1995	Roberts	Cell Genesys	Cabaret Biotech Ltd. (Licensed to Kite)[341]
09/091,608	CD28-CD3ζ	1996	Finney & others	Celltech	N/A
10/399,364	4-1BB-CD3ζ	2001	Finney & others	Celltech	N/A
7,446,190 (60/383,872)	CD28-CD3ζ	2002	Sadelain & others	MSK	MSK (Licensed to Juno)[342]
8,399,645 (60/517,507)	4-1BB-CD3ζ	2003	Campana & Imai	St. Jude Children's Research Hospital	St. Jude Children's Research Hospital (Licensed to Juno, Novartis)[343]

Despite inventors' interest in patent protection, CAR-T cell therapy manufacturers face acute patent challenges beyond those commonly faced in the pharmaceutical field: (1) manufacturing technological complexity; (2) composition patent expiration near regulatory approval; and (3) disclosure requirement uncertainty, especially for composition claims. Composition claim challenges suggest other exclusivity schemes continue to incentivize pharmaceutical companies to commercialize CAR-T therapies, including trade secret protection[344] and regulatory exclusivity.[345]

340. Kite Pharma, Inc., Registration Statement (Form S-1) at Ex. 10.17 (License Agreement with Cabaret Biotech Ltd. on Dec. 12, 2013).

341. *Id.*

342. Second Amended Complaint at ¶ 15, *Juno v. Kite I,* 2020 WL 10460622 (C.D. Cal. Mar. 24, 2020), *rev'd*, 10 F.4th 1330 (Fed. Cir. 2021).

343. Juno Therapeutics, Inc., Annual Report (Form 10-K) at 82 (Feb. 29, 2016).

344. *See infra* Section IV.B.2.

345. *See infra* Section IV.C.

b) Collaborative Licensing Model

Pharmaceutical companies frequently license patents and trade secrets from innovators. Because CAR-T cell therapies require complex manufacturing processes, initial licensing agreements often followed an innovative, collaborative model. Juno referred to its model as "ongoing technology transfer."[346] While technology transfer from academic institutions to companies often ends with a licensing agreement, Juno sought to involve the innovators in its scientific strategy, as co-founders and as collaborators.[347] Indeed, Juno brought together academics from multiple academic institutions with expertise in cell therapy: MSKCC, Seattle Children's Research Institute, and Fred Hutchinson Cancer Center.[348]

c) Composition Patent Expiration

CAR-T cell therapy composition claims provide limited exclusivity to manufacturers because the claims likely expired before or will expire soon after manufacturers receive regulatory approval to market the new therapies.

For patents filed on or after June 8, 1995, exclusivity extends approximately twenty years from the earliest utility application priority date.[349] For patents filed before June 8, 1995, the exclusivity term is the greater of approximately twenty years from the earliest utility application priority date and seventeen years from the date the patent issued.[350]

Because the early CAR-T composition patents' priority dates range from 1993-2003 and the FDA approved the first CAR-T therapies in 2017, composition claims (e.g., those directed to CAR constructs) expired before or soon after the FDA first approved CAR-T therapies (Table 3).

d) Composition Claim Disclosure Uncertainty: *Juno v. Kite* and the Written Description Requirement Example

Even assuming the composition claims remain in force, recent precedent interpreting 35 U.S.C. § 112 creates uncertainty about the validity of

346. *See* Charlotte Schubert, *Juno's Lasting Legacy: How the Cell Therapy Juggernaut Influenced Biotech in Seattle and Beyond*, GEEKWIRE (Feb. 8, 2022), https://www.geekwire.com/2022/junos-lasting-legacy-how-the-cell-therapy-juggernaut-influenced-biotech-in-seattle-and-beyond/.

347. *See id.*; *see also Q&A: Carl June on CAR T-cell Therapy*, 1 BLOOD CANCER DISCOVERY 8 (2020).

348. *See* Bach, *supra* note 164; *see also* Matthew Herper, *Why One Cancer Company Has Raised $300 Million in 12 Months Without an IPO*, FORBES (Aug. 5, 2014), https://www.forbes.com/sites/matthewherper/2014/08/05/why-this-cancer-fighting-company-has-raised-300-million-in-just-12-months/?sh=149b353650d5.

349. *See* MPEP 2701 (citing 35 U.S.C. § 154(a)(2)) (9th ed. Rev. Feb. 2023).

350. *See id.* (citing 35 U.S.C. § 154(c)).

biotechnology composition claims for insufficient written description and lack of enablement.[351] For example, Juno's '190 patent created substantial freedom-to-operate risk for Yescarta, so Kite invested substantially in invalidating it. Although Kite ultimately succeeded, the Federal Circuit's invalidity decision may leave Kite's own composition claims and similarly situated companies' composition claims vulnerable.[352]

The dispute at the heart of *Juno v. Kite* arose from a research collaboration. Sadelain and co-inventors at MSKCC filed a patent application in 2003 leading to the grant of the '190 patent in 2008.[353] Sadelain shared this invention with Rosenberg at NCI.[354] Later, Kite established a collaboration with NCI "for the development and commercialization of novel engineered peripheral blood autologous T cell therapeutics (eACT) for the treatment of multiple cancer indications."[355] The collaboration provided Kite with "exclusive access to the current and future clinical product pipeline of autologous peripheral blood T cells, engineered with the NCI's proprietary tumor-specific TCRs and Chimeric Antigen Receptors (CARs), directed to multiple hematological and solid tumor types."[356] Rosenberg shared Sadelain's invention with Kite without MSKCC's permission; Kite developed this technology into Yescarta.[357]

---

351. *See Juno v. Kite II* at 1338 ("To satisfy written description, however, the inventors needed to convey that they possessed the claimed invention, which encompasses all scFvs, *known and unknown*, as part of the claimed CAR that bind to a selected target.") (emphasis added).

352. Juno Therapeutics, Inc., Registration Statement (Form S-1) at 50 (Nov. 17, 2014) (even before *Juno v. Kite II*, biotech patent strength was "uncertain" due to complexities of patent law); *see also* Tam, *supra* note 321, at 535, 545–47; Jonathan B. Fitzgerald & Jeffrey D. Morton, *Juno v. Kite Case Implications for Functionally Claimed Biological Compositions*, Outsourced Pharma (Nov. 12, 2021), https://www.outsourcedpharma.com/doc/juno-v-kite-case-implications-for-functionally-claimed-biological-compositions-0001; Brachmann, *supra* note 175 (describing § 112 written description interpretation as "ridiculous," "nearly impossible for life sciences inventors to properly meet," and "greatly increase[ing] . . . validity risks for the entire life sciences sector.").

353. *Juno v. Kite IPR Appeal* at *1; Petition for Writ of Certiorari, *Juno v. Kite*, *supra* note 91, at 12.

354. *See* Petition for Writ of Certiorari, *Juno v. Kite*, *supra* note 91, at 13.

355. *Kite Pharma Partners with the National Cancer Institute to Develop Novel Cellular Immunotherapy Clinical Products*, Kite Pharma (Oct. 16, 2012), https://web.archive.org/web/20160303211144/http://amda-2v2xoy.client.shareholder.com/releasedetail.cfm?ReleaseID=852506.

356. *Id.*

357. *See Juno v. Kite I* at *9–10 ("Plaintiffs presented evidence and testimony that Defendant knew that Dr. Rosenberg from National Cancer Institute ("NCI") copied Dr. Sadelain's backbone, as demonstrated by Defendant's attempting to be the first to license and to invalidate the '190 Patent. Plaintiff's fact witness Dr. Dash testified that Dr. Belldegrun was

Kite attempted several strategies to mitigate the '190 patent freedom-to-operate issue. First, Kite challenged the validity of the '190 patent in an *inter partes* review (IPR) petition filed on August 13, 2015.[358] Kite's petition asserted that the '190 patent was invalid on three § 102 and § 103 grounds.[359] The Patent Trial and Appeal Board (PTAB) instituted the IPR on all three grounds.[360] On December 16, 2016, the PTAB found for Juno, declining to find the '190 patent invalid.[361] Kite appealed the PTAB's decision to the Federal Circuit, which affirmed the '190 patent's validity in 2018.[362] After Kite failed to invalidate Sadelain's patent, Kite attempted to license it.[363] MSKCC refused to license Sadelain's patent, choosing instead to found Juno to commercialize it.[364]

Upon FDA approval of Yescarta, Juno sued Kite in district court for infringing the '190 patent.[365] A jury unanimously held for Juno on December 13, 2019—finding the '190 patent valid, willfully infringed by Kite, and awarding Juno $585M upfront payment plus 27.6% royalty on future sales.[366] The district court judge rejected Kite's motions for judgment as a matter of law and new trial.[367] Kite appealed to the Federal Circuit, arguing the '190

---

so desperate to pursue a license to the '190 Patent that he appeared at her office, despite not having a meeting. Dr. Jakobovitz similarly testified that Dr. Belldegrun met with Plaintiffs in an attempt to license the '190 Patent.") (emphasis added), *rev'd*, 10 F.4th 1330 (Fed. Cir. 2021) (reversing on other grounds); *see also* Petition for Writ of Certiorari, *Juno v. Kite*, *supra* note 91, at 13.

358. *Juno v. Kite I* at *2; Petition for Writ of Certiorari, *Juno v. Kite*, *supra* note 91, at 14.

359. Inter Partes Review Petition at 16, Kite Pharma, Inc. v. Sloan Kettering Inst. for Cancer Research, IPR2015-01719 (P.T.A.B. Dec. 16, 2016).

360. Institution Decision at 5, Kite Pharma, Inc. v. Sloan Kettering Inst. for Cancer Research, IPR2015-01719 (P.T.A.B. Dec. 16, 2016).

361. Final Written Decision at 3, Kite Pharma, Inc. v. Sloan Kettering Inst. for Cancer Research, IPR2015-01719 (P.T.A.B. Dec. 16, 2016); *see also Juno v. Kite IPR Appeal* at *2; Petition for Writ of Certiorari, *Juno v. Kite*, *supra* note 91, at 14.

362. *Juno v. Kite IPR Appeal* at *2; Petition for Writ of Certiorari, *Juno v. Kite*, *supra* note 91, at 14.

363. *Juno v. Kite I* at *9–10 ("Plaintiffs presented evidence and testimony that Defendant knew that Dr. Rosenberg from National Cancer Institute ("NCI") copied Dr. Sadelain's backbone, as demonstrated by Defendant's attempting to be the first to license and to invalidate the '190 Patent. Plaintiff's fact witness Dr. Dash testified that Dr. Belldegrun was so desperate to pursue a license to the '190 Patent that he appeared at her office, despite not having a meeting. Dr. Jakobovitz similarly testified that Dr. Belldegrun met with Plaintiffs in an attempt to license the '190 Patent.") (emphasis added); *see also* Petition for Writ of Certiorari, *Juno v. Kite*, *supra* note 91, at 13.

364. *See Juno v. Kite IPR Appeal* at *2; *see also* Petition for Writ of Certiorari, *Juno v. Kite*, *supra* note 91, at 14.

365. *Juno v. Kite I*.

366. *Id.* at *2.

367. *Id.* at *21.

patent was invalid (and admitting infringement).[368] The Federal Circuit found the '190 patent invalid for insufficient written description to support the claims (§ 112) and reversed the jury verdict.[369] In 2022, the Supreme Court denied certiorari leaving the '190 patent invalid.[370]

Although Kite won and avoided massive damages, *Juno v. Kite* leaves biotechnology patents claiming proteins, like CARs, vulnerable to invalidity under § 112. A valid patent must claim an eligible, new, and non-obvious invention and must

> contain a written description of the invention, and the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same.[371]

For claims like those at issue in the '190 patent, directed to a broad range of proteins with common functional characteristics (i.e., a functionally-defined genus), the patent must disclose either a "representative number of species falling within the scope of the genus" or "structural features common to the members of the genus so that one of skill in the art can 'visualize or recognize' the members of the genus."[372] Although the primary innovation was the CD28 co-stimulatory intracellular signaling domain, the Federal Circuit held the '190 patent claims invalid for claiming "a binding element that specifically interacts with a selected target" (i.e., the antibody-derived, extracellular scFv region) without also disclosing "all scFvs, **known and unknown**, as part of the claimed CAR that bind to a selected target" (emphasis added).[373] Such an expansive written description requirement, especially imposed on an arguably well-known element of the claim, threatens to undermine existing biotechnology composition patent claims and future investment in biotechnology innovation.[374]

2. Trade Secret

Biotech companies may mitigate uncertainty around patent composition claims and maintain exclusivity using another area of intellectual property

368. *Juno v. Kite II* at 1334; *see also* Petition for Writ of Certiorari, *Juno v. Kite*, *supra* note 91, at 14.

369. Petition for Writ of Certiorari, *Juno v. Kite*, *supra* note 91, at 4.

370. *Juno v. Kite III*.

371. 35 U.S.C. §§ 101, 102, 103, 112.

372. *Juno v. Kite II* at 1335 (summarizing precedent interpreting § 112).

373. *See id.* at 1333–34, 37–38.

374. Brachmann, *supra* note 175.

protection: trade secret law.[375] Trade secret protection is ideal when detection of patent infringement would be difficult and where sale of a product does not disclose the secret.[376] CAR-T cells' complex manufacturing processes, including extracting autologous T cells from patients, purifying them, engineering them to express the CAR, multiplying them, and administering them back to patients, provide several viable areas for trade secret protection.[377] Both Juno and Kite rely on trade secret protection (in addition to patents) to maintain their exclusivity and a competitive edge.[378] For example, Yescarta's FDA filings include multiple trade secret redactions related to Kite's manufacturing processes, especially Kite's method to induce cells to express the CAR protein.[379] Similarly, Juno redacted its Breyanzi FDA filings to protect trade secrets related to its manufacturing processes, methods to induce cells to express its CAR protein, and process validation and impurity testing methods.[380]

375. *See* Chorong Song, *How Non-Product-Specific Manufacturing Patents Block Biosimilars*, 71 DUKE L.J. 1923, 1934 (2022); Lisa Diependaele et al., *Similar or the Same: Why Biosimilars are Not the Solution*, 46 J.L. MED. & ETHICS 776, 777, 783 (2018).

376. *See* Daniel C. Munson, *The Patent-Trade Secret Decision: An Industrial Perspective*, 78 J. PAT. & TRADEMARK OFF. SOC'Y 689, 692, 708 (1996); *see also* Andrew Beckerman-Rodau, *The Choice Between Patent Protection and Trade Secret Protection: A Legal and Business Decision*, 84 J. PAT. & TRADEMARK OFF. SOC'Y 371, 396–97 (2002); W. Nicholson Price II & Arti K. Rai, *Are Trade Secrets Delaying Biosimilars? Regulations for Approving Biologic Drugs Thwart the Market for Would-Be Competitors*, 348 SCI. 188, 188–89 (2015); Yaniv Heled, *The Case for Disclosure of Biologics Manufacturing Information*, 47 J.L. MED. & ETHICS 54 (2019).

377. *See* June, *supra* note 164 at 614; Hollyman, *supra* note 97, at 173; Beckerman-Rodau, *supra* note 376, at 396–97; *see also* W. Nicholson Price II & Arti K. Rai, *Manufacturing Barriers to Biologics Competition and Innovation*, 101 IOWA L. REV. 1023, 1046–47 (2016); Halabi, *supra* note 189, at 23–24.

378. *See* Juno Therapeutics, Inc., Registration Statement (Form S-1) at 108 (Nov. 17, 2014); Kite Pharma, Inc., Registration Statement (Form S-1) at 30–31 (May 19, 2014).

379. *Clinical Pharmacology BLA Review (BLA 125643)*, U.S. FOOD & DRUG ADMIN. 11 (Mar. 31, 2017), https://www.fda.gov/vaccines-blood-biologics/cellular-gene-therapy-products/yescarta-axicabtagene-ciloleucel (showing "(b)(4)" redactions); *see also* Michael Havert, *Summary Basis for Regulatory Action (BLA 125643)*, U.S. FOOD & DRUG ADMIN. 4–5 (Oct. 18, 2017), https://www.fda.gov/vaccines-blood-biologics/cellular-gene-therapy-products/yescarta-axicabtagene-ciloleucel (same). These redactions related to diagnostics and manufacturing processes indicate trade secrets because Kite used the "(b)(4)" label. *FOI Information*, U.S. FOOD & DRUG ADMIN. (Mar. 28, 2018), https://www.fda.gov/regulatory-information/freedom-information/foi-information ("Exemption 4: Protects trade secrets and confidential commercial or financial information.") (emphasis removed).

380. Kimberly L.W. Schultz, *Summary Basis for Regulatory Action (BLA 125714)*, U.S. FOOD & DRUG ADMIN. 5–8 (Feb. 5, 2021) https://www.fda.gov/vaccines-blood-biologics/cellular-gene-therapy-products/breyanzi-lisocabtagene-maraleucel; *see also CBER CMC BLA Review Memorandum (BLA 125714)*, U.S. FOOD & DRUG ADMIN., https://www.fda.gov/vaccines-blood-biologics/cellular-gene-therapy-products/breyanzi-lisocabtagene-maraleucel.

C. REGULATORY REGIMES

The U.S. Food and Drug Administration (FDA) offers accelerated review and regulatory exclusivity to mitigate the high risk of failure, high clinical study costs, and substantial upfront investment.[381] As one example, drugs "intended to treat a serious condition" and with "preliminary clinical evidence [to] indicate[] . . . the drug may demonstrate substantial improvement over available therapy on a clinically significant endpoint(s)" may receive accelerated review under the "Breakthrough Therapy" designation.[382] After approval, the FDA cannot approve a generic, biosimilar, or interchangeable version of the drug during its regulatory exclusivity.[383] Regulatory exclusivity runs concurrently with patent exclusivity.[384] For example, the Biologics Price Competition and Innovation Act of 2009 (BPCIA) established twelve years regulatory exclusivity for new biological products (i.e., a "reference product").[385] In addition to reference product exclusivity, biologic drugs may receive orphan drug exclusivity, new indication exclusivity, and pediatric exclusivity.[386] The most common regulatory incentives CAR-T cell

381. *See* Renu Lal, *Patents and Exclusivity*, FDA/CDER SBIA CHRONICLES (May 19, 2015), https://www.fda.gov/media/92548/download#:~:text=Exclusivity%20is%20exclusive%20marketing%20rights,with%20a%20patent%20or%20not; *Orphan Drug Act – Relevant Excerpts*, U.S. FOOD & DRUG ADMIN. (Mar. 9, 2018), https://www.fda.gov/industry/designating-orphan-product-drugs-and-biological-products/orphan-drug-act-relevant-excerpts ("[B]ecause so few individuals are affected by any one rare disease or condition, a pharmaceutical company which develops an orphan drug may reasonably expect the drug to generate relatively small sales in comparison to the cost of developing the drug and consequently to incur a financial loss."); Barfield, *supra* note 328, at 18–21; Tam, *supra* note 321, at 552–58; Halabi, *supra* note 189, at 26–29; Stakleff, *supra* note 322, at 28–29, 45–50; *Breakthrough Therapy*, U.S. FOOD & DRUG ADMIN. (Jan. 4, 2018), https://www.fda.gov/patients/fast-track-breakthrough-therapy-accelerated-approval-priority-review/breakthrough-therapy.

382. *Breakthrough Therapy*, U.S. FOOD & DRUG ADMIN. (Jan. 4, 2018), https://www.fda.gov/patients/fast-track-breakthrough-therapy-accelerated-approval-priority-review/breakthrough-therapy.

383. *See* Lal, *supra* note 381; *Guidance for Industry Reference Product Exclusivity for Biological Products Filed Under Section 351(a) of the PHS Act*, U.S. FOOD & DRUG ADMIN. 1 (Apr. 15, 2020), https://www.fda.gov/regulatory-information/search-fda-guidance-documents/reference-product-exclusivity-biological-products-filed-under-section-351a-phs-act [hereinafter *Exclusivity for Biological Products*].

384. *See* Lal, *supra* note 381; *see also Exclusivity for Biological Products*, *supra* note 383, at 2–3.

385. *Exclusivity for Biological Products*, *supra* note 383, at 1.

386. *See* Lal, *supra* note 381.

manufacturers receive are the Breakthrough Therapy designation and orphan drug exclusivity.[387]

1. Breakthrough Therapy Designation

Progressing through clinical studies more quickly enables pharmaceutical companies to begin to profit from their investments sooner. The FDA offers the Breakthrough Therapy designation pathway to expedite review when the drug "treats a serious or life-threatening condition and preliminary clinical evidence indicates that the drug may demonstrate substantial improvement on a clinically significant endpoint(s) over available therapies."[388] Novartis' tisagenlecleucel (later Kymriah) was the first personalized cell therapy for the treatment of cancer to receive Breakthrough Therapy designation status.[389] About one year later, in July 2015, Kite's axicabtagene ciloleucel (later Yescarta) also received Breakthrough Therapy designation.[390] All approved CAR-T cell therapies received Breakthrough Therapy designation for at least one indication (Table 5). Kymriah, Tecartus, and Carvykti received Breakthrough Therapy designation for two indications.

387. *See* Caitlin Owens, *Blockbuster Drugs are Stacking Up Orphan Approvals*, AXIOS (Feb. 19, 2019), https://www.axios.com/2019/02/19/blockbuster-drugs-are-stacking-up-1550264427; Braendstrup, *supra* note 103, at 61; *see also* Ralf Otto, *Rapid Growth in Biopharma: Challenges and Opportunities*, MCKINSEY & CO. (Dec. 1, 2014), https://www.mckinsey.com/industries/life-sciences/our-insights/rapid-growth-in-biopharma (noting Rate of advance from Phase I to Phase II is higher for biologics than for small-molecule therapeutics); Brower, *supra* note 84; *Breakthrough Therapy*, U.S. FOOD & DRUG ADMIN. (Jan, 4, 2018), https://www.fda.gov/patients/fast-track-breakthrough-therapy-accelerated-approval-priority-review/breakthrough-therapy [hereinafter *FDA Breakthrough Therapy*].

388. *Frequently Asked Questions: Breakthrough Therapies*, U.S. FOOD & DRUG ADMIN. (Feb. 3, 2022), https://www.fda.gov/regulatory-information/food-and-drug-administration-safety-and-innovation-act-fdasia/frequently-asked-questions-breakthrough-therapies#:~:text=A%20breakthrough%20therapy%20designation%20is,(s)%20over%20available%20therapies.

389. *See* Braendstrup, *supra* note 103, at 61; *see also* Brower, *supra* note 84; *FDA Breakthrough Therapy*, *supra* note 387.

390. *See* Braendstrup, *supra* note 103, at 61.

Table 5: All CAR-T therapeutics received accelerated FDA review under the Breakthrough Therapy designation.[391]

Breakthrough Therapy	Sponsor	Approval Date	Indication
Kymriah	Novartis Pharmaceuticals, Inc.	Aug. 30, 2017	Patients up to 25 years of age with B-cell precursor acute lymphoblastic leukemia (ALL) that is refractory or in second or later relapse
		May 1, 2018	Adult patients with relapsed or refractory diffuse large B-cell lymphoma (r/r DLBCL) who are ineligible for autologous transplant
Yescarta	Kite Pharma, Inc.	Oct. 18, 2017	Adult patients with relapsed or refractory large B-cell lymphoma after two or more lines of systemic therapy
Tecartus	Kite Pharma, Inc.	July 24, 2020	Adult patients with relapsed/refractory mantle cell lymphoma
		Oct. 1, 2021	Adult patients with relapsed/refractory mantle cell lymphoma
Breyanzi	Juno Therapeutics, a Bristol-Myers Squibb Company	Feb. 5, 2021	Adult patients with relapsed or refractory large B-cell lymphoma after two or more lines of systemic therapy
Abecma	Celgene Corporation, a Bristol-Myers Squibb Company	Mar. 26, 2021	Adult patients with relapsed or refractory multiple myeloma after four or more prior lines of therapy including an immunomodulatory agent, a proteasome inhibitor, and an anti-CD38 monoclonal antibody
Carvykti	Janssen Biotech, Inc.	Feb. 28, 2022	Adult patients with relapsed or refractory multiple myeloma after four or more prior lines of therapy, including a proteasome inhibitor, an immunomodulatory agent, and an anti-CD38 monoclonal antibody

391. *Previous (Cumulative) CY CBER BT Totals*, U.S. FOOD & DRUG ADMIN. 1–2 (Dec. 31, 2023), https://www.fda.gov/regulatory-information/food-and-drug-administration-safety-and-innovation-act-fdasia/cber-approvals-breakthrough-therapy-designated-drugs.

		Dec. 21, 2023	Adult patients with relapsed or refractory multiple myeloma, who previously received a proteasome inhibitor (PI), an immunomodulatory agent (IMiD) and an anti-CD38 antibody

2. Orphan Drug Designation Exclusivity

Congress enacted orphan drug exclusivity in the Hatch-Waxman Act (1984) to incentivize therapeutic development for diseases affecting too few people for pharmaceutical companies to "reasonably expect" to recoup their investment.[392] Drugs treating qualifying indications receive seven years of regulatory exclusivity for each indication approved by the FDA.[393] The FDA may not approve a subsequent application for the "same" drug for the "same" orphan indication for seven years.[394] The FDA determines a subsequent drug is the "same" if it "contains the same principal molecular structural features (but not necessarily all of the same structural features) and is intended for the same use or indication as a previously approved drug," unless the subsequent drug is "clinically superior."[395] The same drug may receive multiple orphan drug exclusivity periods for each additional FDA approval for a qualifying indication.[396]

Cell therapies, and personalized therapeutics more broadly, approach regulatory regimes with different challenges and opportunities than the traditional small molecules available when Congress initially created orphan drug exclusivity. For example, personalized medicines appear to have a lower risk of failure because they often cause fewer off-target effects than small-

392. *Orphan Drug Act – Relevant Excerpts*, U.S. FOOD & DRUG ADMIN. (Mar. 9, 2018), https://www.fda.gov/industry/designating-orphan-product-drugs-and-biological-products/orphan-drug-act-relevant-excerpts ("[B]ecause so few individuals are affected by any one rare disease or condition, a pharmaceutical company which develops an orphan drug may reasonably expect the drug to generate relatively small sales in comparison to the cost of developing the drug and consequently to incur a financial loss.").

393. *See id.*

394. *See Guidance for Industry - Interpreting Sameness of Gene Therapy Products Under the Orphan Drug Regulations*, U.S. FOOD & DRUG ADMIN. 2–3 (Sept. 2021), https://www.fda.gov/media/134731/download#:~:text=The%20orphan%20drug%20regulations%20define,a%20previously%20approved%20drug%2C%20except.

395. *See id.* at 3–4.

396. *See id.*; *see also* Owens, *supra* note 387; Otto *supra* note 387.

molecule therapeutics.[397] But, CAR-T cell therapies require substantially greater manufacturing and supply chain investment: companies must develop entirely new processes *and* create an individual treatment for every patient.[398] These differences from small-molecule therapeutics may require Congress to tailor orphan drug and other exclusivity regimes to more personalized therapeutics.

But, while CAR-T manufacturers routinely seek and receive orphan drug designation, the status does not prevent other CAR-T cell therapies from approval for the same indication. All FDA-approved CAR-T cell therapies currently have at least one orphan drug designation (Table 6).[399] Because the sameness requirement narrows this exclusivity regime, multiple CAR-T cell therapies received orphan drug designation for the same disease. For example, Kymriah and Yescarta both received orphan drug designation for "diffuse large B-cell lymphoma." Kymriah and Yescarta are likely not the "same," at least in part, because their CAR constructs (i.e., their "principal molecular structural features") differ (4-1BB-CD3ζ vs. CD28-CD3ζ).[400] Interestingly, even Abecma and Carvykti (both 4-1BB-CD3ζ CARs with receptors targeting BCMA) received orphan drug designation for the same disease (multiple myeloma). Either Abecma and Carvykti rely on different "principal molecular structural features" (e.g., the BCMA binding elements rely on different amino acid sequences) or one demonstrated clinical superiority to the other.[401] In either case, the Abecma and Carvykti examples demonstrate the narrowness of orphan drug exclusivity.

397. *See* Denise Myshko, *The Business of Biologics*, PHARMAVOICE (Sept. 1, 2018), https://www.pharmavoice.com/news/2018-09-biologics/612566/; *see also* Tam, *supra* note 321 at 557–58.

398. *See* June, *supra* note 164, at 614 (distinguishing CAR-T cell manufacturing from the traditional pharmaceutical company model: spending "half a billion dollars to make the first vial of a new drug, so long as the second vial can be produced for a few dollars"); *see also* Otto, *supra* note 387; Barfield & Calfee, *supra* note 328, at 15–18; Fraiser Kansteiner, *Bristol Myers, Hot Off Breyanzi Nod, Plots New Cell Therapy Factory in Massachusetts*, FIERCE PHARMA (Feb. 23, 2021), https://www.fiercepharma.com/manufacturing/bristol-myers-hot-off-breyanzi-nod-plots-new-cell-therapy-factory-massachusetts.

399. *Orphan Drug Designations and Approvals: Yescarta*, U.S. FOOD & DRUG ADMIN., https://www.accessdata.fda.gov/scripts/opdlisting/oopd/detailedIndex.cfm?cfgridkey=515615 (last visited Nov. 11, 2022).

400. *See Guidance for Industry - Interpreting Sameness of Gene Therapy Products Under the Orphan Drug Regulations*, U.S. FOOD & DRUG ADMIN. 3–4 (Sept. 2021), https://www.fda.gov/media/134731/download#:~:text=The%20orphan%20drug%20regulations%20define,a%20previously%20approved%20drug%2C%20except.

401. *See id.*

Table 6: All FDA-approved CAR-T cell therapies have at least one orphan drug designation, where * indicates the drug candidate received orphan drug status pending approval for the listed indication.[402]

Approved CAR-T Cell Therapy	Composition Claim Expiration[403]	Orphan Drug Exclusivity Ends	Orphan Designation
Kymriah	12/9/2031[404]	Aug. 30, 2024	Acute lymphoblastic leukemia
		May 27, 2029	Follicular lymphoma
		May 1, 2025	Diffuse large B-cell lymphoma
Yescarta	5/28/2023; 5/31/2031[405]	Oct. 18, 2024	Diffuse large B-cell lymphoma
		Oct. 18, 2024	Follicular lymphoma
		-	Extranodal marginal zone lymphoma*
		-	Nodal marginal zone lymphoma*
		Oct. 18, 2024	Primary mediastinal B-cell lymphoma
Tecartus	5/28/2023; 5/31/2031[406]	July 24, 2027	Mantle cell lymphoma
		Oct. 1, 2028	Acute lymphoblastic leukemia
Breyanzi	5/28/2023[407]	Feb. 5, 2028	Primary mediastinal large B-cell lymphoma
		Feb. 5, 2028	Follicular lymphoma
		Feb. 5, 2028	Diffuse large B-cell lymphoma
		-	Chronic lymphocytic leukemia*
		-	Mantle cell lymphoma*
Abecma	7/23/2035[408]	Mar. 26, 2028	Multiple myeloma
Carvykti	8/10/2036[409]	Feb. 28, 2029	Multiple myeloma

402. *See Search Orphan Drug Designations and Approvals*, U.S. FOOD & DRUG ADMIN., https://www.accessdata.fda.gov/scripts/opdlisting/oopd/.

403. The estimated expiration dates are 20 years after the earliest utility application filing date and reflect any patent term extension.

404. *See* U.S. Provisional Patent Application No. 61/421,470 (filed on Dec. 9, 2010) (converted to many applications, including U.S. Patent No. 9,499,629 (filed on Dec. 9, 2011)).

405. *See* '190 patent, *supra* note 77; '465 patent, *supra* note 319. The '465 patent approximate expiration date reflects patent term extension. *See Applications for patent term extension and patent terms extended under 35 U.S.C. § 156*, U.S. PAT. & TRADEMARK OFF., https://www.uspto.gov/patents/laws/patent-term-extension/patent-terms-extended-under-35-usc-156 (last visited Oct. 6, 2023).

406. *See* sources cited, *supra* note 405; Alissa Poh, *Treating MCL with CAR T Cells*, 10 CANCER DISCOVERY 9 (2020).

407. *See* Brachmann, *supra* note 175.

408. *See* PCT/US2015/041722.

409. *See* PCT/CN2016/094408; U.S. Patent No. 10,934,363 (filed Feb. 9, 2018).

V. CONCLUSION

Because cancer is a pervasive and diverse disease, cancer therapeutic development requires basic research, discovery, and innovation across multiple fields. CAR-T cell therapy required foundational research in immune system processes as well as practical advances in gene sequencing, genetic engineering, cell culture methods, and antibody production methods. Government and charitable foundation grants largely funded the riskiest early-stage innovation. Patents, trade secret protections, and regulatory exclusivity incentivized companies and private investors to fund research when small-scale CAR-T clinical studies showed promising results. Relative to other pharmaceutical products, patents provide less incentive for CAR-T cell manufacturers due to early composition claim expiration dates, disclosure requirement uncertainty, and fragmented patent ownership. As a result, trade secret and regulatory exclusivity appear to be more important incentives for pharmaceutical companies.

CAR-T cell therapies are already transforming cancer treatment. U.S. policy makers should learn from the CAR-T cell therapy innovation drivers to ensure the next-generation of life-changing treatments reach patients.

THE INVENTION OF NEXT-GENERATION SEQUENCING

Caressa N. Tsai†

TABLE OF CONTENTS

DOI: https://doi.org/10.15779/Z38V40K11S

† Ph.D., McMaster University, Department of Biochemistry and Biomedical Sciences, 2021; J.D. Candidate, University of California, Berkeley, School of Law, Class of 2024. I am grateful to Peter Menell and Allison Schmitt for their guidance in preparing this Article. Special thanks to Christine O'Brien Laramy, Hunter Kolon, Will Kasper, Duane Yoo, and the participants of the 2022–23 Life Sciences & Innovation Workshop, for feedback, editorial assistance, and many helpful discussions.

I. INTRODUCTION

In the 1950s, the discovery of the structure of DNA[1] and the theory behind its function as the fundamental blueprint of life[2] launched modern

1. James D. Watson & Francis H. C. Crick, *Molecular Structure of Nucleic Acids*, 171 NATURE 737 (1953) (describing, as one leading example from the 1950s, the double helix structure of DNA); *see also* Rosalind E. Franklin & Raymond G. Gosling, *Molecular Configuration in Sodium Thymonucleate*, 171 NATURE 740 (1953).

2. Francis H. C. Crick, *On Protein Synthesis*, 12 SYMPS. SOC'Y FOR EXPERIMENTAL BIOLOGY 138 (1958) (suggesting that genetic information flows through biological systems

molecular biology. Scientists recognized that DNA is: (1) the genetic code of all living organisms; and (2) composed of two twisted strands of base-paired nucleotides.[3] As soon as the molecular biology community recognized the importance of DNA and its composition, the race to develop DNA sequencing technologies—methods to determine the order of the nucleotides in a strand of DNA—commenced.[4] Today, DNA sequencing is among the most important techniques driving life sciences research, with DNA aptly perceived as the key to unlocking new diagnostic and therapeutic strategies.[5]

Scientists began developing "first-generation" methods of DNA sequencing in the 1970s. This early research led to the invention of Sanger sequencing, which enabled the Human Genome Project (HGP). By the completion of the Project in 2003, the pursuit of "next-generation" DNA sequencing—comprising methods that were faster and cheaper than their first-generation counterparts—had begun in earnest. And in 2006, a Cambridge-based company called Solexa launched one of the first next-generation sequencing (NGS) machines. The next year, Solexa was acquired by Illumina, a company that would go on to dominate the NGS market.

The advent of NGS launched an "omics" era of modern medicine. Omics broadly encompasses all approaches aimed at comprehensively interrogating the "building blocks"[6] of life, primarily: DNA (genomics), RNA (transcriptomics), and protein (proteomics). The omics revolution, fueled by NGS, shifted scientific inquiry from reductionist to holistic strategies.[7] With

---

only in certain directions, two of which being from DNA to RNA, and from RNA to protein, but other directions being possible as well); *see also* Matthew Cobb, *60 Years Ago, Francis Crick Changed the Logic of Biology*, 15 PLOS BIOLOGY e2003243 (2017).

3. *A Brief Guide to Genomics*, NAT'L HUM. GENOME RSCH. INST., https://www.genome.gov/about-genomics/fact-sheets/A-Brief-Guide-to-Genomics (last visited Nov. 24, 2022).

4. *See Frederick Sanger Interview,* NOBEL PRIZE (Dec. 9, 2001), https://www.nobelprize.org/prizes/chemistry/1958/sanger/interview/.

5. Marcos Morey et al., *A Glimpse Into Past, Present, and Future DNA Sequencing*, 110 MOLECULAR GENETICS & METABOLISM 3, 3–4 (2013) (noting that "genetic diagnostics, biotechnology, microbiological studies, forensic biology, and systematic[] . . . taxonomy" have all benefited from NGS development).

6. Relevant to this concept is the central dogma, which explains the flow of genetic information from DNA, to RNA, to protein (or RNA to protein). *See generally* James A. Shapiro, *Revisiting the Central Dogma in the 21st Century*, 1178 ANNALS N.Y. ACAD. SCIS. 6 (2009).

7. *See* Rebecca K. Delker & Richard S. Mann, *From Reductionism to Holism: Toward a More Complete View of Development Through Genome Engineering*, *in* PRECISION MEDICINE, CRISPR, AND GENOME ENGINEERING: MOVING FROM ASSOCIATION TO BIOLOGY AND THERAPETUICS 45, 46–47 (Stephen H. Tsang ed., 2017); *Beyond Conventional Cell and Molecular Biology Research Methods*, ILLUMINA, https://www.illumina.com/areas-of-interest/cellular-molecular-biology-research.html (last visited Sept. 24, 2022) (explaining that traditional methods in molecular biology "seek[] to understand the function of a single gene, gene family, or signal transduction

NGS, scientists could produce "big" data quickly and inexpensively, which ushered in new perspectives in biology. Researchers recognized that biological systems were not discrete units, but complex, networked landscapes, and that phenotypes often resulted from not just individual genes, but full genomic profiles.[8] NGS allowed the scientific and medical communities to approach disease treatment at a previously unfathomable resolution.

This Article explores the development of NGS for DNA studies (genomics) with a focus on the Illumina sequencing platform as the leading technology in this space, and the motivational factors critical for Illumina's success. The discovery story that led to Illumina's ongoing dominance in the NGS market spans multiple countries, companies, universities, and scientists. Over several years, a mixture of factors contributed to the remarkable innovation that resulted in the Illumina NGS platform, clustering into two separate stages. First, scientific curiosity, altruism, public funding sources, academic recognition, and serendipity motivated foundational research. Then, as the Solexa team expanded their idea into a dominating NGS platform, the landscape of "innovation drivers" shifted to private funding sources, patent protection, well-timed licensing, dedication to commercialization potential, and aggressive litigation.

Part II summarizes the foundational "first-generation" technology that inspired NGS development, the technical details of the modern-day Illumina NGS platform, and the modern life sciences applications of NGS. Part III traces the history and development of the NGS platform in five phases, from the use of Sanger sequencing in the HGP to the early 2000s competition between Solexa and other startup companies in bringing the first NGS machine to market. Part IV analyzes the interplay of several innovation drivers that contributed to the Illumina NGS discovery story in two distinct stages. Finally, Part V discusses the state of modern DNA sequencing technologies.

II. TECHNICAL BACKGROUND

The Illumina NGS platform is a complex system, with technical features that can be traced back to innovations in molecular biology research from the

family" while NGS technologies "broaden cell and molecular biology research . . . [and] enable[] analysis across the genome, transcriptome, and epigenome").

8. *See* Delker & Mann, *supra* note 7, at 49; Jeffrey Gagan & Eliezer M. Van Allen, *Next-Generation Sequencing to Guide Cancer Therapy*, 7 GENOME MED. 1, 1 (2015) (explaining the shift in cancer research from reductionist thinking (that all types of cancers developed from individual genetic mutations, minimizing the number of relevant biological actors) to systems-wide thinking (that only some cancers are caused by single mutations, but most are genetically complex and involve dysregulation of multiple *pathways* rather than genes)).

1970s. This Part first describes the foundational processes of *in vivo* DNA replication, polymerase chain reaction (PCR), and Sanger sequencing, and then turns to the technical details of the Illumina NGS platform and the modern-day applications of NGS.

A. FOUNDATIONAL TECHNOLOGY

NGS technologies rely on two foundational inventions: PCR and Sanger sequencing. PCR, Sanger sequencing, and NGS technologies—while remarkably innovative—are also *in vitro*, synthetic mimics of *in vivo* DNA replication, which occurs naturally in all organisms. This Section explains *in vivo* DNA replication, PCR, and Sanger sequencing and highlights shared components between all three processes and NGS (**Table 1**).

Table 1: Key technical components of foundational and modern DNA sequencing technologies.

<table>
<tr><th></th><th>In vivo DNA Replication</th><th>Polymerase Chain Reaction</th><th>Sanger Sequencing</th><th>Next-Generation Sequencing</th></tr>
<tr><td>Template</td><td colspan="4">Single-stranded DNA</td></tr>
<tr><td>Nucleotides</td><td colspan="2">Unmodified nucleotides</td><td>Unmodified nucleotides and labeled dideoxynucleotides</td><td>Reversible terminator nucleotides</td></tr>
<tr><td>Primers</td><td>Primase enzyme</td><td>Forward and reverse primers</td><td colspan="2">Sequencing primer</td></tr>
<tr><td>Enzyme</td><td colspan="4">Polymerase</td></tr>
<tr><td>Kinetics</td><td>Polymerase enzyme adds unmodified nucleotides to produce a complementary strand of the template DNA</td><td>Polymerase enzyme adds unmodified nucleotides to produce millions of copies of the template DNA</td><td>Polymerase enzyme adds unmodified nucleotides to produce a complementary strand of the template DNA; sometimes will add a labeled dideoxynucleotide instead and induce chain termination</td><td>Polymerase enzyme adds reversible terminator nucleotides to produce a complementary strand of the template DNA</td></tr>
</table>

1. In vivo *DNA Replication*

In living organisms, DNA exists as a double-stranded helix, with two complementary strands comprised of four types of nucleotides (adenosine (A), thymidine (T), cytidine (C), guanosine (G)) paired together.[9] These strands are also referred to as chains, and are intertwined due to base-pair complementarity between the purine-based (A, G) and pyrimidine-based (T, C) nucleotides.[10] For replication, a protein separates DNA into two single strands, so that each one can serve as a template for a complementary strand.[11] Cellular machinery builds a complementary strand based on base pairing between nucleotides.[12] The entire set of DNA within an organism is called its genome and is organized into chromosomes.[13]

There are four main components required for *in vivo* DNA replication, all of which have analogs in PCR, Sanger sequencing, and NGS: (1) a single-stranded template DNA strand; (2) nucleotides (free A, T, C, G to be added); (3) a primase enzyme (to establish a double-stranded foundation from replication to proceed from); and (4) a polymerase enzyme (to catalyze the addition of each nucleotide to the growing complementary strand).[14] Briefly, the polymerase enzyme attaches to the primase-defined region and physically moves along the template DNA strand, sequentially adding nucleotides to a new strand based on complementarity to bases in the template (**Figure 1A**).[15] The end product is a freshly synthesized, complementary chain of DNA.[16] This replication process starts at many randomly distributed points throughout genomes[17] and ends at similarly distributed points.[18] Therefore, the length of

9. BRUCE ALBERTS ET AL., MOLECULAR BIOLOGY OF THE CELL (2002).

10. *Id.*

11. *Id.*

12. *Id.*

13. *A Brief Guide to Genomics*, *supra* note 3.

14. This is a simplified explanation that omits some of the molecular players in this process. A more comprehensive summary of DNA replication is described elsewhere. *Id.*

15. *Id.*

16. *Id.* Polymerase enzymes specifically catalyze the formation of phosphodiester bonds between nucleotides, linking them together in growing DNA chains. The bond forms between the 3' end (hydroxyl) of one nucleotide and the 5' end (phosphate) of the next nucleotide. *Sanger Sequencing Steps & Method*, SIGMA ALDRICH, https://www.sigmaaldrich.com/US/en/technical-documents/protocol/genomics/sequencing/sanger-sequencing (last visited Sept. 27, 2022) [hereinafter Sigma on Sanger].

17. Michalis Fragkos et al., *DNA Replication Origin Activation in Space and Time*, 16 NATURE REVS. MOLECULAR CELL BIOLOGY 360 (2015).

18. James M. Dewar & Johannes C. Walter, *Mechanisms of DNA Replication Termination*, 18 NATURE REVS. MOLECULAR CELL BIOLOGY 507 (2017).

template DNA to be complemented in each round of replication is indeterminate, but is certainly smaller than the length of the entire genome.[19]

2. Polymerase Chain Reaction

PCR is an *in vitro*, experimental analog of *in vivo* DNA replication.[20] The reagents required for PCR are similar to those for *in vivo* DNA replication: (1) a single-stranded template DNA strand (to be amplified); (2) nucleotides (free A, T, C, G to be added); (3) forward and reverse primers (to establish double-stranded foundations from which amplification can begin); and (4) a polymerase enzyme (to catalyze the addition of each nucleotide to the growing strand copy). The steps of PCR are also essentially the same as those of *in vivo* DNA replication: the polymerase enzyme attaches to the primer-defined regions and physically moves along the template DNA strand, sequentially adding nucleotides to a new strand based on complementarity to bases in the template (**Figure 1B**).[21] However, this PCR process repeats iteratively across several cycles, amplifying the template strand millions of times.[22] External temperature triggers mirror the physiological conditions that help *in vivo* DNA replication proceed.[23] Most importantly, high temperature cycles induce repeated denaturing of double-stranded DNA (the complementary DNA strands that are synthesized are, at first, bound to the original template strand) into the single-stranded form required for the cycle to repeat.

A key difference between PCR and *in vivo* DNA replication is the *target region* of DNA to be amplified (i.e., the boundaries of the template strand). As described in Section II.A.1 *supra*, *in vivo* DNA replication occurs at multiple points throughout an organism's genome.[24] For PCR, researchers may extract the entire composite of genomic DNA from a target organism to use as a template, but focus on a specific target region to be amplified based on the selection of primer sequences (replacing the primase enzyme of *in vivo* DNA replication). These forward and reverse primers face inwards towards each other and define the boundaries of the target template strand to be synthesized.

---

19. *See id.*

20. For a graphic illustration of the PCR process, see *infra* Figure 1B.

21. Elizabeth Pelt-Verkuil et al., *A Brief Comparison Between In Vivo DNA Replication and In Vitro PCR Amplification*, *in* PRINCIPLES AND TECH. ASPECTS OF PCR AMPLIFICATION 9, 12 (2008).

22. *Id.*

23. *In vivo* DNA replication requires the concerted activity of many different proteins and physiological conditions, to maintain growing DNA chains in appropriate configurations throughout the process. The temperature changes used in PCR essentially mirror these activities and corresponding configurations of DNA, in a more simplistic way. *See id.*

24. Fragkos et al., *supra* note 17.

Generally, primers sit approximately 1,000 bases apart.[25] PCR can produce millions of copies of DNA sequences by changing the kinetics of naturally occurring *in vivo* DNA replication into an exponential amplification process.

3. Sanger Sequencing

Like PCR, Sanger sequencing is another mimic of *in vivo* DNA replication. But, instead of exponentially amplifying DNA, Sanger sequencing determines the order of nucleotides in a DNA strand. The reagents required for Sanger sequencing are similar to those of PCR: (1) a single-stranded template DNA strand (to be sequenced); (2) nucleotides (free A, T, C, G to be added); (3) a sequencing primer (to establish a double-stranded foundation for sequencing to begin from); and (4) a polymerase enzyme (to catalyze the addition of each nucleotide to the growing complementary strand). Critically, Sanger sequencing reactions also include a fifth reagent: labeled dideoxynucleotides. There are two differences between labeled dideoxynucleotides and standard nucleotides, which, together, enable DNA sequencing.[26] Labeled dideoxynucleotides are: (1) modified to omit the 3'-OH group in the deoxyribose sugar group of their structure (hence the *dideoxy* prefix); and (2) tagged with a fluorescent dye, with each of A, T, C, and G having a different dye color (hence the *labeled* preface).

Sanger sequencing typically begins with PCR; having multiple copies of the template strand to be sequenced boosts efficiency.[27] Researchers extract the entire composite of genomic DNA from a target organism to use as a template, but then define the exact boundaries of a small template region using primer sequences. Once amplification of this template region occurs, Sanger sequencing begins on all PCR-amplified copies of this template at once. Again, the kinetics of Sanger sequencing reactions are the same as for *in vivo* DNA replication and PCR: the polymerase enzyme attaches to and physically moves along template DNA strands, sequentially adding nucleotides to a new strand based on complementarity to bases in the template strands, producing freshly synthesized, complementary DNA chains that mirror the templates.[28]

However, during Sanger sequencing, the polymerase enzyme occasionally adds a labeled dideoxynucleotide to a growing complementary DNA chain, instead of a standard, unmodified nucleotide. This happens randomly among all the growing DNA strands in the sequencing reaction—some strands start

25. *See* Pelt-Verkuil et al., *supra* note 21, at 11. At template lengths longer than 1,000 base pairs, fidelity and efficiency of the PCR process begin to decline.

26. For a graphic illustration of different nucleotide structures, see *infra* Figure 2.

27. Sigma on Sanger, *supra* note 16.

28. *Id.*

with a labeled dideoxynucleotide at the first possible position, some strands include one following many standard nucleotides, and some strands complete elongation entirely without ever adding one. Each time the polymerase adds a labeled dideoxynucleotide, the elongation of the growing DNA chain terminates at the position of incorporation. Chain termination occurs because the labeled dideoxynucleotides lack the 3'-OH required for addition of the next nucleotide in the DNA chain.[29] The labeled dideoxynucleotides also "color code" the terminated DNA chains with a unique fluorescent dye corresponding to the terminating nucleotide (**Figure 1C**). This process, importantly, is irreversible—the DNA chain cannot resume elongation once a labeled dideoxynucleotide has been added. Sanger sequencing is sometimes aptly called "chain-termination" sequencing.[30]

Therefore, like PCR, Sanger sequencing generates many copies of DNA, originating from a template strand that is typically no more than 1,000 base pairs in length.[31] However, all DNA copies generated by PCR are of the same length, mirroring the entire template sequence initially selected for amplification. Sanger-generated DNA copies are non-uniform in length because of the random processes of labeled dideoxynucleotide addition and subsequent chain termination. That is, after the sequencing reaction, the resulting product will include every possible length of DNA fragment, up to the full template length.[32] These fragments are referred to as oligonucleotides.

The different chain-terminated oligonucleotide lengths allow researchers to deduce the order of nucleotides in a template DNA strand. First, researchers will use gel electrophoresis to physically separate the chain-terminated oligonucleotides and arrange DNA fragments based on size. This process essentially lines up each chain-terminated oligonucleotide in order of decreasing size, from top to bottom on a gel.[33] Then, laser excitation of the fluorescent tags on each dideoxynucleotide enables researchers to visualize the physical distribution of the DNA fragments. Each DNA fragment shows up as a color-coded "band" on the gel, depending on the type of labeled dideoxynucleotide added to the final position on each fragment. Researchers can "read" these color-coded bands from smallest to largest, indicating the exact sequence of nucleotides from the first to last position of the template

29. The 3'-OH group participates in phosphodiester bond formation in typical strand elongation. *Id.*

30. *Id.*

31. *Id.* More typically, template fragments are 300–500 base pairs long.

32. To illustrate with an oversimplified example: a template strand that is 100 base pairs long will generate fragments of 100 different lengths: 1 base pair long, 2 base pairs long, 3 base pairs long, up until 100 base pairs long.

33. Sigma on Sanger, *supra* note 16.

DNA strand. This is a time-intensive process, as preparing gels for electrophoresis and running out DNA fragments is quite laborious.

The steps described in this Section illustrate the sequencing of just *one* template region of DNA, which practically cannot exceed approximately 1,000 bases.[34] To determine the entire genome sequence of an organism, Sanger sequencing must be repeated in 1,000 base pair increments. The haploid human genome is 3.055 billion base pairs long[35]—making Sanger sequencing prohibitively low-throughput for many modern applications.[36] However, Sanger sequencing remains the "gold-standard" for molecular biologists to sequence short regions of DNA (i.e., individual genes rather than entire genomes), with unmatched accuracy and fidelity compared to other techniques, including NGS.[37]

Despite its bottlenecked throughput, researchers used Sanger sequencing to sequence entire genomes before alternative approaches were developed.[38] In doing so, given the 1,000 base pair limitation of Sanger sequencing, researchers would have to process an entire genome into multiple 1,000 base pair regions, and then computationally stick them back together (formally termed "assembly") using a "shotgun" approach.[39] Some scientists initially preferred the idea of implementing a highly ordered process; that is, for a

34. The threshold of 1,000 base pairs is generally considered to be the maximum length of a template for Sanger sequencing. Beyond this, quality and accuracy plummet, as the size separation gel electrophoresis step of Sanger becomes unable to separate DNA fragments at an appropriate resolution. Henrik Stranneheim & Joakim Lundeberg, *Stepping Stones in DNA Sequencing*, 7 BIOTECHNOLOGY J. 1063 (2012).

35. Sergey Nurk et al., *The Complete Sequence of a Human Genome*, 376 SCI. 44 (2022).

36. One study estimated the reagents needed for Sanger sequencing to cost ~$500/Mb, and for NGS to cost $0.50/Mb. PHG FOUND., NEXT STEPS IN THE SEQUENCE: THE IMPLICATIONS OF WHOLE GENOME SEQUENCING FOR HEALTH IN THE UK 31 (2011), https://www.phgfoundation.org/media/140/download/Next%20steps%20in%20the%20sequence.pdf?v=1&inline=1.

37. *What is Next-Generation Sequencing (NGS)?*, THERMOFISHER SCI., https://www.thermofisher.com/us/en/home/life-science/sequencing/sequencing-learning-center/next-generation-sequencing-information/ngs-basics/what-is-next-generation-sequencing.html (noting that NGS results are often verified using Sanger sequencing); *see also* Gagan & Van Allen, *supra* note 8, at 2 (addressing the loss in coverage (the depth of sequencing) and accuracy that occurs when the genic length to be sequenced is increased); *Key Differences Between Next-Generation Sequencing and Sanger Sequencing*, ILLUMINA, https://www.illumina.com/science/technology/next-generation-sequencing/ngs-vs-sanger-sequencing.html (last visited Oct. 2, 2022) (advertising that while NGS is more cost-effective for high numbers of gene targets, Sanger sequence is more cost-effective for low (e.g., 1-20) numbers of gene targets) [hereinafter Illumina on NGS vs Sanger].

38. *See* discussion *infra* Part III.

39. *See* Robert H. Waterston et al., *On the Sequencing of the Human Genome*, 99 PROCS. NAT'L ACAD. SCIS. 3712, 3712 (2002).

10,000 base pair genome, the first 1,000 base pair fragment might be from base 1 to base 1,000, the next fragment from base 500 to 1,500 (to maintain some overlap in case of inaccuracies at the tail ends), and so on. But such an ordered process required the assembler to have some form of mental "map" of the entire genome before beginning the process. The subsequent development of "shotgun" Sanger sequencing overcame this "map" requirement. With shotgun sequencing, researchers randomly break up ("shear") the genomic DNA into small fragments, sequence the fragments without a precise idea of their order, and then computationally assemble a genome sequence by comparing the base pairs that overlap between the fragments.[40] The sequencing products of the fragments are called *reads*; the reads after they have been assembled in the correct order are called *contigs*.[41]

40. Many were involved in the formulation of the shotgun strategy in the context of Sanger sequencing. A description of the shotgun approach closely followed the first articulation of Sanger sequencing in 1977. It seems that Rodger Staden was the first to suggest a shotgun strategy, in 1979. Rodger Staden, *A Strategy of DNA Sequencing Employing Computer Programs*, 6 NUCLEIC ACIDS RSCH. 2601 (1979). Then, Frederick Sanger published another report elaborating on the concept in 1980. Frederick Sanger et al., *Cloning in Single-Stranded Bacteriophage as an Aid to Rapid DNA Sequencing*, 143 J. MOLECULAR BIOLOGY 161 (1980). Joachim Messing followed similarly in 1981. Joachim Messing et al., *A System for Shotgun DNA Sequencing*, 9 NUCLEIC ACIDS RSCH. 309 (1981). Then, finally, Sanger applied the approach to a real genome sequence in 1982. Frederick Sanger et al., *Nucleotide Sequence of Bacteriophage λ DNA*, 162 J. MOLECULAR BIOLOGY 729 (1982).

41. Waterston et al., *supra* note 39, at 3712.

Figure 1: Foundational technology for DNA sequencing.

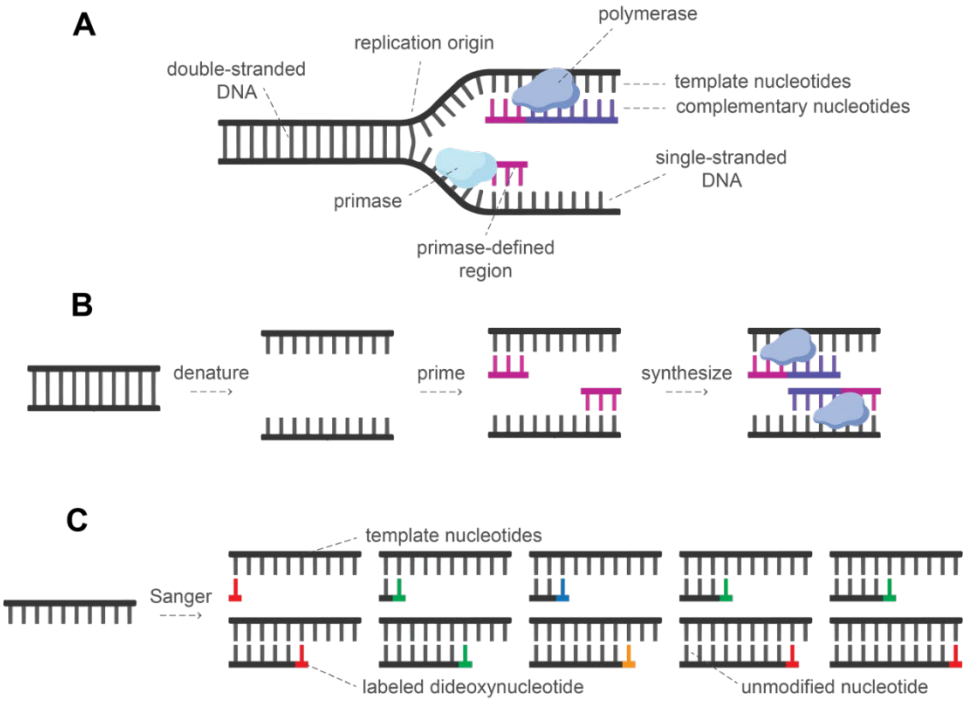


Figure 1 provides illustrations of the three foundational genetic replication processes described in Section II.A. **(A)** *In vivo* DNA replication requires the enzymatic activity of both polymerase (dark blue) and primase (light blue) enzymes (among others). After separation of double-stranded DNA into single-stranded DNA available for polymerase-mediated synthesis activity, primase enzymes introduce small defined regions from which replication can begin. Polymerase enzymes add complementary nucleotides to template single-stranded regions of DNA. **(B)** PCR mirrors the kinetic steps of in vivo DNA replication, beginning with initial denaturation of double-stranded DNA into single-stranded regions, priming with artificial oligonucleotides, and then using synthetic polymerase enzymes (dark blue) to grow a complementary DNA strand. **(C)** Sanger sequencing introduces unmodified nucleotides in iterative rounds of limited pseudo-replication, but occasionally adds labeled dideoxynucleotides for strand identification (red, green, blue, orange).

B. MODERN NGS TECHNOLOGY

Beginning in the early 2000s, the scientific community shifted away from Sanger sequencing toward NGS technologies.[42] NGS is a broad term that encompasses "massively parallel," high-throughput sequencing methods.[43] It is easiest to define NGS in reference to the previous "first generation" approach: Sanger sequencing examines individual template DNA strands in sequencing reactions that occur in separate environments; NGS examines millions of template DNA strands in parallel sequencing reactions, all in the same environment. With NGS, scientists can sequence the entire human genome in one day, for approximately $1,000.[44] Generally, in the context of DNA sequencing, researchers use NGS to sequence whole genomes, or large target regions within a genome, rather than individual genes.[45]

All NGS platforms apply the same basic approach, consisting of four steps.[46]

1. **Library preparation.** As in shotgun Sanger sequencing, researchers extract genomic DNA from a target organism, then randomly shear it into smaller fragments to use as template strands.
2. **Amplification.** Again, as in Sanger sequencing, PCR makes several copies of each fragmented template strand, to boost efficiency and generate a sufficient amount of substrate material.
3. **Read generation.** NGS platforms vary the most amongst each other and from Sanger sequencing in this step. Instead of the chain-terminating, dideoxynucleotide-based method of Sanger sequencing, some higher-throughput version of read generation occurs at this stage.[47]
4. **Data analysis.** Depending on the read generation method used in the third step, base calling and contig assembly proceed using various computational approaches. Briefly, researchers reassemble the entire

42. Michael L. Metzker, *Sequencing Technologies—The Next Generation*, 11 NATURE REVS. GENETICS 31, 31 (2010).

43. Dale Muzzey et al., *Understanding the Basics of NGS: From Mechanism to Variant Calling*, 3 CURRENT GENETIC MED. REPS. 158, 159 (2015) (defining NGS as "a diverse collection of post-Sanger sequencing technologies").

44. *Id.* at 158–59.

45. Illumina on NGS vs Sanger, *supra* note 37.

46. *See* Keegan Schroeder, *A History of Sequencing*, FRONTLINE GENOMICS (Apr. 19, 2022), https://frontlinegenomics.com/a-history-of-sequencing/.

47. For a description of other non-Illumina NGS platforms and the read generation techniques used at this stage, see discussion *infra* Part V.

genome sequence from the short shotgun-fragmented strands of DNA.[48]

Although there are countless NGS platforms and read generation approaches, Illumina sequencing technology—the focus of this Article—dominates the NGS market. In late 2019, the Federal Trade Commission (FTC) characterized Illumina as allegedly generating more than 90% of the world's sequencing data.[49] The characteristic, "massively parallel" aspect of Illumina sequencing arises from three unique elements of Illumina, described in the next Section.

1. Three Illumina Elements

The three unique elements of Illumina are integrated into steps two (amplification) and three (read generation) of the sequencing pipeline: (1) the use of a solid support (step two); (2) the bridge PCR amplification of DNA fragments to generate clusters (step two); and (3) the technique of sequencing-by-synthesis (step three). This Section describes each element.

a) Solid Support Array

The first "massively parallel" element of Illumina technology is a solid support to physically attach template DNA strands prior to PCR amplification, in contrast to the aqueous suspension of DNA fragments in Sanger sequencing.[50] Illumina uses a solid support called a flow cell, which is coated with a lawn of two types of oligonucleotides (short DNA strands) physically anchored to the flow cell surface.[51] After breaking the genomic DNA of the target organism into smaller fragments in step one (library preparation), researchers attach two types of adapters to the ends of each single-stranded fragment through a process called ligation.[52] All the fragments have the same type of adapter at their "start" (called the 5' end) and a different type of adapter at their "end" (called the 3' end).[53] Both the 5' adapter and the 3' adapter are complementary to the two types of oligonucleotides anchored to the flow cell surface, such that the entire library of template DNA strands bind to the

48. *A Brief Guide to Genomics*, *supra* note 3.

49. Complaint ¶¶ 1, 34, 35, Illumina, Inc. & Pacific Biosciences California, Inc. v. F.T.C., No. 9387 (Dec. 17, 2019).

50. *See* Muzzey et al., *supra* note 43, at 159.

51. *More Data, Reduced Costs, and Faster Runs*, ILLUMINA, https://www.illumina.com/science/technology/next-generation-sequencing/sequencing-technology/patterned-flow-cells.html (last visited Nov. 24, 2022).

52. *Uniformity, Precision and Reliability in Library Preparation*, ILLUMINA, https://www.illumina.com/techniques/sequencing/ngs-library-prep/ligation.html (last visited Nov. 24, 2022).

53. *Id.*

oligonucleotides, at either their 5' or 3' ends.[54] This process physically anchors all the template strands to the flow cell in a random array.[55] While Sanger sequencing maintains DNA fragments in suspension and carries out *size separation* after the sequencing reactions are completed, Illumina sequencing uses the solid support to establish *positional separation* between DNA fragments before the sequencing reactions begin.

b) Bridge PCR Clustering

The second "massively parallel" element of Illumina technology is bridge PCR clustering to amplify template DNA strands, instead of the standard PCR step conducted prior to Sanger sequencing. This bridge PCR process requires that DNA be fixed to a solid support, as in the Illumina platform. In routine PCR, as described in Section II.A.2 *supra*, polymerase enzymes repeatedly synthesize complementary strands of DNA from template strands, producing double-stranded DNA fragments that are repeatedly denatured for iterative rounds of amplification. This process occurs stochastically in liquid suspension. For the PCR that occurs during Illumina sequencing, some fraction of template strands must always remain physically anchored to the flow cell throughout the amplification process, complicating the requirement for repeated denaturation and iterative amplification.

The Illumina platform solves this anchored denaturing problem with 5' and 3' adapter sequences and complementary oligonucleotides on the flow cell. After each template strand attaches to the flow cell at one end, the strands fold over and form a bridge with the oligonucleotide complementary to the adapter sequence at the other end.[56] That is, a template strand bound to the flow cell at its 5' end folds over and binds to a different oligonucleotide, complementary to its 3' end.[57] After this, the kinetics of bridge PCR follows routine PCR, with similar reagents: (1) a single-stranded template DNA strand, in bridge format (to be amplified); (2) nucleotides (free A, T, C, G to be added); and (3) a polymerase enzyme (to catalyze the addition of each nucleotide to the growing strand copy).[58] A polymerase enzyme attaches to the adapter-oligonucleotide

54. *Id.*

55. ILLUMINA, AN INTRODUCTION TO NEXT-GENERATION SEQUENCING FOR CARDIOLOGY 4 (2015) [hereinafter ILLUMINA GUIDE].

56. *Id.* at 3, 7 (2015).

57. James M. Heather & Benjamin Chain, *The Sequence of Sequencers: The History of Sequencing DNA*, 107 GENOMICS 1, 3 (2016).

58. Unlike routine PCR, forward and reverse primers are not needed for bridge PCR clustering, as the binding of the template DNA strand adapters to the flow cell-anchored oligonucleotides creates the double-stranded foundations that polymerase enzymes require for attachment.

paired region and physically moves along the template DNA strand bridge, sequentially adding nucleotides to a new strand based on complementarity to bases in the template. The resulting product is a double-stranded bridge, rather than the linearized double-stranded DNA chain of routine PCR. The bridge then denatures in response to the same temperature trigger as in routine PCR, so the original template strand and the newly synthesized complementary strand release from the flow cell at one end and remain anchored physically to the flow cell at only the 5' or 3' end.[59]

The bridging, amplification, and denaturation process repeats itself iteratively, for every unique template strand fragment distributed randomly throughout the flow cell. Importantly, Illumina sequencing platforms have a maximum read length of 300 base pairs, with 150 base pair reads as the most common length.[60] This short length—even shorter than the read length used in Sanger sequencing—means that each template strand folds over and forms a bridge more frequently with complementary oligonucleotides that are physically proximal to the original oligonucleotide anchor. Thus, bridge PCR produces a characteristic *clustering* effect, as the bridges continue to form in the same, localized area, outwards from each template strand fragment.[61] In other words, the resulting DNA lawn preserves the positioning of the initial fragments of unique template DNA strands, with entire clusters of template DNA strands positionally separated.

c) Sequencing-by-Synthesis (SBS) Read Generation

The third "massively parallel" element of Illumina technology is SBS, which replaces the chain termination aspect of Sanger sequencing. Among the three critical elements outlined in this Section, Illumina's unique approach to SBS is the most essential component of its platform.[62] As in Sanger sequencing reactions, SBS reactions also use: (1) a single-stranded template DNA strand; (2) a sequencing primer; and (3) a polymerase enzyme. However, rather than standard, unmodified nucleotides or labeled dideoxynucleotides, SBS reactions

59. *See* ILLUMINA GUIDE, *supra* note 55, at 4.

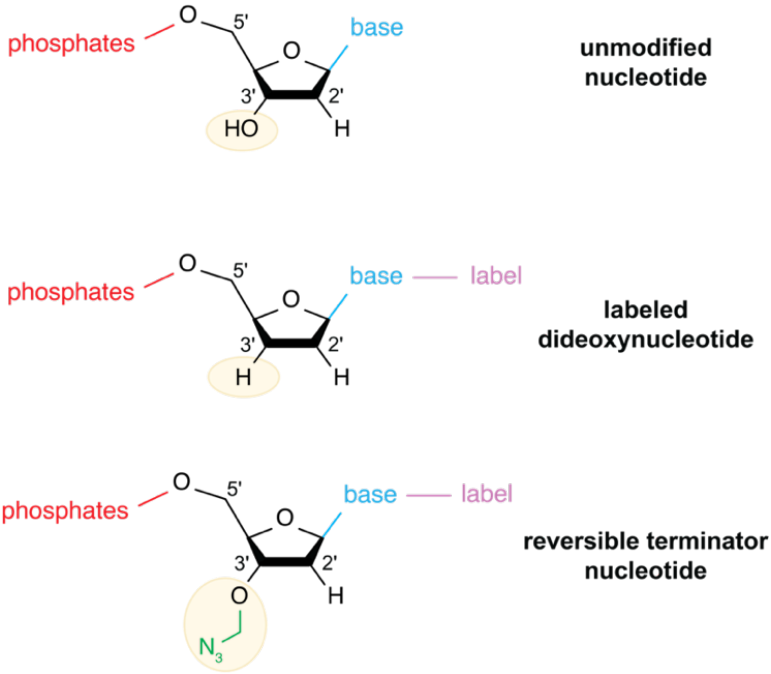
60. *Maximum Read Length for Illumina Sequencing Platforms*, ILLUMINA, https://support.illumina.com/bulletins/2020/04/maximum-read-length-for-illumina-sequencing-platforms.html (last visited Oct. 2, 2022). Illumina sequencing is limited to relatively short read lengths to preserve accuracy—at lengths longer than 300 base pairs, fidelity of the sequencing process declines. *Id.*

61. *See* ILLUMINA GUIDE, *supra* note 55, at 3–4.

62. *See* Jason A. Reuter et al., *High-Throughput Sequencing Technologies*, 58 MOLECULAR CELL 586, 586 (2015) (summarizing developments in NGS technologies).

use only a single nucleotide type: reversible terminator nucleotides (**Figure 2**).[63]

Figure 2: SBS chemistry in the Illumina NGS platform.



There are two critical differences between reversible terminator nucleotides and standard nucleotides. Reversible terminator nucleotides: (1) have a 3'-*O*-blocking group instead of the 3'-OH group in the deoxyribose sugar group; and (2) are tagged with a cleavable fluorescent dye, with each of A, T, C, and G having a different dye color.[64] These nucleotides may seem similar to the labeled dideoxynucleotides of Sanger—but they have unique chemistry. While labeled dideoxynucleotides completely lack the 3'-OH group in the deoxyribose sugar, reversible terminator nucleotides simply have a blocking group added to the 3'-OH.[65] Uniquely, this blocking group can be chemically cleaved off. And while both labeled dideoxynucleotides and reversible terminator nucleotides are tagged with a fluorescent dye, the tag on reversible terminator nucleotides—just like the blocking group—can be

63. ILLUMINA GUIDE, *supra* note 55, at 3.

64. David R. Bentley et al., *Accurate Whole Human Genome Sequencing Using Reversible Terminator Chemistry*, 456 NATURE 53, 53 (2008) (sequencing a human genome).

65. *Id.*

chemically cleaved off.[66] Critically, the addition of a *single* chemical reagent can simultaneously cleave both the 3'-*O*-blocking group and the fluorescent tag.[67]

The SBS process includes several steps in common with *in vivo* DNA replication, PCR, and Sanger sequencing: the polymerase enzyme attaches to and physically moves along template DNA strands, sequentially adding nucleotides to a new strand based on complementarity to bases in the templates and producing freshly synthesized chains of DNA complementary to the templates. The difference in SBS, compared to Sanger sequencing, is that *only* reversible terminator nucleotides are incorporated into growing complementary DNA chains, not standard nucleotides or labeled dideoxynucleotides. And instead of the *irreversible* chain termination that stochastically occurs with the addition of a labeled dideoxynucleotide to growing DNA strands in Sanger sequencing, the addition of a reversible terminator nucleotide results in *reversible* chain termination of growing DNA strands in SBS. In Sanger sequencing, labeled dideoxynucleotides irreversibly terminate chain elongation because they lack the 3'-OH group of standard nucleotides. On the other hand, in SBS, reversible terminator nucleotides reversibly pause chain elongation because of the 3'-*O*-blocking group.[68] After a chemical reagent is added to cleave off the blocking group, chain elongation resumes with the addition of the next reversible terminator nucleotide.[69] Cleavage of the blocking group also removes the fluorescent dye so that a new color code can be introduced with the next nucleotide.[70]

This mechanism of reversible termination separates SBS from Sanger sequencing in two ways. First, Sanger sequencing reactions generate entire libraries of oligonucleotides of varying lengths, with each one permanently color-coded based on the terminal labeled dideoxynucleotide. SBS reactions only generate oligonucleotides of the same length as the template strand, and color-coding exists only transiently, between the moment of incorporation of a reversible terminator nucleotide and the subsequent cleavage of its

66. *Sequencing-by-Synthesis: Explaining the Illumina Sequencing Technology*, BITESIZEBIO (Aug. 30, 2012), https://bitesizebio.com/13546/sequencing-by-synthesis-explaining-the-illumina-sequencing-technology/. In the Illumina reversible terminator nucleotides, the fluorescent tag is attached to the nucleobase.

67. *Id.* At the 3' position, the reagent removes the blocking group and regenerates a 3'-OH group so strand elongation can proceed; at the position where the fluorescent dye is attached, the dye itself is removed but a scar remains in its place. *Id.*

68. Bentley et al., *supra* note 64, at 53.

69. *Explore Illumina Sequencing Technology*, ILLUMINA, https://www.illumina.com/science/technology/next-generation-sequencing/sequencing-technology.html (last visited Sept. 27, 2022). As in Sanger sequencing at the gel imaging step, a characteristic fluorescent signal is emitted per nucleotide type (A, T, C, G).

70. *See* Bentley et al., *supra* note 64, at 53.

fluorescent tag. Second, the products of Sanger sequencing reactions must be separated based on size through gel electrophoresis, to sort through the multi-length oligonucleotide library generated from the process and to visualize the fluorescent labels through laser excitation. SBS replaces this labor-intensive separation process with laser excitation integrated directly into the sequencing platform.

At the exact moment that a reversible terminator nucleotide incorporates into a growing DNA chain, elongation pauses due to the 3'-*O*-blocking group, a laser excites the fluorescent tag, and the system records the emitted signal for the corresponding spatial position in the template strand. This process is called "base calling." Then, after cleavage of both the 3'-*O*-blocking group and the fluorescent tag, the next reversible terminator nucleotide incorporates, elongation pauses, and a laser excites the new fluorescent tag corresponding to the just-added nucleotide once again, at a spatial position one "layer" above the previous signal. Base calling, or sequencing, occurs continuously, in real-time, as strands elongate—hence, the name sequencing-*by-synthesis*.

2. Integration into "Massively Parallel" Sequencing

Together, the three elements outlined for SBS, *supra*, allow for synchronous sequencing of millions of DNA fragments in real-time. First, positional separation produced by the anchoring of fragments to a solid support locks each fragment in a single position. Second, bridge PCR and cluster generation maintain this positional separation through the amplification step and subsequent sequencing reactions, providing an adequate signal for base calling. Third, the use of reversible terminator chemistry in SBS transiently color-codes each incorporated nucleotide, so that base calling may occur at the moment of nucleotide incorporation into each template strand during continuous growth in a fixed cluster. The combination of these elements enables laser excitation to image a bird's eye view of the entire flow cell. After the incorporation of each reversible terminator nucleotide to each template strand, the system captures an image that depicts, for each cluster, the fluorescent signal from the last nucleotide added to the growing DNA chains.[71] Therefore, millions of strands complementary to the template strand are read simultaneously within each cluster, and millions of clusters are sequenced simultaneously within the flow cell.

C. LIFE SCIENCES APPLICATIONS OF NGS

DNA sequencing can link observable, health-relevant phenotypes (i.e., observable physical characteristics) with underlying genotypes (i.e., DNA

71. ILLUMINA GUIDE, *supra* note 55, at 3–4.

sequences). DNA contains the instructional material for the synthesis of mRNA, which, in turn, contains the instructional material for protein synthesis.[72] Proteins control our biological functions.[73] Mutated DNA can create aberrant proteins, which can produce disease-causing abnormalities—"[v]irtually every human ailment has some basis in our genes."[74]

Because NGS can sequence whole human genomes at a much faster rate than Sanger sequencing, NGS empowers scientists to identify many potentially causal genetic differences ("variants") between patient genomes and healthy ("reference") genomes.[75] NGS has radically improved three main areas of life sciences applications: diagnostic testing, personalized medicine, and direct-to-consumer genomics.

1. Diagnostic Testing

NGS revolutionized the diagnostics field and is now a routine and increasingly affordable technique to identify disease-indicating genetic variants in patient DNA samples. Unlike Sanger sequencing, NGS users need not know what type of genetic variant they are looking for, nor where in a patient's genome to look for it.[76] In complex diseases with multiple underlying mutations in coding and non-coding regions of DNA—and often a complete lack of prior knowledge—this is a critical advantage.[77] For example, doctors previously diagnosed many subtypes of cancer based on morphology or other phenotypic signatures; now, they can distinguish cancers from genetic profiles at earlier stages[78]—"an unattainable fantasy" prior to the advent of NGS.[79] More generally, NGS also facilitates genome-wide association studies that correlate variants to disease phenotypes at the population level using statistical analyses.[80] These large-scale studies generate pools of data that help optimize

72. *A Brief Guide to Genomics*, *supra* note 3.

73. *Id.*

74. *Id.*

75. Muzzey et al., *supra* note 43, at 158 (dividing variants of interest into (1) changes to DNA sequences (e.g., single nucleotide polymorphisms, insertions, deletions), and (2) large deletions or duplications of whole genes). A genome—the target molecule of genomics—is the entire composite of DNA within an organism, stored in linearized or circular form.

76. *See* Sam Behjati & Patrick S. Tarpey, *What is Next Generation Sequencing?*, 98 ARCHIVES DISEASE CHILDHOOD 236, 236 (2013).

77. *Complex disease genomics*, ILLUMINA, https://www.illumina.com/areas-of-interest/complex-disease-genomics.html (last visited Sept 23, 2022).

78. *See* Gagan & Van Allen, *supra* note 8, at 5.

79. Stratton et al., *The Cancer Genome*, 458 NATURE 719, 722–23 (2009) (stating that "the arrival of second-generation sequencing technologies promise[d] a new era for cancer genomics").

80. *Disease association studies*, ILLUMINA, https://www.illumina.com/areas-of-interest/complex-disease-genomics/gwas.html (last visited Sept. 23, 2022).

how physicians approach disease screening to guide more targeted diagnostic approaches.[81]

2. Personalized Medicine

When NGS identifies variants for disease diagnostics, the variants themselves might be the root cause of the disease of interest. Other times, those variants might simply be associated with the presence of disease for an unknown reason. But non-causal "associated" variants might still indicate something useful for personalizing disease treatment.[82] For example, certain genetic mutations increase the likelihood that a patient will either respond to or resist a therapeutic strategy. With a patient's genetic profile, a physician might be able to select a specific type of chemotherapy or treatment approach.[83] And as sequencing methods continue to improve in both speed and miniaturization, physicians can make personalized decisions based on genetic information at or close to the point-of-care using portable technologies, even for rare or novel genetic mutations.[84] Integrating genotypic assessments into clinical examinations means physicians can consider genetic data holistically along with pathology and symptom assessments.[85]

3. Direct-to-Consumer Genomics

The efficiency of NGS technologies has made it possible to sell personalized genetic testing kits to interested consumers, allowing for general

81. *See id.* Genome-wide association studies provide correlational evidence of variants that are present at different frequencies in human populations lacking a certain disease, compared to healthy populations. David J. Hunter et al., *Letting the Genome Out of the Bottle – Will We Get Our Wish?*, 358 NEW ENG. J. MED. 105, 105 (2008).

82. *See* Gagan & Van Allen, *supra* note 8, at 8 ("NGS is inextricably intertwined with the realization of precision medicine in oncology.").

83. *See* Monica Avila & Funda Meric-Bernstam, *Next-Generation Sequencing for the General Cancer Patient*, 17 CLINICAL ADVANCES HEMATOLOGY & ONCOLOGY 447 (2019); Gagan & Van Allen, *supra* note 8, at 6 (listing several types of disease for which certain DNA mutations are indications or contraindications for therapeutic approaches in Table 2).

84. *See, e.g.*, Brandon S. Sheffield et al., *Point of Care Molecular Testing: Community-Based Rapid Next-Generation Sequencing to Support Cancer Care*, 29 CURRENT ONCOLOGY 1326 (2022) (discussing one example of NGS use in a clinical setting, where a workflow was implemented to get genetic profiling results back to patients in 3 business days).

85. *See, e.g.*, Yaoting Gui et al., *Frequent Mutations of Chromatin Remodeling Genes in Transitional Cell Carcinoma of the Bladder*, 43 NATURE GENETICS 875 (2011) (bladder); Guangwu Guo et al., *Frequent Mutations of Genes Encoding Ubiquitin-Mediated Proteolysis Pathway Components in Clear Cell Renal Cell Carcinoma*, 44 NATURE GENETICS 17 (2011) (kidney); Michael F. Berger et al., *The Genomic Complexity of Primary Human Prostate Cancer*, 470 NATURE 214 (2011) (prostate); Xose S. Puente et al., *Whole-Genome Sequencing Identifies Recurrent Mutations in Chronic Lymphocytic Leukemia* 475 NATURE 101 (2012) (CLL); Timothy J. Ley et al., *DNA Sequencing of a Cytogenetically Normal Acute Myeloid Leukemia Genome*, 456 NATURE 66 (2008) (AML).

susceptibility testing and genetic profiling.[86] Genetic testing irrespective of disease state can facilitate early surveillance and detection in some populations, if interpreted properly and paired with appropriate medical direction.[87]

III. DEVELOPMENT OF THE ILLUMINA NGS PLATFORM

The Illumina NGS platform has a long history, from early developments in first-generation sequencing in the 1970s, to the massive technological leap pushed forward by the Solexa scientists at the turn of the century. This Part chronicles this history in five phases: (1) optimization and commercialization of Sanger sequencing; (2) implementation of Sanger sequencing in the HGP; (3) preliminary research driving key pre-Illumina advances in NGS; (4) creation of the NGS Solexa idea; and (5) expansion and commercialization of Solexa (now Illumina).

A. PHASE 1: OPTIMIZATION AND COMMERCIALIZATION OF SANGER SEQUENCING

Frederick Sanger, a biochemist at the Laboratory of Molecular Biology funded through the Medical Research Council in the United Kingdom, published a description of the first form of "Sanger sequencing" in 1977.[88] At approximately the same time, Harvard scientists Allan Maxam and Walter Gilbert independently developed a similar approach.[89] Their method—termed Maxam-Gilbert sequencing—was initially more popular, but fell out of favor as scientists recognized the comparative technical ease of Sanger sequencing.[90]

---

86. *See* Hunter et al., *supra* note 81.

87. *See id.* (warning that such test kits may be inaccurate and yield false positives, and that consumers may incorrectly interpret results without appropriate guidance). Some have termed at-home genetic testing "recreational genomics," and remarked that this phenomenon carries high risks of misinformation. James P. Evans, *Recreational Genomics; What's in it for You?*, 10 GENETICS MED. 709, 710 (2008).

88. Frederick Sanger et al., *DNA Sequencing with Chain-Terminating Inhibitors*, 74 PROCS. NAT'L ACAD. SCIS. 5463 (1977). Sanger's 1977 publication, cited here, is the first report using *dideoxynucleotides* in the sequencing reactions, producing the chain-terminating element of Sanger sequencing. However, it is worth noting that Sanger first published the "plus and minus" sequencing method in 1975, which was later refined in his 1977 publication. Frederick Sanger & Alan R. Coulson, *A Rapid Method for Determining Sequences in DNA by Primed Synthesis with DNA Polymerase*, 94 J. MOLECULAR BIOLOGY 441 (1975).

89. Maxam-Gilbert sequencing was first reported in 1977. This method still uses chain-termination, but not due to an intrinsic structural modification of the nucleotides to be incorporated (i.e., no *dideoxy* element). Allan M. Maxam & Walter Gilbert, *A New Method for Sequencing DNA*, 74 PROCS. NAT'L ACAD. SCIS. 560, 560 (1977).

90. *See* Christopher M. Holman, *Advances in DNA Sequencing Lead to Patent Disputes*, 30 NATURE BIOTECHNOLOGY 1054, 1054 (2012).

Immediately after the initial publication of Sanger sequencing, researchers began trying to automate the method, which set the stage for the eventual leap into NGS technologies. In its first form, Sanger sequencing involved an entirely manual process—for example, the process initially used radioactive labeling, rather than fluorescence.[91] Because all four nucleotides had the same type of tag (instead of four distinct color codes), users had to run four separate sequencing reactions for each DNA fragment to be sequenced, to track each nucleotide.[92] Then, in the final gel electrophoresis step, visualization had to occur via autoradiography rather than laser excitation and without computational automation of the base calling step.[93] Manual Sanger sequencing also used rectangular slab gels, which each require their own separate dock and typically run on a vertical or horizontal plane.[94]

Leroy Hood, a professor at the California Institute of Technology ("Caltech"), spearheaded the automation of Sanger sequencing. Beginning in the 1980s, Hood suggested fluorescence instead of radiolabeling, so the four nucleotides could each have their own color codes.[95] Fluorescent labelling enabled researchers to combine the four separate sequencing reactions into one and to image the fluorescent tags with simple laser excitation, rather than the lengthy autoradiography process.[96] James Prober then refined this labeling method, labeling the dideoxynucleotides themselves with fluorescent dyes, instead of the indirect primer-mediated tagging of Sanger and Hood's preliminary methods.[97] Other scientists also proposed replacing the manual gel electrophoresis step with capillary electrophoresis.[98] Instead of rectangular gel slabs, capillary electrophoresis uses gels polymerized in capillary tubes, arrayed

91. Jeffrey M. Perkel, *An Automated DNA Sequencer*, 18 SCIENTIST 40, 40 (2004).

92. *Id.*; Sanger, *supra* note 88, at 5464.

93. Sanger, *supra* note 88, at 5464.

94. *See id.*

95. Lloyd M. Smith et al., *The Synthesis of Oligonucleotides Containing an Aliphatic Amino Group at the 5' Terminus: Synthesis of Fluorescent DNA Primers for Use in DNA Sequence Analysis*, 13 NUCLEIC ACIDS RSCH. 2399 (1985).

96. Lloyd M. Smith et al., *Fluorescence Detection in Automated DNA Sequence Analysis*, 321 NATURE 674 (1986); *see* Schroeder, *supra* note 46. The fluorescent readout of the laser excitation is then computationally processed to generate chromatograms. These are four-color plots that depict color-coded nucleotide "peaks," corresponding to the fluorescent signals emitted from each type of nucleotide. Researchers examine chromatograms to infer the identity and order of the base pairs in a sequenced DNA strand.

97. James M. Prober et al., *A System for Rapid DNA Sequencing with Fluorescent Chain-Terminating Dideoxynucleotides*, 238 SCI. 336 (1987).

98. Aharon S. Cohen et al., *Rapid Separation and Purification of Oligonucleotides by High-Performance Capillary Gel Electrophoresis*, 85 PROCS. NAT'L ACAD. SCIS. 9660 (1988); John A. Luckey et al., *High Speed DNA Sequencing by Capillary Electrophoresis*, 18 NUCLEIC ACIDS RSCH. 4417 (1990).

in 384-tube format.[99] Improvements to the labeling and the electrophoresis processes combined with an integrated laser detection system allowed for "automated" Sanger sequencing. In 1985, Hood developed the first machine implementing automated Sanger Sequencing (the ABI 370) at his then-newly founded company, Applied Biosystems.[100]

B. PHASE 2: IMPLEMENTATION OF SANGER SEQUENCING IN THE HUMAN GENOME PROJECT

With the inclusion of fluorescent dyes, capillary electrophoresis, and automated laser detection, DNA sequencing exploded in popularity.[101] In addition to sequencing the genomes of several small organisms,[102] the scientific community sought to use Sanger sequencing to determine the complete sequence of the human genome.[103] This idea, at first, was polarizing. Some felt that the genome contained mostly "junk" DNA[104] and its sequence would be a useless resource, and that focusing on such "big" science would "divert[]

99. *Electrophoresis with Sanger Sequencing*, THERMOFISHER SCI., https://www.thermofisher.com/us/en/home/life-science/sequencing/sanger-sequencing/sanger-dna-sequencing/electrophoresis-sanger-sequencing.html?socid=social_btb_abseq (last visited Mar. 14, 2024).

100. Marina Barba et al., *Historical Perspective, Development and Applications of Next-Generation Sequencing in Plant Virology*, 6 VIRUSES 106 (2014); *Leroy Hood*, LEMELSON-MIT, https://lemelson.mit.edu/award-winners/leroy-hood#:~:text=Working%20with%20a%20team%20at,strings%20of%20DNA%20in%20cells. (last visited May 2, 2023).

101. *See* Alice Maria Giani et al., *Long Walk to Genomics: History and Current Approaches to Genome Sequencing and Assembly*, 18 COMPUTATIONAL & STRUCTURAL BIOTECHNOLOGY J. 9, 11 (2020); Frederick Sanger, *Sequences, Sequences, and Sequences*, 57 ANN. REV. BIOCHEMISTRY 1, 25 (1988).

102. A complete genome sequence of a live organism (not bacteriophage) was reported for the first time in 1995. Robert D. Fleischmann et al., *Whole-Genome Random Sequencing and Assembly of Haemophilus influenzae Rd*, 269 SCI. 496 (1995) (reporting the use of Sanger sequencing to obtain the complete sequence of the ~ 1.8 million base pair genome of a *Haemophilus* bacterium, out of Craig Venter's group). Before this, a few groups had reported bacteriophage genome sequences. *See, e.g.*, Sanger, *supra* note 40.

103. *See* Reuter et al., *supra* note 62, at 586.

104. With an entire research field now devoted to the analysis of non-coding DNA, the "junk" DNA terminology has been more or less debunked. Indeed, several regions of the human genome do not encode for specific proteins. But those regions are often functionally critical for other purposes (e.g., to regulate gene expression). *The Complex Truth About 'Junk DNA'*, QUANTAMAGAZINE, https://www.quantamagazine.org/the-complex-truth-about-junk-dna-20210901/ (last visited Nov. 24, 2022); David Brown & Hristio Boytchev, *'Junk DNA' Concept Debunked by New Analysis of Human Genome*, WASH. POST (Sept. 5, 2012), https://www.washingtonpost.com/national/health-science/junk-dna-concept-debunked-by-new-analysis-of-human-genome/2012/09/05/cf296720-f772-11e1-8398-0327ab83ab91_story.html. Unfortunately, the "junk" terminology continues to plague the legal field, especially in the context of forensic analysis. Jennifer K. Wagner, *Out with the "Junk DNA" Phrase*, J. FORENSIC SCI. (2012).

resources from the 'real' small science."[105] Others felt that uncovering the genome sequence would establish "an unparalleled medical and research tool for studying mutations," "the grail of human genetics,"[106] and be "crucial for progress in human physiology and pathology," especially in the context of cancer research.[107] After several preliminary meetings and discussions in the late 1980s, the National Institutes of Health (NIH) and the Department of Energy formally initiated the HGP in October 1990—motivated primarily by a desire to understand the broad effects of radiation exposure on the human genome.[108] Formally, the HGP was an international agreement between researchers to work together on the production of a single reference human genome sequence.[109] Hood's improvements to Sanger sequencing—and the resulting automated sequencer machines that he developed—are credited as the technology that made the HGP possible.[110]

The HGP is now fondly regarded as "the largest single undertaking in the history of biological science,"[111] yielding sequencing data for "over 90% of the human genome."[112] However, the story of the HGP also illustrates the inability for Sanger sequencing, even automated, to keep pace with modern life sciences sequencing inquiries. The Project—which sequenced *one* human genome—cost an estimated $3 billion[113] and lasted for twelve years, ending only in April 2003.[114] With the lofty goal of sequencing *billions* of human genomes,

105. Leroy Hood & Lee Rowen, *The Human Genome Project: Big Science Transforms Biology and Medicine*, 5 GENOME MED. 1, 1 (2013).

106. Robert Kanigel, *The Genome Project*, N.Y. TIMES (Dec. 13, 1987), https://www.nytimes.com/1987/12/13/magazine/the-genome-project.html.

107. Renato Dulbecco, *A Turning Point in Cancer Research: Sequencing the Human Genome*, 231 SCI. 1055, 1055 (1986).

108. Hood & Rowen, *supra* note 105, at 1.

109. U.S. DEP'T HEALTH & HUM. SERVS. & U.S. DEP'T ENERGY, UNDERSTANDING OUR GENETIC INHERITANCE, THE U.S. HUMAN GENOME PROJECT: THE FIRST FIVE YEARS (1990).

110. Andrew Pollack, *SCIENTIST AT WORK: LEROY HOOD; A Biotech Superstar Looks at the Bigger Picture*, N.Y. TIMES (Apr. 17, 2001), https://www.nytimes.com/2001/04/17/science/scientist-at-work-leroy-hood-a-biotech-superstar-looks-at-the-bigger-picture.html.

111. SIMON TRIPP & MARTIN GRUEBER, ECONOMIC IMPACT OF THE HUMAN GENOME PROJECT (2011).

112. *Human Genome Project Fact Sheet*, NAT'L HUM. GENOME RSCH. INST., https://www.genome.gov/about-genomics/educational-resources/fact-sheets/human-genome-project (last visited Mar. 14, 2024) [hereinafter HGP Fact Sheet].

113. This estimate is based on the initially projected cost for the HGP, as "precise cost-accounting [is] difficult to carry out, especially across the set of international funders." *Id.*

114. *The Human Genome Project*, NAT'L HUM. GENOME RSCH. INST., https://www.genome.gov/human-genome-project (last visited Mar. 14, 2024) [hereinafter HGP Basics]. A draft of the human genome was initially published in 2001. Int'l Human Genome Sequencing Consortium, *Initial Sequencing and Analysis of the Human Genome*, 409 NATURE 860

researchers needed to improve sequencing technology throughput significantly.[115] The HGP largely motivated the development of NGS technologies and systems biology, which together precipitated the "omics" era.[116]

Some consider the HGP key to advancing the concepts of "open science" and data sharing, because such a complicated international effort required coordination between the participating researchers.[117] The HGP researchers (later termed the International Human Genome Sequencing Consortium) worked without commercial funding sources.[118] To effectively coordinate, the Consortium agreed on the "Bermuda Principles" in 1996, which required all participants to make their sequence data available in public databases within approximately twenty-four hours of generation.[119]

Other perspectives on the commercialization of the human genome loomed in the background. In the middle of 1998, with the HGP in full swing, Craig Venter announced his plans to found Celera Genomics and launch a competing effort to sequence the human genome using a variation of shotgun assembly that others dismissed as too computationally intensive for the human genome.[120] Venter's announcement—and his subsequent suggestion that the HGP should move on and try the mouse genome instead—sparked panic that

(2001) [hereinafter HGP First Draft]. The full sequence was finalized in a subsequent publication in 2004. Int'l Human Genome Sequencing Consortium, *Finishing the Euchromatic Sequence of the Human Genome*, 431 NATURE 931 (2004).

115. HGP Basics, *supra* note 114.

116. Muzzey et al., *supra* note 43, at 158 (noting that "by the end of the Human Genome Project in 2002, [Sanger sequencing] was already operating at nearly peak efficiency"); Hood & Rowen, *supra* note 105, at 5.

117. *See* Kendall Powell, *The Broken Promise that Undermines Human Genome Research*, NATURE NEWS FEATURE (Feb. 10, 2021), https://www.nature.com/articles/d41586-021-00331-5 (referring to David Haussler, one of the developers of the first web-based tool for viewing the human genome sequence, stating that before the HGP, "there had not been a serious discussion about data sharing in biomedical research," and that "[t]he standard was that a successful investigator held onto their own data as long as they could").

118. HGP Fact Sheet, *supra* note 112 (noting that the project was "one of the most ambitious and important scientific endeavors in human history," seeking to sequence the entire human genome and the genomes of several model organisms: bacteria, yeast, flies, nematodes, and mice). Funding for the HGP was congressionally approved through the National Institutes of Health and the Department of Energy, and also separately from the Wellcome Trust and the Medical Research Council in the United Kingdom.

119. *Id.* (noting that the Bermuda Principles are "credited with establishing a greater awareness and openness to the sharing of data in biomedical research," and that they are "one of the most important legacies of the [HGP]").

120. Jan Witkowski, *A Life Worth Writing About*, 449 NATURE 785, 786 (2007) (providing more information on Venter's storied career, as a scientist and entrepreneur); Waterston et al., *supra* note 39, at 3712.

a private company would own the human genome sequence and that Congress would pull funding from the HGP.[121] Venter indicated that Celera would seek patent protection on all gene sequences obtained from their effort, and would not comply with the Bermuda Principles.[122]

Galvanized by Venter's threat, the HGP continued in full force.[123] And Celera began a parallel sequencing effort shortly after Venter's announcement. In 2000, former U.S. President Bill Clinton and former U.K. Prime Minister Tony Blair delivered a joint statement advocating that the human genome sequence "be made freely available to scientists everywhere."[124] Shortly after, in 2001, both the HGP and Celera teams published their first drafts of the human genome, one day apart.[125] The HGP used Sanger sequencing with hierarchical "clone-by-clone" assembly; Celera used Sanger sequencing with whole-genome shotgun assembly to generate almost the exact same sequencing product as the HGP in one-tenth of the time.[126]

The HGP is now viewed as "instrumental in pushing the development of high-throughput [sequencing] technologies."[127] The frustratingly slow speed of the Project—exacerbated by the competitive environment sparked by the Celera effort—encouraged scientists to improve sequencing technologies.[128]

---

121. Waterston et al., *supra* note 39, at 3712.

122. Caroline Barranco, *The Human Genome Project*, NATURE MILESTONES (Feb. 10, 2021), https://www.nature.com/articles/d42859-020-00101-9 (last visited Oct. 1, 2022).

123. *See, e.g.*, *id.*; Hunter et al., *supra* note 81, at 107.

124. Joint Statement by President Clinton and Prime Minister Tony Blair of the United Kingdom (Mar. 14, 2000), https://www.govinfo.gov/content/pkg/WCPD-2000-03-20/pdf/WCPD-2000-03-20-Pg550.pdf.

125. HGP First Draft, *supra* note 114 (making all sequencing data available in the journal *Nature*); J. Craig Venter et al., *The Sequence of the Human Genome*, 291 SCI. 1304 (2001) (publishing only some sequencing data, with restrictions, as agreed to by the journal *Science*) [hereinafter Celera First Draft]. The HGP used DNA extracted from a set of volunteers to assemble their draft human genome sequence, so it represents an average, composite genetic profile. HGP Fact Sheet, *supra* note 112. The human genome sequence published by Celera is allegedly derived mostly from Venter's own DNA. Witkowski, *supra* note 120, at 786.

126. Waterston et al., *supra* note 39, at 3712; *see* Jeffrey A. Schloss, *How to Get Genomes at One Ten-Thousandth the Cost*, 26 NATURE BIOTECHNOLOGY 1113, 1113 (2008). Celera generated an ordered sequence of the human genome using whole-genome shotgun assembly in less than 1 year, with sequencing initiated on September 8, 1999 and assembly completed on June 25, 2000. Celera First Draft, *supra* note 125, at 1306. Notably, the whole-genome shotgun sequencing approach used by Celera relied upon preliminary data generated by the HGP effort, with hierarchical sequencing of bacterial artificial chromosome clones. Barranco, *supra* note 122.

127. Hood & Rowen, *supra* note 105, at 2.

128. *See In the Crossfire: Collins on Genomes, Patents, and 'Rivalry'*, 287 SCI. 2396 (2000) (transcribing an interview with Francis Collins, the head of the National Human Genome Research Institute and leader of the HGP).

In 2001, when the Project was nearing its completion, the National Human Genome Research Institute (NHGRI) began planning the next phase of genomics research: reducing the cost of sequencing the human genome to $1000.[129] Advances in Sanger sequencing technology during the HGP had already increased throughput and reduced costs from ten dollars to ten cents per base pair.[130] Five large centers emerged as leaders in genome sequencing throughout the HGP (the Wellcome Trust Sanger Institute, the Broad Institute, the Genome Institute of Washington University in St. Louis, the Joint Genome Institute, and the Whole Genome Laboratory at Baylor College of Medicine), which, together, paved the way for continued improvements in sequencing technologies.[131] Hoping to even further reduce the cost and time of sequencing, the NHGRI invested over $100 million in research grants dedicated to the development of new sequencing technologies.[132] Applicants developing sequencing-by-synthesis, sequencing-by-ligation, and nanopore approaches received the most grants, as NHGRI predicted these technologies to be most likely to "achiev[e] orders-of-magnitude improvements in sequencing."[133] And in a matter of years, sequencing-by-synthesis (used by Illumina) became the dominating approach in the NGS market.

C. PHASE 3: PRELIMINARY RESEARCH DRIVING KEY PRE-ILLUMINA ADVANCES IN NGS

As discussed in Section III.B *supra*, the HGP catalyzed several efforts to develop NGS. By the midpoint of the HGP, scientists in the United States and Europe had already established an array of startup companies that each sought to develop and sell the first NGS machine. Although Illumina—then called Solexa—later emerged as the winner of this race, technology from several different researchers, academic labs, and startup companies set the stage for the modern Illumina platform (**Table 2**). This Section outlines the early advances that inspired the three "massively parallel" elements of the Illumina platform.[134]

129. Schloss, *supra* note 126, at 1113.

130. *Id.*

131. Hood & Rowen, *supra* note 105, at 2.

132. Schloss, *supra* note 126, at 1114.

133. *Id.*; *Genome Technology Program*, NAT'L HUMAN GENOME RSCH. INST., https://www.genome.gov/Funded-Programs-Projects/Genome-Technology-Program#6 (last visited May 2, 2023).

134. *See* discussion *supra* Section II.B.1.

Table 2: List of critical people and institutions involved in the Illumina discovery story.

Phase	People	Institutions	Main Contributions	Relevant Active Years
Pre-Illumina	Frederick Sanger	Laboratory of Molecular Biology, United Kingdom	First-generation Sanger sequencing	1977
	Allan Maxam & Walter Gilbert	Harvard, United States	First-generation Maxam-Gilbert sequencing	1977
	Leroy Hood	Caltech, United States	Automation of Sanger sequencing	1980–1985
	Craig Venter	National Institutes of Health, United States	Celera Genomics, parallel HGP effort	1998–2003
	George Church	Harvard & Massachusetts Institute of Technology (MIT), United States	Multiplexing and solid support NGS	1984–1988
	Pascal Mayer	Serono Pharmaceutical Research Institute & Manteia Predictive Medicine, Switzerland	Bridge PCR clustering	1996–2004
	Pål Nyrén	Royal Institute of Technology, Sweden	Pyrosequencing	1986–1996
	Bruno Canard & Robert Sarfati	Pasteur Institute, France	Reversible terminator chemistry	1993–1994

Illumina	Shankar Balasubramanian & David Klenerman	University of Cambridge & Solexa, United Kingdom	Solexa, original platform	1997–2008
	John Milton	Solexa, United Kingdom	Medicinal chemistry at Solexa	2001–2008
	Nick McCooke & John West	Solexa, United Kingdom	Business development and expansion of Solexa	2001–2008
	Clive Brown, Klaus Maisinger & Tony Cox	Solexa, United Kingdom	Bioinformatics development at Solexa	2001–2008
	Sydney Brenner	Lynx Therapeutics, United States	Merged with Solexa	2005
	David Walt	Illumina, United States	Acquired Solexa	2007

1. Solid Support Array

As discussed in Section II.B.1.a) *supra*, the Illumina platform uses a solid support array to immobilize the DNA strands undergoing sequencing. Immobilization has been a component of the Illumina platform since it was first visualized in 1998.[135] Many different DNA sequencing researchers independently conceived of this same immobilization idea around the same time as Illumina researchers. In fact, so many groups simultaneously pursued the use of a solid support that it is difficult to identify who invented it. Indeed, the positional separation of DNA achieved by a solid support is the main feature that sets apart many NGS technologies from their "first-generation" analogs.[136]

George Church, a professor at Harvard University and MIT, was a key advocate for the use of solid support arrays to improve DNA sequencing—earning him a reputation as the "founding father of genomics."[137] Church was

135. *See* discussion *infra* Section II.B.1.

136. Sanger sequencing, and its many permutations, all separate DNA by size, only at the end of the sequencing process. *See* discussion *supra* Section II.A.3.

137. Stephanie Huie, *Dr. George Church, Founding Father of Genomics*, WINDWARD INST. (Apr. 15, 2020), https://www.thewindwardschool.org/the-windward-institute/the-beacon/article/~board/beacon-archives/post/dr-george-church-founding-father-of-genomics.

likely the first scientist to envision solid support immobilization in the context of DNA sequencing, as described in a 1984 publication[138] with Gilbert, one of the scientists who invented Maxam-Gilbert sequencing.[139] In that publication, Church and Gilbert disclosed the idea of DNA immobilization on nylon membranes.[140] Then, in a 1988 publication, Church and Stephen Kieffer-Higgins described the advantage of "multiplex" sequencing—mixing a series of different DNA samples together, and then sequencing the entire pool—as "greatest when the mixing occurs as early as possible and separation occurs as late as possible."[141] Church and Kieffer-Higgins envisioned a method of DNA sequencing with an initial multiplexing step and subsequent DNA separation based on nylon membrane immobilization.[142] Church continued to pursue NGS technologies, and eventually moved into nanopore-based sequencing—which launched a third generation of sequencing approaches.[143]

The original notion of immobilizing DNA by anchoring it against some other physical surface—not for the purposes of sequencing—traces back to Stephen Fodor's proposal for the "DNA chip" in the 1980s.[144] Inspired by computer chips, the DNA chip idea suggested the possibility of fixing DNA molecules to a small chip for analysis.[145] This concept may have been disclosed for the first time in 1994 in both a scientific publication[146] and a patent

138. George M. Church & Walter Gilbert, *Genomic Sequencing*, 81 PROCS. NAT'L ACAD. SCIS. 1991 (1984).

139. *See supra* text accompanying note 89.

140. *Id.* at 1992.

141. George M. Church & Stephen Kieffer-Higgins, *Multiplex DNA Sequencing*, 240 SCI. 185, 185 (1988).

142. *Id.*

143. *See* discussion *infra* Part V. In 1995, Church filed a patent application claiming a method of sequencing DNA anchored to an interface between two pools of media, U.S. Patent No. 5,795,782 (filed Mar. 17, 1995, issued Aug. 18, 1998). This patent is the first disclosure of George Church's nanopore sequencing idea, and was eventually licensed to Oxford Nanopore Technologies.

144. *See Stephen P.A. Fodor, Michael C. Pirrung, J. Leighton Read, Lubert Stryer (Affymax Research Institute, Palo Alto, USA)*, EUR. PAT. OFF., https://www.epo.org/en/news-events/european-inventor-award/meet-the-finalists/stephen-pa-fodor-michael-c-pirrung-j (last visited Mar. 13, 2024). For additional foundational research in this area, see, e.g., Robert L. Letsinger & V. Mahadevan, *Oligonucleotide Synthesis on a Polymer Support*, 87 J. AM. CHEM. SOC'Y 3526 (1965) (synthesizing DNA on a surface in the 1960s); M. D. Matteucci & Marvin H. Caruthers, *Synthesis of Deoxyoligonucleotides on a Polymer Support*, 103 J. AM. CHEM. SOC'Y 3185 (1981) (same but in the 1980s); *see also* Christine R. Laramy, Matthew N. O'Brien & Chad A. Mirkin, *Crystal Engineering with DNA*, 4 NATURE REVS. MATERIALS 201 (2019) (reviewing early work involving DNA attachment).

145. *Id.*

146. Jeffrey W. Jacobs & Stephen P.A. Fodor, *Combinatorial Chemistry—Applications of Light-Directed Chemical Synthesis*, 12 TRENDS BIOTECHNOLOGY 19 (1994).

application.[147] The possibility of then actually *sequencing* that immobilized DNA, in a manner distinct from that used by Church, Gilbert, and Kieffer-Higgins, was discussed by Andrei Mirzabekov in 1994.[148] And even earlier, another group of scientists filed a 1992 patent application on a method of amplifying DNA immobilized to a surface.[149] A 1995 scientific publication also disclosed attaching DNA to a surface.[150]

Tracking these early developments, a 2008 review noted that "[a]ll of the recently released, or soon-to-be-released, non-Sanger [NGS] commercial sequencing platforms . . . fall under the rubric of a single paradigm . . . [where] DNA (as a single molecule or in multiple copies) [is] *physically immobilized* on [an] array."[151] A 2010 review similarly identified "[a] common theme among NGS technologies is that the template is attached or immobilized to a solid surface or support."[152] The spatial separation achieved by physical immobilization of DNA provides unparalleled organizational power.

2. Bridge PCR Clustering

Again, as detailed in Section II.B.1.b *supra*, the Illumina platform uses bridge PCR clustering to amplify template DNA strands, a unique approach that maintains physical anchoring to a solid support despite ongoing rounds of amplification. The amplification process produces groups of DNA molecules that Illumina terms "clusters." Illumina incorporated the bridge PCR clustering technology into its platform in 2004.[153] However, Pascal Mayer proposed an early version of bridge PCR clustering in 1996.[154] Back then, researchers called the characteristic Illumina clusters "colonies."

Mayer's work was pivotal to the eventual success of the Illumina platform. From 1996 to 2000, Mayer worked as a scientist in Geneva at the Biomedical Research Institute of GlaxoWellcome, which became the Serono

147. European Patent No. 0,476,014 (file June 7, 1990) (granted Aug. 31, 1994).

148. Andrei D. Mirzabekov, *DNA Sequencing by Hybridization—a Megasequencing Method and A Diagnostic Tool?*, 12 TRENDS BIOTECHNOLOGY 27 (1994).

149. U.S. Patent No. 5,616,478 (filed Oct. 26, 1992) (granted Apr. 1, 1997).

150. Mark Schena et al., *Quantitative Monitoring of Gene Expression Patterns with a Complementary DNA Microarray*, 270 SCI. 467 (1995).

151. Jay A. Shendure et al., *Overview of DNA Sequencing Strategies*, 81 CURRENT PROTOCOLS MOLECULAR BIOLOGY 1, 4 (2008) (emphasis added).

152. Metzker, *supra* note 42, at 32.

153. *See* discussion *infra* Section III.D.

154. Lucie Aubourg, *French Scientist Recognized for Rapid DNA Sequencing Technique Key in COVID Fight*, PHYSORG (Sept. 9, 2021), https://phys.org/news/2021-09-french-scientist-rapid-dna-sequencing.html.

Pharmaceutical Research Institute.[155] In these years, he developed the "colony" approach to DNA sequencing,[156] first disclosing the idea in two 1997 patent applications.[157] A slide from a 1998 Mayer presentation shows the proposed DNA colonies in the distinctive "bridged" position—now synonymous with Illumina sequencing.[158] At the turn of the century, Mayer pushed for Serono to launch an independent startup company called Manteia Predictive Medicine to continue development of this new, "massively parallel" DNA sequencing approach.[159] Manteia further optimized the colony technology, as publicly disclosed in a 2003 presentation.[160] But the company remained unable to actually generate complete sequencing data and, that year, took half of their staff members off the project.[161] Manteia's investors lost interest and eventually withdrew funding.[162] The reduced investor interest motivated Manteia to eventually license the colony patents to the company established by Balasubramanian and Klenerman.[163]

3. SBS Read Generation

Finally, as described in Section II.B.1.c *supra*, the Illumina platform uses a technology for read generation called SBS.[164] SBS is "massively parallel" because it allows for bases to be called at the moment of nucleotide incorporation, rather than indirectly at the end of the sequencing reaction. For Illumina, SBS is facilitated by the reversible terminator chemistry on the nucleotides that are incorporated, which was likely first outlined by the Solexa researchers in a 1998 patent application.[165] However, other scientists

155. Pascal Meyer, LINKEDIN, https://fr.linkedin.com/in/pascal-mayer-6b652a13 (last visited Oct. 23, 2022).

156. Aubourg, *supra* note 154.

157. Pascal Mayer, *Breakthrough Prize 2022: Behind Every Success Story There Are Great Teams*, LINKEDIN (Sept. 9, 2021), https://www.linkedin.com/pulse/breakthrough-prize-2022-behind-every-success-story-great-pascal-mayer.

158. Pascal Mayer, *A Very Large Scale, High Throughput and Low Cost DNA Sequencing Method Based on a New 2-Dimensional DNA Auto-Patterning Process*, Presentation at the Fifth International Automation in Mapping and DNA Sequencing Conference, St. Louis, MI (Oct. 7-10, 1998) (depicting an early variant of "colony" DNA sequencing on slides 3-5).

159. Mayer, *supra* note 157.

160. Manteia Predictive Medicine, Corporate Presentation (Sept. 2003), https://www.slideshare.net/pascalmayer/manteia-non-confidentialpresentation200309 (depicting a bridge PCR clustering pipeline on slides 19-23).

161. Barry Whyte, *Once in a Generation: Pascal Mayer and the Birth of a Billion-Dollar Industry*, 1 GEN BIOTECHNOLOGY 49, 55 (2022).

162. *Id.* at 56.

163. Mayer, *supra* note 157; *see* discussion *infra* Section III.D.

164. *Explore Illumina sequencing technology*, *supra* note 69.

165. WO 2000/006770 (filed July 30, 1999, claiming priority date of July 30, 1998).

developed the idea of SBS well before Solexa developed their reversible terminator version.

A 1985 patent, filed by Robert Melamede, was likely the earliest discussion of SBS as a DNA sequencing strategy.[166] The specification highlighted the labor-intensive methodology of Maxam-Gilbert and Sanger sequencing, even with automation, and proposed DNA sequencing without radioactivity or gel electrophoresis.[167] Without much detail as to the method, Melamede described that detection of nucleotide incorporation might occur as part of the sequencing process, based on a decrease in nucleotide absorbance.[168]

In parallel, without knowledge of the Melamede '849 patent from 1985,[169] Pål Nyrén conceived of the SBS idea "[o]ne late afternoon in the beginning of January 1986, bicycling from the lab over the hill to the small village of Fullbourn."[170] Nyrén described SBS as "follow[ing] the activity of DNA polymerase during nucleotide incorporation into a DNA strand."[171] However, rather than Melamede's method of monitoring nucleotide absorbance, or the eventual Illumina method of monitoring fluorescence, Nyrén envisioned a method of monitoring pyrophosphate release. Pyrophosphate synthesis occurs naturally as DNA strands elongate,[172] so rather than adding fluorescent tags to nucleotides, Nyrén suggested a sequencing method that continuously monitored naturally-occurring pyrophosphate production throughout DNA replication.[173] However, given several technical issues and other complications, almost a decade passed before Nyrén published a workable design for this approach.[174] Nyrén's method—termed *pyrosequencing*—increased the sensitivity of Melamede's SBS proposal by 100–1000-fold, overcoming a critical

166. U.S. Patent No. 4,863,849 (filed July 18, 1985) [hereinafter the '849 patent].

167. *Id.*

168. *See id.*

169. *See* Pål Nyrén, *The History of Pyrosequencing*, *in* PYROSEQUENCING PROTOCOLS 1, 1–2 (Sharon Marsh ed., 2007) ("Much later, I learned that Bob Melamede, whom I met in Stockholm in 1997, had described the general principles of DNA sequencing-by-synthesis in a previously obtained patent.").

170. *Id.* at 2.

171. *Id.*

172. Pyrophosphate is a transient molecule that is released naturally at the incorporation of each nucleotide into growing DNA strands, based on ATP hydrolysis by DNA polymerase. Jithesh Kottur & Deepak T. Nair, *Pyrophosphate Hydrolysis is an Intrinsic and Critical Step of the DNA Synthesis Reaction*, 46 NUCLEIC ACIDS RSCH. 5875 (2018).

173. *See* Nyrén, *supra* note 169, at 1–2.

174. Mostafa Ronaghi et al., *A Sequencing Method Based on Real-Time Pyrophosphate*, 281 SCI. 363 (1998). The approach adds luciferase into the sequencing mixture, so that luminescence can be monitored as a readout for pyrophosphate production during nucleotide incorporation. *Id.* The different nucleotides are distinguished based on the intensity of the luminescence signal emitted. *Id.*

impediment of the approach as previously articulated.[175] In 2005, pyrosequencing became the basis of the first commercialized NGS platform: the 454 Life Sciences system.[176]

Researchers also considered other elements of reversible terminator chemistry prior to the Solexa idea. The first mention of reversible terminator chemistry as the backbone of SBS was possibly in an unpublished 1993 French patent application.[177] The inventors, Bruno Canard and Robert Sarfati, filed a few other patent applications in this family, but none issued.[178] Then, in a 1994 scientific publication, Canard and Sarfati described their synthesis of modified nucleotides for DNA sequencing.[179] Their idea involved protecting the 3'-end of the extending DNA molecule (where Illumina uses a 3'-*O*-azidomethyl blocking group) with a blocking group, chemically or enzymatically removing that blocking group, and regenerating a free 3'-hydroxyl group to resume strand elongation.[180] This method is quite similar to the SBS read generation method now used in the Illumina platform. However, the specific chemistry proposed by Canard and Sarfati was distinct from that of the Solexa team.[181] Canard and Sarfati envisioned a different 3'-moiety for each distinct nucleotide and also incorporated the fluorescent label at the 3'-substituted end itself.[182]

A group at Columbia published another early conceptualization of the reversible terminator chemistry idea for DNA sequencing in 2003.[183] Reversible terminator chemistry has flourished over the years, with scientists continuing to explore 3'-*O*-blocked and 3'-*O*-unblocked terminators.[184]

175. *See* Nyrén, *supra* note 169, at 3–4 ("When I later met Bob [Melamede], he was very happy to hear that his sequencing-by-synthesis concept worked and that I had circumvented the problem of DNA polymerase-activity monitoring.").

176. Marcel Margulies et al., *Genome Sequencing in Microfabricated High-Density Picolitre Reactors*, 437 NATURE 376 (2005) (describing the pyrosequencing protocol out of Jonathan Rothberg's group at 454 Life Sciences, with a purported 100-fold increase in throughput compared to Sanger sequencing).

177. French Patent No. 2,703,052 (filed Mar. 26, 1993), https://patents.google.com/patent/FR2703052B1/en.

178. *See* https://globaldossier.uspto.gov/#/result/publication/FR/2703052/1.

179. Bruno Canard & Robert S. Sarfati, *DNA Polymerase Fluorescent Substrates with Reversible 3'-Tags*, 148 GENE 1, 1 (1994).

180. *Id.*

181. *See id.* at 2–3.

182. *Id.*

183. Zengmin Li et al., *A Photocleavable Fluorescent Nucleotide for DNA Sequencing and Analysis*, 100 PROCS. NAT'L ACAD. SCIS. 414 (2003).

184. Fei Chen et al., *The History and Advances of Reversible Terminators Used in New Generations of Sequencing Technology*, 11 GENOMICS, PROTEOMICS & BIOINFORMATICS 34 (2013).

D. PHASE 4: DISCOVERY OF THE NGS SOLEXA IDEA

Section III.C, *supra*, explained that scientists outside of the Solexa team also worked on the use of solid support arrays, bridge PCR clustering, and SBS read generation. And much of this preliminary research occurred before, or at least in parallel to, the evolution of the Illumina platform. But two professors working at the Chemistry Department at the University of Cambridge established the Illumina NGS system, as it exists today: Shankar Balasubramanian and David Klenerman. Their approach, as initially proposed and refined over several years, combines the three "massively parallel" elements outlined earlier: the solid support array, bridge PCR clustering, and SBS read generation.

The Balasubramanian and Klenerman method was unique compared to the work discussed in Section III.C, *supra*, along two axes. First, the Solexa team developed new ideas and approaches within each of the three sequencing elements. Second, and more critically, the Solexa team revolutionarily chose to combine all three elements—something no other company pursued at the time. These two features set Solexa's platform apart from its competitors. This Section describes the evolution of the Illumina platform, from the initial Solexa idea in 1998 to their first scientific publication in 2008.

In the late 1990s, with the HGP underway, Balasubramanian and Klenerman began working together.[185] The two professors met in 1997, when Balasubramanian—a biochemist studying DNA polymerase—needed help with laser excitation for an experiment during manuscript revisions[186] and sought help from Klenerman—a physical chemist with expertise in laser spectroscopy.[187] This initial collaboration sparked discussions about visualizing DNA polymerase while adding nucleotides in real-time, which combined both of their experimental areas.[188] Specifically, they wanted to

185. Shankar Balasubramanian & David Klenerman, *Journeys of Discovery: Rapid Genome Sequencing*, YOUTUBE (May 18, 2021), .

186. Kevin Davies, *The Solexa Story*, BIOIT WORLD (Sept. 30, 2010), https://www.bio-itworld.com/news/2010/09/30/the-solexa-story (last visited Oct. 2, 2022).

187. *Id.*; Phil Prime, *The Award-Winning Researcher Behind Next Generation Sequencing*, CANCER RSCH. UK (Oct. 15, 2021), https://news.cancerresearchuk.org/2021/10/15/the-award-winning-researcher-behind-next-generation-sequencing/ (transcribing an interview with Balasubramanian).

188. Prime, *supra* note 187. This is essentially a version of SBS. But it is unclear whether Balasubramanian and Klenerman were aware of any other groups pursuing SBS research at this time. The Nyrén paper was released only in 1998, and before that, the only other report of SBS seemed to be in the 1985 Melamede '849 patent—and it is not unexpected that the Cambridge team would not have come across a United States patent when planning basic research projects. Some reports of the Solexa story seem to suggest that Balasubramanian and Klenerman independently conceived of their own SBS idea. Louise Walsh, *Journeys of Discovery*,

capture the exact moment of nucleotide incorporation as it happened—not for the purposes of DNA sequencing, but simply to interrogate the enzyme kinetics of DNA polymerase. To this end, Balasubramanian and Klenerman envisioned the use of a solid support array to anchor a strand of DNA during nucleotide addition, and the use of fluorescent tagging to monitor the addition of nucleotides.[189]

In August 1997, the two decided to use their idea to for "massively parallel," NGS-type DNA sequencing. Balasubramanian, Klenerman, and their two postdocs (Mark Osborne, Colin Barnes) met at the Panton Arms, a pub near Cambridge where they routinely met to brainstorm ideas.[190] There, the group "saw the pieces of the jigsaw come together."[191] Their attempts to watch DNA be synthesized one molecule at a time, on a surface, had been repeatedly failing—they were constantly missing the actual moment of nucleotide incorporation.[192] To overcome this issue, the group proposed the idea of "watch[ing] lots of molecules in parallel at the same time."[193] This parallelization option had two implications: (1) probabilistically, they had be a better chance of "catching" the actual event of incorporation for at least one molecule; and (2) they could determine the sequence of all the DNA molecules on the surface, in parallel.[194] Sketching out the implications of this "massively parallel" sequencing plan on a piece of paper, the Cambridge team calculated that they could improve existing DNA sequencing technologies by up to 100,000-fold.[195]

The exact contours of the Panton Arms idea remain unknown, least of all the underlying biochemistry.[196] But a few months later, in November 1997, Balasubramanian and Klenerman approached venture capitalists at the Abingworth investment firm and presented their 100,000-fold "massively parallel" improvement plan.[197] After nine months of due diligence, in 1998,

---

UNIV. CAMBRIDGE, https://www.cam.ac.uk/stories/journeysofdiscovery-rapidgenomesequencing (last visited Oct. 2, 2022) ("They realised [sic] that if they could *watch* the enzyme copying a genome then they were inadvertently also *reading* the genome. They had discovered a radically new way to sequence DNA").

189. Prime, *supra* note 187. It is unclear what their inspiration for this idea was—whether independent or based on the previous publications suggesting solid support arrays for sequencing.

190. Davies, *supra* note 186; Prime, *supra* note 187.

191. Balasubramanian & Klenerman, *supra* note 185.

192. *Id.*

193. Prime, *supra* note 187.

194. *Id.*

195. *Id.*; Balasubramanian & Klenerman, *supra* note 185.

196. *See* Prime, *supra* note 187.

197. Davies, *supra* note 186.

Abingworth provided seed funding for the team to form a company called Solexa.[198] At this time, Osborne and Barnes were Solexa's only bench chemists.[199]

Solexa first publicly disclosed their sequencing plan in a PCT application filed in 1999 that claimed priority to an unpublished EPO application from 1998.[200] This publication detailed the combination of two out of three modern "massively parallel" elements of modern Illumina sequencing: a solid support array to which fragmented template DNA strands bind; and a roughly outlined sketch of fluorescent nucleotides for SBS (which would later become reversible terminator chemistry).[201] Critically, the publication lacked the bridge PCR clustering step, as the initial Solexa plan focused on *single-molecule* sequencing.[202] As described previously, DNA sequencing typically begins with some form of PCR amplification step to generate sufficient template for eventual base calling. Single-molecule sequencing omits the amplification step so that each individual fragment remains at low copy number.[203]

In the years after this early articulation, Solexa researchers focused primarily on refining the chemistry of their approach to SBS to further improve throughput and reduce technical complexity.[204] During these years, the company began to slowly grow. Additional funding from Abingworth allowed Solexa's facilities to move from the Chemistry Department at Cambridge to a lab at Chesterford Research Park.[205] Solexa hired four new employees: a research director (Harold Swerdlow), a CEO (Nick McCooke), a

198. *Id.*; Balasubramanian & Klenerman, *supra* note 185.

199. Davies, *supra* note 186; Balasubramanian & Klenerman, *supra* note 185.

200. Patent Appl. No. WO 2000/006770 (filed July 30, 1999, claiming priority date of July 30, 1998). The 1998 EPO patent application seems to be the first patent filed by Solexa.

201. *Id.* ("hybridising a polynucleotide molecule to its immobilised complement on the array . . . wherein each nucleotide triphosphate is conjugated at its 3' position to a different label capable of being characterised [sic] optically, determining which label (and thus which nucleotide) has undergone the polymerisation [sic] reaction, and removing the label").

202. *See What happened to Illumina's Single Molecule Sequencing Or Do You Remember Solexa's SMA-seq?*, ENSEQLOPEDIA, http://enseqlopedia.com/2012/08/what-happened-to-illuminas-single-molecule-sequencing-or-do-you-remember-solexas-sma-seq/ (last visited Oct. 2, 2022); Simon Bennett, *Solexa Ltd*, 5 PHARMACOGENOMICS 433, 434–35 (2004).

203. John F. Thompson & Patrice M. Milos, *The Properties and Applications of Single-Molecule DNA Sequencing*, 12 GENOME BIOLOGY 1 (2011).

204. *See* Davies, *supra* note 186.

205. *Id.*; *Solexa: Second-Gen Genetic Sequencing*, UNIV. CAMBRIDGE (July 13, 2015), https://www.enterprise.cam.ac.uk/case-studies/solexa-second-generation-genetic-sequencing/; *History of Sequencing by Synthesis*, ILLUMINA, https://www.illumina.com/science/technology/next-generation-sequencing//llumine-sequencing-history.html (last visited Oct. 2, 2022).

chief science officer (Tony Smith), a medicinal chemist (John Milton), and a bioinformatician (Clive Brown).[206]

Milton focused on redesigning the chemistry of the sequencing platform, modifying aspects of both the solid support array and the SBS reversible terminator nucleotides.[207] In parallel, Solexa diversified their patent portfolio by filing patents on all different aspects of the sequencing technology.[208] However, the actual detection of the fluorescent tags on the SBS nucleotides was failing.[209] Constrained by the single-molecule sequencing format, each incorporated fluorescent nucleotide on a single template strand could not yield a light signal intense enough for accurate base calling.[210] And the template strands themselves, though successfully adhered to the solid support array on one end, kept falling over, rather than standing straight up, which sterically prevented the growth of a complementary strand.[211]

Luckily, Manteia already had a solution to this steric hindrance problem. The Manteia team had visited the Solexa facilities in 2003 and noted Solexa's strength in reversible terminator chemistry but absence of actual sequencing data.[212] Given that Manteia was in a similar position, but with a different strength—functional cluster technology—Mayer found Solexa attractive.[213] So, in 2004, the Manteia group agreed to sell their clustering technology patents to Solexa.[214] Many view the Manteia acquisition as rescuing the Solexa platform: the low signal intensity from *un-amplified* DNA molecules was an insurmountable hurdle of the single-molecule format.[215] With the new possibility of clustered, bridge PCR amplification, Solexa almost instantly sequenced their first genome in 2005.[216] Their target was the bacteriophage phi X174 genome, which Sanger previously sequenced using the pre-Sanger

206. Davies, *supra* note 186.

207. *Id.*

208. *See* discussion *infra* Section IV.B.2.

209. Davies, *supra* note 186.

210. *Id.*

211. *Id.* ("Klenerman tried putting a loudspeaker under the chip blasting high-frequency sound waves to make the DNA stand on end . . . that didn't work.").

212. *See* Whyte, *supra* note 161, at 56.

213. *Id.* at 57.

214. Davies, *supra* note 186.

215. *See* Clara Rodríguez Fernández, *The Man Behind Next-Generation Sequencing* (Mar. 11, 2019), https://www.labiotech.eu/interview/next-generation-sequencing-nick-mccooke/ (quoting McCooke, the former CEO of Solexa, stating that "the bridge amplification technology . . . from a Swiss company called Manteia . . . really saved the day . . . [i]f we hadn't been able to acquire that technology, the project would have failed").

216. *Id.*

sequencing "plus and minus" method.[217] Over a February weekend, Brown, along with two newly hired bioinformaticians (Klaus Maisinger and Tony Cox), assembled the genome by short-read alignment, revealing more than 99.9% accuracy.[218]

To summarize, the Illumina sequencing platform combined three independent elements into a massively parallel process: (1) the use of a solid support; (2) the bridge PCR amplification of DNA fragments to generate clusters; and (3) the technique of SBS. All three elements represent remarkable innovations on their own, with each addressing important bottlenecks at stages of the sequencing process. However, as noted in Section III.C, *supra*, these inventions each existed in some primitive form before Solexa. Therefore, Solexa's key "inventive steps" were: (1) refining the biochemical techniques introduced into each of the three elements, especially in the reversible terminator chemistry for SBS; and (2) uniquely choosing to combine all three features, especially in licensing the bridge PCR clustering technology from Manteia.

E. PHASE 5: EXPANSION AND COMMERCIALIZATION OF SOLEXA/ILLUMINA

The Solexa team had the technological capacity to dominate the NGS market as early as 2005. But to take the next steps in expanding the company and commercializing their NGS method as a platform technology, Solexa required more robust business development practices. Key to this phase of the Illumina story is John West, the CEO of Solexa from 2004 to 2007.[219] West previously worked at Applied Biosystems on automated Sanger sequencing technology, and aspired to turn Solexa into an international company for its next phase of development.[220] Soon after becoming CEO, West negotiated a merger with Lynx Therapeutics, a biotechnology company based in California.[221] Lynx was led by Sydney Brenner, who for a time worked at the Laboratory of Molecular Biology (affiliated with the Medical Research Council), and then moved to California to establish the Molecular Sciences Institute. Lynx was also working on NGS technologies, but focused on a bead-

217. Frederick Sanger et al., *Nucleotide Sequence of Bacteriophage phi X174 DNA*, 265 NATURE 687 (1977).

218. Davies, *supra* note 186.

219. John West, *"A Celebration of Solexa" – A Short Tour of DNA Sequencing History*, https://www.personalis.com/a-celebration-of-solexa-a-short-tour-of-dna-sequencing-history/ (last visited Oct. 2, 2022).

220. *Id.*; Davies, *supra* note 186.

221. Davies, *supra* note 186.

based immobilization approach (rather than a solid support array).[222] Brenner has stated that he began thinking about the Lynx platform in the late 1980s while still in the United Kingdom, but failed to raise the requisite investment to begin the project.[223]

With the Solexa-Lynx merger in March 2005, just one month after Solexa had sequenced its first genome, Solexa became an international public company on NASDAQ.[224] And in 2006, Solexa launched its first sequencer machine, called the 1G Genome Analyzer (GA).[225] This machine could sequence one gigabase of data per run, and an entire genome for $100,000 in three months.[226] The Solexa GA was almost the first high-throughput sequencer on the market, but missed the mark by just one year. The 454 Life Sciences GS20 machine, which used automated Sanger sequencing, was released in 2005.[227]

Across the pond, Illumina had been slowly growing since 1998, founded based on the microarray platform developed by David Walt at Tufts University.[228] The company was focusing on gene expression analysis, using bead-based technology.[229] However, in January 2007, Illumina entered the NGS market with the acquisition of Solexa for approximately $650 million.[230] Again, West was critical in negotiating this acquisition.[231] And in the first month after the acquisition, Illumina sold twelve Solexa GA machines; by the end of 2007, Illumina installed more than 200 GAs in various institutes.[232] Genome sequencing centers and core facilities became more popular, as NGS became more economically feasible. In 2008, Illumina introduced an updated,

222. Nicholas Wade, *SCIENTIST AT WORK: SYDNEY BRENNER; A Founder of Modern Biology Shapes the Genome Era, Too*, N.Y. TIMES (Mar. 7, 2000), https://www.nytimes.com/2000/03/07/science/scientist-work-sydney-brenner-founder-modern-biology-shapes-genome-era-too.html.

223. William A. Wells, *Life After Worms, Lynx Therapeutics, Inc.*, 7 CHEMISTRY & BIOLOGY R191, R191 (2000) ("Most people thought it was too risky . . . [t]hey were pretty much right.").

224. *History of sequencing by synthesis*, *supra* note 205.

225. *Id.*

226. *Id.*

227. *Saying goodbye to 454: how to choose your next NGS platform*, BITESIZEBIO (Dec. 17, 2014), https://bitesizebio.com/22147/saying-goodbye-to-454-how-to-choose-your-next-ngs-platform/ (last visited Oct. 24, 2022).

228. *See generally* Deirdre Bradford Parsons, *Seminal Genomic Technologies: Illumina, Inc. & High-Throughput SNP Genotyping Beadarray Technology* (Nov. 19, 2007) (M.S. thesis, Duke University) (outlining a history of the Illumina company, with a focus on their pioneering microarray system).

229. *See* Davies, *supra* note 186.

230. *Id.*

231. West, *supra* note 219.

232. *Id.*

increased-throughput sequencing machine ("GAII").[233] Finally, in November 2008, Balasubramanian, Klenerman, and approximately 100 other authors published the use of Solexa (now Illumina) sequencing technology for the first time in *Nature*.[234]

Since the initial Panton Arms proposal by Balasubramanian and Klenerman, Illumina has added another 10,000-fold increase in throughput with further optimization.[235] Now, the technology can sequence a human genome for $1,000 in one day, and the life sciences applications of Illumina sequencing go far beyond the basic research purposes that the Cambridge group initially envisioned.[236]

IV. INNOVATION DRIVERS IN THE DEVELOPMENT OF ILLUMINA NGS

Part III, *supra*, described the development history of the Illumina NGS platform, distilled into five distinct phases (**Figure 3**). One practical, motivating goal persisted throughout this story: the desire to facilitate faster and cheaper sequencing of human genomes. However, many additional sources of motivation, features of scientific research, and intellectual property protection strategies catalyzed the development of the Illumina NGS platform. The five stages of development illustrate many different innovation drivers that propelled the Illumina story forward.

This Part describes and analyzes the relevant motivational factors for the scientists and institutions, tracking with the chronological development of Illumina's NGS platform technology. At the highest level, the innovation drivers fall into two distinct categories: an initial foundational period rooted in scientific fascination and altruism, and then a business development period characterized by intellectual property protection and commercialization.

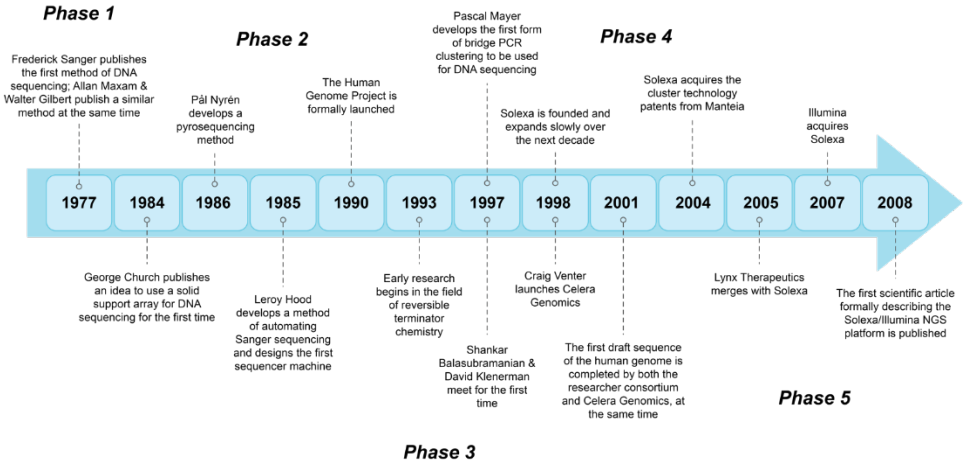
233. *Id.*

234. Bentley et al., *supra* note 64, at 59.

235. Balasubramanian & Klenerman, *supra* note 185.

236. *Id.*; *see* Walsh, *supra* note 188 ("Their hopes for the technology have been exceeded over and over again.").

Figure 3: Timeline of NGS development.



A. FOUNDATIONAL INNOVATION DRIVERS

While several innovation drivers contributed to the remarkable innovation of the Illumina NGS platform, scientific curiosity, altruism, public funding sources, academic recognition, and serendipity motivated researchers to establish a foundation from which the Solexa technology could grow.

1. Initial Scientific Curiosity and a Lack of Patent Protection

In the early stages of the Illumina discovery story, scientists seemed largely motivated by scientific curiosity, rather than commercialization or intellectual property protection. As discussed in Section III.A, *supra*, the first two methods of DNA sequencing were published almost simultaneously in 1977: Maxam-Gilbert sequencing at Harvard University,[237] and Sanger sequencing at the Laboratory of Molecular Biology in Cambridge.[238] The scientists at this stage seem to have been motivated primarily by basic scientific curiosity. DNA sequencing began as a way of answering scientific questions to supplement basic molecular biology research.

Neither foundational sequencing method was patented, although the landscape at the time suggests that Maxam-Gilbert sequencing could have been.[239] At the time, U.S. universities and scientists rarely sought molecular biology patents based on academic research, though some existed: for

237. Maxam & Gilbert, *supra* note 89 and accompanying text.

238. Sanger et al., *supra* note 88.

239. *See* Holman, *supra* note 90, at 1054; Robert Cook-Deegan & Christopher Heaney, *Patents in Genomics and Human Genetics*, 11 ANN. REV. GENOMICS & HUM. GENETICS 383, 392 (2010).

example, Purdue University held a patent (granted in 1973) on a rudimentary method of DNA sequencing and Johns Hopkins University held a patent (granted in 1977) on pro-inflammatory nucleic acids.[240] But the decision for Maxam and Gilbert to forgo patent rights was not atypical; patent protection for U.S. university inventions only became normal practice after the 1980 Bayh-Dole Act and the Cohen-Boyer patent.[241] Indeed, Gilbert described having the sequencing invention in hand two years before publishing it in 1977, but noted that he had not considered patenting at all, given the ethos of the time.[242] Gilbert even prepared handouts on how to perform sequencing and distributed them to other scientists to encourage use—activity that would limit potential patent rights[243]—because he considered it merely a "basic research method[]."[244] Gilbert stated that his perspective on patenting was only shifted in the late 1970s, leading up to the Bayh-Dole Act, which he described as the government instructing university scientists to file patents for commercialization purposes.[245]

Sanger also forewent patent rights to his method of DNA sequencing. He received funding through the Medical Research Council, which at the time did not allow funded researchers to seek patent protection.[246] In 2001, during his Nobel Prize interview, Sanger expressed that even without this policy, he would not have wanted to patent the approach because he "wouldn't want to keep [his] work secret."[247] This anti-patent perspective, at the time, was not uncommon among basic science researchers.

240. *See* Cook-Deegan & Heaney, *supra* note 239, at 392; U.S. Patent No. 3,730,844 (filed Aug. 27, 1971); U.S. Patent No. 4,024,222 (filed Oct. 30, 1973).

241. *See* Cook-Deegan & Heaney, *supra* note 239, at 392; U.S. Patent No. 4,237,224 (filed Nov. 4, 1974).

242. *Walter Gilbert Interview*, NOBEL PRIZE (Mar. 22, 2009), https://www.nobelprize.org/prizes/chemistry/1980/gilbert/interview/.

243. *Id.*

244. Cook-Deegan & Heaney, *supra* note 239, at 392.

245. Gilbert expressed that even if he had patented his method of chemical DNA sequencing, it would not have made a difference, as the patent would have expired before the HGP (an entirely non-commercialized effort) was even completed. *See Walter Gilbert Interview*, *supra* note 242 (stating that he learned that patenting was necessary for commercialization, and that he "stopped thinking of patenting as an evil, [and] began to realize it as a social benefit," given the public disclosure aspect). In 1978—one year after the Maxam-Gilbert sequencing publication—Gilbert filed his first patent on bacterial-mediated production of insulin. U.S. Patent No. 4,411,994 (filed June 8, 1978). This patent was later licensed to Biogen. Marjorie Sun, *Biogen Pays High Price for Harvard Patent*, 222 SCI. 1309 (1983).

246. *Frederick Sanger Interview*, *supra* note 4.

247. *Id.* ("I wouldn't have wanted to [take patents] I don't think because I wouldn't want to keep my work secret . . . I don't think it would be fair.").

Overall, it appears that the foundational first-generation work needed to set the stage for later development in NGS did not specifically require patent protection or commercialization potential as incentivizing forces. The scientists appear to have been driven by a primary interest in molecular biology and biochemistry research.

2. *Altruism and Commercialization Antagonism in the Human Genome Project Era*

Two competing perspectives emerged in the second phase of the Illumina story, when scientists around the world recognized the potential impact of sequencing the first human genome.

Some scientists saw the HGP as a step towards revolutionizing healthcare and theorized that global access to a complete reference human genome sequence would be invaluable for modern medicine. Many felt that the HGP was the first step towards a world in which patients could routinely have their genomes sequenced in doctor's offices. In keeping with this altruistic ideology, researchers participating in the HGP received noncommercial, public funding through the NIH and the Department of Energy in the United States and through the Medical Research Council and the Wellcome Trust in the United Kingdom.[248] Ultimately, the goal of the HGP was to produce a human genome sequence that was entirely unpatented and freely accessible.[249]

Other scientists saw the human genome sequence as a potential trove of marketable data. The competing sequencing effort launched by Venter's company, Celera, received private funding and sought to generate a proprietary human genome sequence with patent protection on as many as 6,500 genes.[250] Although Venter's patent strategy fell through, Celera briefly licensed its genomic data to various institutions.[251]

Both the HGP and Celera completed their respective human genome sequences at the same time in 2001, with the HGP publishing a complete sequence in *Nature* and Celera publishing a partial one in *Science*. Researchers initially considered the Celera version "superior to the public [HGP] sequence"[252]—likely due to Celera's use of shotgun assembly[253]—allowing Celera to transiently profit from their data.[254] However, over the next year, the

248. HGP Fact Sheet, *supra* note 112.
249. *See id.*
250. Jeff Fox, *Sequencing, Patenting Surge*, 17 NATURE BIOTECHNOLOGY 1148, 1148 (1999).
251. Jim Kling, *Where the Future Went*, 6 EMBO REPS. 1012, 1012 (2005).
252. *Id.*
253. *See* discussion *supra* Section III.B.
254. Heidi L. Williams, *Intellectual Property Rights and Innovation: Evidence from the Human Genome*, 121 J. POLITICAL ECON. 1, 2 (2010).

costly Celera sequence lost its appeal, as the publicly accessible HGP data increased in quality.[255] With this, Celera bowed out of the genomics race to instead pursue drug discovery and diagnostic development.[256] By 2003, Celera turned their sequence data entirely over to the public domain.[257]

The HGP and Celera outlooks fundamentally split along ideological lines. Most of the scientific community was averse to the idea of commercializing DNA, viewing DNA as the most fundamental building block of life, generating research that "touches human lives directly," with "human beings or their cells . . . [as] the objects of [that] research."[258] For these scientists, gene patents were extremely controversial.[259] The Supreme Court initially enabled these patenting efforts in the 1980 *Diamond v. Chakrabarty* decision by allowing inventors to patent living organisms.[260] Based on this decision, Venter sought patent protection for expressed sequence tags (ESTs)—fragments of cDNA, not whole genes—in the early 1990s.[261] Many disapproved of this trajectory, given the concern that an EST patent landscape would restrict future research.[262] And when Venter pushed for a similar path during the HGP, much of the scientific community was even more troubled.[263] These years also saw the attempted patenting of the *BRCA1* and *BRCA2* genes, which was met with "overwhelmingly negative" public perception.[264] Some expressed concern that as many as 20% of human genes had been patented as of 2005,[265] possibly precluding the development of future sequencing technologies and diagnostic tests.[266]

255. *Id.* The HGP data was uploaded to the National Center for Biotechnology Information database.

256. *Id.*

257. *Id.*

258. Cook-Deegan & Heaney, *supra* note 239, at 388.

259. *Id.* at 389.

260. *See* Diamond v. Chakrabarty, 447 U.S. 303 (1980).

261. Daniel J. Kevles & Ari Berkowitz, *The Gene Patenting Controversy: A Convergence of Law, Economic Interests, and Ethics*, 67 BROOK. L. REV. 233, 235 (2001).

262. *Id.* at 237–39.

263. *Id.* at 245–48.

264. Cook-Deegan & Heaney, *supra* note 239, at 389–90.

265. *See* Kyle Jensen & Fiona Murray, *Intellectual Property Landscape of the Human Genome*, 310 SCI. 239 (2005).

266. Christopher M. Holman, *Debunking the Myth that Whole-Genome Sequencing Infringes Thousands of Gene Patents*, 30 NATURE BIOTECHNOLOGY 240 (2012). This turned out to not be entirely true. The substantive patentability doctrines, even for pre-*Myriad* gene patents, dictated sufficient specificity in claim language. With this, many of the alleged 20% of human gene patents were fairly narrow in scope, suggesting that whole-genome sequencing was never at risk of infringing on thousands of gene patents. Holman argues that these fears were based on a misinterpretation of the Jensen & Murray article. *Id.*

In the end, however, a perspective more aligned with the Bermuda Principles—which implicitly denounced gene patenting—won out. Post-*Chakrabarty* case law restricted patent eligibility for biological inventions,[267] the public increasingly viewed Venter as a villain,[268] and a global distaste for gene patents grew.[269] The idea that a company might profit from DNA sequence data eventually dissipated, leaving only DNA sequencing *instruments* up for patent protection.

Thus, overall, it seems that the central motivating factor for sequencing technology development during the HGP era was altruism. To a lesser extent, practical considerations were also likely important. In addition to the desire to secure a full-length, globally available human genome sequence, the HGP researchers also innovated out of frustration with the slow speed of the existing sequencing methods. Indeed, despite its eventual success, the HGP dramatically revealed the prohibitive costs associated with Sanger sequencing technologies, even once automated.

3. Academic Recognition with Science and Technology Prizes

In addition to altruism, professional recognition also likely motivated NGS researchers. Many knew that improving DNA sequencing technologies would provide great social value, but not everyone agreed with the level of importance. Anecdotally, in the early 2000s—when many different sequencing startups were in the early stages of development—high impact journals accepted many publications related to DNA sequencing development. This likely incentivized further research in this area.

Prize-awarding bodies have now recognized many of the discoveries associated with the development of the Illumina platform. For example, in 1980, Sanger, Gilbert, and Paul Berg jointly received the Nobel Prize in Chemistry for Sanger and Gilbert's DNA sequencing research and Berg's recombinant DNA studies.[270]

267. *See, e.g.*, Shahrokh Falati, *Patent Eligibility of Disease Diagnosis*, 21 N.C. J.L. & TECH. 63 (2020).

268. *See, e.g.*, Witkowski, *supra* note 120, at 786 (recounting the various epithets ascribed to Venter, including "maverick, publicity hound, risk-taker, brash, controversial, genius, manic, rebellious, visionary, audacious, arrogant, feisty, determined, provocative").

269. Cook-Deegan & Heaney, *supra* note 239, at 390–96.

270. *The Nobel Prize in Chemistry 1980*, NOBEL PRIZE, https://www.nobelprize.org/prizes/chemistry/1980/summary/ (last visited Nov. 25, 2022). Gilbert later went on to pursue other commercial endeavors. *See* Kanigel, *supra* note 106. Sanger remained with the Medical Research Council, and personally disavowed patent protection and other forms of commercialization for the rest of his life on the bench. *See Frederick Sanger Interview*, *supra* note 4.

Other NGS researchers received prizes that were focused on the practical implications of NGS. Over the years, the scientific community began to feel that Nobel Prizes were too restricted to "basic" science discoveries.[271] To fulfill the perceived gap in awards for more "applied" technological research, Finland established the Technology Academy in 2003,[272] which now awards the Millennium Technology Prize to innovations that "promote the well-being of humankind and society," and are specifically "appli[ed] with global commercial viability."[273] The Nobel Prize and the Millennium Technology Prize each award approximately $1 million. Balasubramanian and Klenerman each received the 2020 Millennium Technology Prize for NGS technology.[274] Notably, however, this prize did not exist during the critical years of technological advancement in the Illumina discovery story (i.e., from 1998 to the early 2000s)—and likely did not serve as a motivating factor for the scientists.

Yet another scientific prize was established in 2013, called the Breakthrough Prize in Life Sciences.[275] With funding from Mark Zuckerberg, Priscilla Chan, Sergey Brin, Yuri Milner, and Anne Wojcicki, [276] the Breakthrough Prizes each offer $3 million—the largest scientific award currently available.[277] Balasubramanian, Klenerman, and Mayer jointly received the 2022 Breakthrough Prize in Life Sciences.[278] This award was one of the first explicit recognitions of Mayer's critical involvement in the Illumina discovery story, as his work at Manteia went relatively unrecognized for several years.[279]

---

271. *See DNA sequencing pioneers win 1mn euro tech 'Nobel' prize*, PHYSORG (May 18, 2021), https://phys.org/news/2021-05-dna-sequencing-1mn-euro-tech.html.

272. *Technology Academy Finland*, MILLENNIUM TECH. PRIZE, https://millenniumprize.org/about-us/in-english/ (last visited Nov. 25, 2022).

273. *Story*, MILLENNIUM TECH. PRIZE, https://millenniumprize.org/prize/story/ (last visited Nov. 25, 2022).

274. *2020 Next Generation DNA Sequencing*, MILLENNIUM TECH. PRIZE, https://millenniumprize.org/winners/next-generation-dna-sequencing/ (last visited Nov. 25, 2022).

275. *Life Sciences Breakthrough Prize*, BREAKTHROUGH PRIZE, https://breakthroughprize.org/Prize/2 (last visited Nov. 25, 2022).

276. Rory Carroll, *Breakthrough Prize announced by Silicon Valley entrepreneurs*, GUARDIAN (Feb. 20, 2013, 12:00 AM), https://www.theguardian.com/science/2013/feb/20/breakthrough-prize-silicon-valley-entrepreneurs.

277. J.P., *Take that, Alfred*, ECONOMIST (Feb. 20, 2013), https://www.economist.com/babbage/2013/02/20/take-that-alfred.

278. *Winners of the 2022 Breakthrough Prizes in Life Sciences, Fundamental Physics and Mathematics Announced*, BREAKTHROUGH PRIZE, https://breakthroughprize.org/News/65 (last visited Nov. 25, 2022).

279. Mayer, *supra* note 157; Aubourg, *supra* note 154. Mayer noted that his inspiration for the bridge PCR clustering idea came from his post-doctoral research at the University of

Finally, a unique form of prize recognition occurred in 2017, when Queen Elizabeth II knighted Balasubramanian. The English monarchy has routinely granted damehood and knighthood to people who make significant scientific contributions, including Isaac Newton, Tim Berners-Lee, Jane Goodall, and Sarah Gilbert.[280] Balasubramanian's knighthood was attributed to his "services to science and medicine."[281] He has independently received several other, smaller scientific awards over the years.[282]

4. Federal Funding for Early Academic Research

Most of the people involved in the Illumina discovery story began their careers as scientists working in universities or other academic settings (**Table 2**). Each person or team followed a similar trajectory in the competitive NGS era of the early 2000s. As each group made progress in the development of a marketable NGS platform, the group would typically establish a startup company and run the company in parallel with their academic research. For example, Hood (Applied Biosystems), Venter (Celera Genomics), Brenner (Lynx Therapeutics), and Balasubramanian and Klenerman (Solexa) all followed this path.

With this canonical structure, national governments funded the bulk of research and development in the early phases of the Illumina development story. The researchers who developed first-generation sequencing technologies (Sanger, Maxam, Gilbert, Hood) all received federal research grants in the United States and/or the United Kingdom. Sanger received funding from the Medical Research Council in the United Kingdom, which is similar to the NIH in the United States. Maxam, Gilbert, and Hood received NIH grants. In a 2002 lecture, Hood explained that he viewed venturing into commercialization as requiring an appreciation of "long-term vision and

Strasbourg and the University of Ottawa. Mayer, *supra* note 157. His original terminology for the technique—"colony" sequencing—was later adopted by Church and other scientists, who developed a similar immobilization-based sequencing technique that they termed "polony" sequencing. Jay Shendure et al., *Accurate Multiplex Polony Sequencing of an Evolved Bacterial Genome*, 309 SCI. 1728 (2005) (describing the polony protocol out of George Church's group at Harvard). This concept would eventually become a key component of third-generation sequencing. *See* discussion *infra* Part V.

280. *Scientists Who Have Received a CBE, OBE, MBE, Knighthood or Damehood*, GAZETTE, https://www.thegazette.co.uk/all-notices/content/103527 (last visited Nov. 25, 2022).

281. *Professor Sir Shankar Balasubramanian FRS*, ROYAL SOC'Y, https://royalsociety.org/grants-schemes-awards/career-pathway-tracker/shankar-balasubramanian/ (last visited Nov. 25, 2022).

282. *Honour for Trinity Fellow Professor Shankar Balasubramanian*, TRINITY COLL. CAMBRIDGE, https://www.trin.cam.ac.uk/news/honour-for-trinity-fellow-professor-shankar-balasubramanian/ (last visited Nov. 25, 2022).

potential" and that "it is often true that radical new opportunities can progress more effectively as new startups rather than through the licensing to preexisting companies."[283] Hood's development of the automated sequencer machines relied on National Science Foundation funding, which generated "one of the most outstanding [programs] ever funded by the federal government."[284]

The geographic localization of NGS research suggests government funding was a key innovation driver. Despite *global* investment into the HGP—and general, widespread interest in sequencing technology development—the participants in the Illumina development story operated mainly in the United States and the United Kingdom. One explanation for this is the unique culture surrounding DNA and molecular biology-based research in both geographical areas. Decades of research investment turned both regions of the world into epicenters of discovery and expertise.

In later stages of pre-NGS research, scientists including Venter, Church, Mayer, Nyrén, Canard, Sarfati, Balasubrmanian, and Klenerman, also received federal funding through government grant programs in the United States, Canada, and Europe. Balasubramanian and Klenerman, for example, received funding from the Biotechnology and Biological Sciences Research Council.[285] Eventually, however, private funding sources took over.[286]

5. Serendipity in the Initial Solexa Idea

The Solexa team credits the August 1997 meeting at the Panton Arms as being the moment that the NGS idea was truly launched. This meeting highlights an instance of serendipity in the NGS invention story. Balasubramanian and Klenerman began working together for a project entirely unrelated to NGS, with Balasubramanian simply seeking out Klenerman's laser spectroscopy expertise to help with paper revisions. And the initial focus of Balasubramanian and Klenerman's research was on understanding the enzyme kinetics of DNA polymerase, not designing a commercialized NGS platform. Only at the Panton Arms did the team decide to implement a parallelization

283. Leroy Hood, President and Director, Institute for Systems Biology, Commemorative Lecture for the 2002 Kyoto Prize in Advanced Technologies, My Life and Adventures Integrating Biology and Technology (2002).

284. *Id.*

285. *Blog: Into the Unknown – Why Blue-Sky Research is Vital for Scientific Breakthroughs*, MILLENNIUM TECH. PRIZE (Jan. 31, 2022), https://millenniumprize.org/news-articles/blog/into-the-unknown-why-blue-sky-research-is-vital-for-scientific-breakthroughs/ [hereinafter Balasubramanian & Klenerman Millennium Prize Blog].

286. *See* discussion *infra* Section IV.B.1.

approach in their experiments, creating the possibility for DNA sequencing as an application.

Even after Balasubramanian and Klenerman turned their focus to NGS technologies, they described their work as basic, "blue skies" research.[287] Like most of the scientists that contributed to NGS technologies, Balasubramanian and Klenerman focused on solving general problems of molecular biology and biochemistry, such as the functionality of DNA. The prospect of translating this fundamental work into a commercialized sequencing technology was not necessarily an initial motivator for many involved, including the two Solexa founders. As Balasubramanian and Klenerman have explained, they "were just following [their] curiosity about the molecular machines that nature uses to copy . . . DNA."[288] And in fact, much of the Solexa team lost interest in the project when its goals became more "clinical" or "applied" in nature. Brown and several other scientists left Solexa specifically when the "scientific and commercial priorities chang[ed]," with Brown stating that he "wouldn't have left had we not done a human genome."[289]

B. BUSINESS-ORIENTED INNOVATION DRIVERS

Once the Solexa scientists launched their NGS platform, a different set of innovation drivers began to take over in relative importance. Increased research and development costs for the growing Solexa NGS platform necessitated private funding sources, a robust patent portfolio, well-timed licensing, dedication to commercialization, and aggressive litigation.

1. Transitioning into Private Funding Sources

By the time Balasubramanian and Klenerman launched their collaboration, the innovative landscape propelling NGS researchers forward had shifted. As discussed in Section III.C, *supra*, the turn of the century saw the independent discovery and development of many similar DNA sequencing techniques, which would later fit together into the now-canonical four-step NGS platform. These new, exciting ideas all shared one critical feature: their increased cost, relative to first-generation sequencing methods. To expedite the sequencing process, scientists in the United States and the United Kingdom focused on pursuing new types of terminator chemistry and solid support array configurations, requiring significant resources for long-term optimization.

Because of the significant increase in research and development costs at this later stage of the Illumina development story, private funding sources

287. Prime, *supra* note 187; Balasubramanian & Klenerman, *supra* note 185.
288. Balasubramanian & Klenerman Millennium Prize Blog, *supra* note 285.
289. Davies, *supra* note 186.

became much more important for many companies. Indeed, part of Solexa's (now Illumina's) success likely arose from the early influx of funding the Solexa team received from Abingworth, an investment firm interested in supporting DNA sequencing research, among other life sciences technologies. At this time, many scientists around the world had founded sequencing-based startup companies, and investor conferences to recruit funding from firms interested in DNA sequencing were becoming quite common. As discussed in Section III.E, *supra*, Solexa deliberately recruited several business-oriented team members to attend these conferences and present data from their nascent sequencing platform. Compared to other participants at these conferences, the Solexa team offered a more functional platform at earlier stages—likely justifying the financial support they received.[290] Indeed, more recently, Mayer has expressed his view that the difference between Solexa and Manteia was that "Solexa had the confidence of their investors, something [Manteia] didn't have . . . [Solexa's investors] believed in the project and wanted it to happen; ours saw out-of-core cash burn and wanted to cease diverting their attention."[291]

2. Developing a Strong Patent Portfolio

Unlike the scientists in the "first-generation" DNA sequencing era, Balasubramanian and Klenerman sought patent protection almost immediately after they envisioned the Solexa idea, to lay a foundation for future commercialization. Balasubramanian initially pitched their idea to researchers participating in the non-commercialized HGP.[292] But because they had not yet developed the technology, the HGP had little use for their idea and the Cambridge team "couldn't think of any other way[, besides starting a company,] of pulling together the kind of resource[s] that [they] need[ed]."[293] Indeed, the team approached Abingworth mere months after the Panton Arms meeting and founded Solexa the very next year, filing their first patent in July.[294]

Strong patent protection remained core to the Solexa (now Illumina) story throughout its development. And now, Illumina owns patents on virtually every eligible aspect of their technology.[295] For example, the physical

290. *See id.*

291. Whyte, *supra* note 161, at 57.

292. Prime, *supra* note 187.

293. *Id.*

294. Davies, *supra* note 186; Patent Appl. No. WO 2000/006770 (filed July 30, 1999, claiming priority date of July 30, 1998).

295. *See Illumina virtual patent marking*, ILLUMINA, https://www.illumina.com/company/legal/patents.html (last visited Oct. 22, 2022).

sequencer machines that house the sequencing reactions are protected by patents on methods of imaging the growing DNA strands, the imaging system itself, and structural aspects of the flow cell surface.[296] Similarly, the ancillary biochemical components of the sequencing reactions are protected by patents on various polymerases and buffers.[297] Many of these features are outside of the scope of this Article. However, they are also not the "core" elements that make the Illumina platform "massively parallel." That is, if not for the patents on the three key Illumina elements, a competing sequencing company could likely construct an Illumina-style sequencer machine that functioned with some equivalence.[298] It is the protection over the solid support array, bridge PCR clustering, and SBS chemistry (specifically, the modified reversible terminator nucleotides) that ties up the Illumina platform among other types of NGS. Each Section *infra* traces the development of a patent portfolio for these three core elements, beginning at the turn of the century and persisting with continuation patents still being filed on each element today.

a) Solid Support Array

The use of a solid support array was always part of the Solexa idea, originating from its ancestral basic science project. Solexa's first publicly available patent application (filed in 1999) claimed "[a] device comprising an array of molecules capable of interrogation and immobilised [*sic*] on a solid surface . . . wherein each molecule is immobilised [*sic*] at one or more points, by specific interaction with the surface."[299] After this first disclosure, they patented several other permutations of the solid support concept, spawning several patent families on different array architectures. For example, the "Arrayed Biomolecules" U.S. patent family begins in 2001 with an application claiming a slightly narrower articulation of the solid support array, including the use of oligonucleotides anchored to the array to bind to target DNA molecules.[300]

Over time, the solid support array patents became more complex, requiring integration with other aspects of the platform—likely to overcome the patent novelty and nonobviousness hurdles. Now, Solexa's patents primarily focus on many of the secondary biochemical factors that support immobilization, e.g., the ligase enzymes used for adapter attachment, the

296. *See id.*

297. *See id.*

298. *See The Next Few Years in DNA Sequencing*, 41J BLOG (May 23, 2021, 3:53 AM), https://41j.com/blog/2021/05/the-next-few-years-in-dna-sequencing/.

299. Patent Appl. No. WO 2000/006770 claim 1.

300. U.S. Patent No. 6,787,308 (filed Jan. 30, 2001) (granted Sept. 7, 2004).

methods of adapter attachment, the adapters themselves, and the siderophores used to help with preparation.[301]

b) Bridge PCR Clustering

Manteia filed the first PCT applications on Mayer's bridge PCR clustering technology in 1997.[302] These early applications were directed to a method of DNA amplification that includes a possible bridge configuration, with claims specifying the degree of immobilization of different ends of DNA strands.[303] The "Method of Nucleic Acid Amplification" U.S. patent family begins in 2001, with an application describing the use of a solid support featuring bridge PCR amplification in moderate detail.[304] A similar 2003 patent application (granted in 2011) has equally broad claims, but also includes drawings indicating a more detailed conception of the bridge PCR technique.[305] After Manteia licensed these patents to Solexa,[306] Solexa filed continuation applications regularly until each family's expiration (occurring from 2018 to 2020), gradually narrowing claim breadth regarding the specifics of the PCR process on the solid support.[307]

Notably, another U.S. patent family, filed earlier than the Manteia patent portfolio, also discloses bridge PCR clustering. Researchers at Mosaic Technologies and the Whitehead Institute for Biomedical Research filed the first application was filed in 1994.[308] The inventors, Christopher Adams and Stephen Krohn, filed a series of continuation applications up until 2000.[309] However, they lacked a complete understanding of the clustering process—while it was clear that some degree of localized amplification was occurring,

301. *See, e.g.*, U.S. Patent No. 8,877,939 (filed Feb. 23, 2011) (granted Nov. 4, 2014) (claiming ligation methods); U.S. Patent No. 10,525,437 (filed Jan. 8, 2018) (granted Jan. 7, 2020) (claiming adapter layout on solid support array and sequences of those adapters).

302. Patent Appl. No. WO 1998/044151 (filed Apr. 1, 1998) (published Oct. 8, 1998); Patent Appl. No. WO 1998/044152 (filed Apr. 1, 1998) (published Oct. 8, 1998). Mayer noted that the initial concept was "separated in two distinct inventions at the demand of [GlaxoWellcome's] patent department." Mayer, *supra* note 157.

303. *See, e.g.*, Patent Appl. No. WO 1998/044151 claim 27.

304. U.S. Patent Appl. No. 2004/0096853 (filed Dec. 7, 2001) (published May 20, 2004).

305. U.S. Patent No. 7,985,565 (filed June 2, 2003) (granted July 26, 2011) (illustrating the amplification strategy in FIG. 1B).

306. *See* discussion *supra* Section III.D.

307. *See, e.g.*, U.S. Patent No. 9,593,328 (filed Jan. 20, 2015) (granted Mar. 14, 2017); U.S. Patent No. 10,370,652 (filed Feb. 22, 2016) (granted Aug. 6, 2019).

308. U.S. Patent No. 5,641,658 (filed Aug. 3, 1994) (granted June 24, 1997).

309. *See, e.g.*, U.S. Patent No. 6,468,751 (filed June 9, 2000) (granted Oct. 22, 2002).

they lacked the imaging data to support a determination of clustering.[310] Manteia later acquired this patent family and licensed it to Solexa.[311]

c) SBS Read Generation

As discussed in Section II.B.1.c, *supra*, reversible terminator nucleotides facilitate the SBS element of the Illumina platform. One of the first Solexa disclosures, a 2000 PCT application, claims a nascent conceptualization of reversible termination.[312] Although other researchers had suggested versions of SBS before,[313] the 2000 PCT application is one of the first publications to articulate an SBS method with an exogenous, removable label.[314] The only prior discussion of reversible terminator chemistry in the context of DNA sequencing was most likely in the 1994 Canard and Sarfati publication.[315] Notably, the early Solexa application did not focus specifically on the nucleotides. It covered almost the entire Solexa platform as envisioned at the time, with claims directed to a sequencing device, the immobilization of DNA strands on a surface, and the method of sequencing itself.

Soon after, however, Solexa began to file patents on the more individualized components of its technology, with an emphasis on the reversible terminator nucleotides. The "Modified/Labelled Nucleotides" U.S. patent family begins in 2002, with a patent application (granted in 2006) containing broad genus claims directed to a nucleotide with: (1) a "protecting group" attached to the deoxyribose sugar at the 2' or 3' oxygen atom; and (2) a "detectable label" attached to the base via a "cleavable linker."[316] These two elements correspond to the modern-day 3'-*O*-blocking group and the fluorescent dye, respectively.[317] At this stage, this patent family provided no details as to the chemical structures of the protecting group, the detectable

310. Whyte, *supra* note 161, at 54.

311. *See id.*

312. Patent Appl. No. WO 2000/006770 (filed July 30, 1999, claiming priority date of July 30, 1998); *see supra* text accompanying note 165.

313. *See* discussion *supra* Section III.C.3.

314. Patent Appl. No. WO 2000/006770 (claiming a method where "each nucleotide triphosphate is conjugated . . . to a different label . . . determining which label . . . has undergone the polymerisation [sic] reaction, and removing the label"). There is, at least, a single 1994 patent (claiming a 1989 priority date) that claimed a similar modified nucleotide, but integrated into an entire sequencing method: "optically-labeled derivatives of four nucleotide 4'-triphosphates . . . where said optically-labeled derivatives comprise a *blocking group at the 3' portion thereof*, said blocking group comprising *an optical label capable of being removed to expose the 3' portion thereof*" (emphasis added). U.S. Patent No. 5,302,509 (granted Apr. 12, 1994).

315. *See* Canard & Sarfati, *supra* note 179.

316. U.S. Patent No. 7,057,026 (granted June 6, 2006).

317. *See* discussion *supra* Section II.B.1.

label, or the cleavable linker, aside from a single dependent claim to the detectable label as a fluorophore.

In subsequent years, Solexa filed increasingly narrower continuation applications, swirling around the single reversible terminator species that Illumina uses today: a nucleotide with an azidomethyl 3'-*O*-blocking group.[318] In 2003, a PCT application claimed a nucleotide with a "removable 3'-OH blocking group" where the 3' carbon atom has an oxygen atom bonded to any one of several chemical moieties.[319] This application also specified some parameters for the detectable label and cleavable linker, specifically, that the label may be a fluorophore and the linker may be "acid labile, photolabile, or contain[] a disulfide linkage."[320] Another 2003 application (granted in 2008) claimed specific chemical structures for the cleavable linker.[321] Solexa continued this rigorous patent acquisition strategy for several years.[322] The most recent patent in this family, filed in 2020, claims a much narrower genus: a nucleotide with a 3'-*O*-azidomethyl group, a single cleavable linker structure family (benzene-based, but with several permutations possible), and a fluorophore tag.[323] Milton, the first medicinal chemist hired when Solexa began to expand, is an inventor on even the newest applications.

As suggested in Section III.C.3, *supra*, the Solexa researchers were not the first to propose SBS. They were also not the first to disclose the idea of reversible terminator chemistry in the context of nucleotides. For example, Andrew Hiatt and Floyd Rose filed a 1995 patent application that claimed nucleotides with 3' removable blocking moieties.[324] These two inventors hold several other early U.S. patents directed to critical chemical structures in the

318. Bentley et al., *supra* note 64, at 53. Notably, 3-*O*-azidomethyl nucleosides were reported in 1991, but with no detectable label added. Sergey Zavgorodny et al., *1-alkylthioalkylation of Nucleoside Hydroxyl Functions and Its Synthetic Applications: A New Versatile Method in Nucleoside Chemistry*, 32 TETRAHEDRON LETTERS 7593 (1991).

319. Patent Appl. No. WO 2004/018497 claims 1-5 (where claim 4 is specifically directed to an azidomethyl group) (filed Aug. 22, 2003).

320. *Id.*

321. U.S. Patent No. 7,414,116 (filed Aug. 22, 2003) (granted Aug. 19, 2008).

322. *See Illumina virtual patent marking*, *supra* note 295.

323. U.S. Patent No. 11,028,115 (filed Sept. 28, 2020) (granted June 8, 2021).

324. U.S. Patent No. 5,872,244 (filed June 7, 1995) (granted Feb. 16, 1999).

reversible terminator nucleotide space.[325] Solexa licensed this patent family in 2005.[326]

Overall, it seems that the Solexa researchers recognized, very early on, that they would incur substantial research and development costs in putting together a robust NGS platform. They then chose to invest considerable effort in establishing a robust patent portfolio, as one way of scaffolding around this goal. The contrast between this approach and that of the researchers dedicated to first-generation sequencing technologies is striking. Prior to the passage of the Bayh-Dole Act (and the Solexa collaboration), molecular biologists tended to eschew the notion of intellectual property protection. Indeed, Sanger sequencing existed for quite some time before researchers sought any patents. But Sanger sequencing was initially a low-cost method performed at a very small scale. As soon as researchers saw the potential in scaling up Sanger sequencing, they also recognized that it could become cost-prohibitive. Thus, Hood's pursuit of an automated sequencer machine—to speed up the sequencing process—almost immediately dovetailed with iterative patent filing. The Solexa researchers likely attracted more investor support than their competitors, and certainly than their first-generation sequencing predecessors, due to their robust intellectual property rights.

3. Strategic Licensing

During the business expansion phase of the Solexa/Illumina story, the company licensed the cluster technology patents from Manteia. This licensing deal likely rescued the Solexa platform, which was at a standstill and had failed to generate any meaningful sequencing data. Compared to other sequencing companies working on similar NGS platforms at the same time, this was a remarkably unique decision. When Solexa acquired the cluster patents from Manteia, the scientific team effectively abandoned the alternative flow cell configurations they were pursuing. Relative to other groups which were seemingly attached to specific pipeline components, the Solexa team prioritized only the *ultimate* output of an effective sequencing method—rather than certain features (e.g., their former flow cell configurations). Solexa's pivot to cluster technology reflects a prioritization of business goals, rather than scientific ideals. This approach can likely be attributed to the business leaders that Solexa hired in the early 2000s.

325. *See, e.g.*, U.S. Patent No. 5,763,594 (filed June 7, 1995) (granted June 9, 1998); U.S. Patent No. 5,808,045 (filed June 7, 1995) (granted Sept. 15, 1998); U.S. Patent No. 6,214,987 (filed June 7, 1995) (granted Apr. 10, 2001).

326. *Solexa Strengthens Patent Position in Next-Generation Genetic Analysis*, TECH. NETWORKS GENOMICS RSCH. (Nov. 9, 2005), https://www.technologynetworks.com/genomics/news/solexa-strengthens-patent-position-in-nextgeneration-genetic-analysis-209745.

4. Commercialization Potential

The prospect of being the first company to commercialize an NGS machine motivated Solexa and other startup companies during the early 2000s. Those involved in the Illumina NGS journey—from the initial Solexa idea at the Panton Arms to the currently available sequencing machines—repeatedly attribute the success of the platform to their timing, rather than a specific innovation. Klenerman has stated that he believes the Solexa platform is now used so widely simply because their team was one of the first to commercialize the technology.[327] Milton similarly expressed that "Illumina dominates [because] they got there first," highlighting that once a genome sequencing center implements a specific NGS company's machine, the center's staff adapt to that machine's methodology, and are less likely to switch to a different type of technology.[328] And Smith suggested that if the GA machines reached the market just two years later, the difference in competition would have been enormous.[329] Indeed, in the years that followed the entry of the Solexa sequencer machine onto the market, many competitor sequencing companies successfully assembled their own sequencers and launched them.[330] But none of those companies experienced the same astounding success as Illumina, and in the past decade, almost all of those later-launched machines have since been taken off the market.[331] Now, new competitors looking to enter the NGS market "take[] care to ease adoption by developing conversion kits for Illumina sequencing libraries," in an attempt to smooth the transition to non-Illumina sequencer machines for interested institutions.[332]

The dynamics of the market for Illumina sequencer machines likely explain why and how the company established the near monopoly they enjoy today. Illumina derives significant profit from licensing patents and selling sequencer machines, which are routinely placed in: sequencing core facilities; individual labs; hospitals that run diagnostic genome sequencing for patients; and other sequencing companies that run whole-genome sequencing reactions to support academic research. In addition to the machines themselves, Illumina

327. Balasubramanian & Klenerman, *supra* note 185.

328. *See* Davies, *supra* note 186.

329. *Id.*

330. Andreas von Bubnoff, *Next-Generation Sequencing: The Race Is On*, 132 CELL 721 (2008).

331. *Id.* (explaining that most of the other competing companies have since filed for bankruptcy, switched out of the DNA sequencing space, or begun to pursue third-generation sequencing methods instead of NGS).

332. Michael Eisenstein, *Illumina faces short-read rivals*, 41 NATURE BIOTECHNOLOGY 3, 5 (2023) (quoting Shawn Baker, head of the genomics industry consultancy SanDiegOmics, saying that "[i]t's kind of a big deal, switching over" between sequencing platforms).

also sells ancillary technology, including: sample collection kits; DNA extraction reagents; library preparation kits; analysis software ("Basespace"); and other accessories that supplement sequencer machine functionality. Illumina also profits from service contracts with the various institutions that house Illumina sequencer machines.

Illumina's commercialization approach likely also explains their acquisition of Solexa. At the time of the merger, Illumina already dominated in the protein and RNA sequencing fields with their bead array technology, entirely independent of progress within the DNA sequencing market. The Solexa acquisition enabled Illumina to dominate across all macromolecule sequencing platforms, explaining the next decade of their success.

5. Aggressive Litigation

With the proliferation of genomics companies working across all three generations of sequencing technology, patent infringement suits between Illumina and other companies have surged in the past decade. A summary of many patent disputes between sequencing technology companies—including those without Illumina as a party—is available in an excellent 2012 review.[333] This Section briefly discusses Illumina's aggressive litigation strategy, involving allegations of infringement against many competitor sequencing machine companies.

Illumina began enforcing their patents via litigation as early as 2007, shortly after it merged with Solexa. For example, Illumina alleged that Applied Biosystems' sequencing-by-ligation SOLiD system infringed three of its patents directed to methods of chain elongation combined with solid support immobilization.[334] These patents came from Lynx Therapeutics (acquired in the Solexa merger in 2005). The inventor on the three Lynx patents was Stephen Macevicz, who previously worked as a patent attorney at Applied Biosystems.[335] Despite the inventor's association with the accused infringer, the Federal Circuit ruled in favor of Illumina.[336] Illumina continued to bring infringement suits, with a particularly strong peak occurring between 2009 and 2014.[337] Illumina has also initiated trade secret lawsuits against various companies.[338]

333. Holman, *supra* note 90.

334. U.S. Patent No. 5,750,341; U.S. Patent No. 5,969,119; U.S. Patent No. 6,306,597.

335. Holman, *supra* note 90, at 1056.

336. Applera Corp.-Applied Biosystems Grp. V. Illumina, Inc., 375 F. App'x 12 (Fed. Cir. 2010).

337. *See* Holman, *supra* note 90.

338. *See, e.g.*, Jonathan Wosen, *Illumina Sues Guardant Health, Saying Former Employees Stole Trade Secrets to Launch Liquid Biopsy Firm*, STAT BIOTECH (Mar. 17, 2022), https://

In addition to inter-genomics company litigation, Illumina has also been involved in multiple instances of FTC litigation, given its attempted acquisition of several other major companies in the sequencing space. Most notably, Illumina announced an initial merger agreement with Pacific Biosciences ("PacBio")—a third-generation sequencing company[339]—in 2018.[340] The FTC sued to block the merger, given Illumina's estimated ~90% share of the NGS market, over PacBio's estimated ~2–3% share.[341] Illumina and PacBio mutually agreed to terminate the merger in 2020.[342]

Similarly, in 2021, Illumina announced its intention to acquire Grail, a company that develops cancer tests.[343] While Grail did not work in the NGS market, the company's testing method relied on DNA sequencing.[344] The FTC sued to block this acquisition because "Illumina [was] the only provider of DNA sequencing that [was] a viable option" for the types of cancer tests developed by Grail.[345] In April 2023, the FTC ordered Illumina to divest Grail to block this vertical acquisition.[346]

---

www.statnews.com/2022/03/17/Illumina-sues-guardant-health-saying-former-employees-stole-trade-secrets-to-launch-liquid-biopsy-firm/.

339. *See* discussion *infra* Section V.C.

340. *Illumina to Acquire Pacific Biosciences for Approximately $1.2 Billion, Broadening Access to Long-Read Sequencing and Accelerating Scientific Discovery*, PACBIO (Nov. 1, 2018), https://www.pacb.com/press_releases/Illumina-to-acquire-pacific-biosciences-for-approximately-1-2-billion-broadening-access-to-long-read-sequencing-and-accelerating-scientific-discovery/.

341. Complaint, Illumina, Inc., FTC Matter No. 1910035 (Dec. 17, 2019); *Cancer Genomics Research*, ILLUMINA, https://www.illumina.com/areas-of-interest/cancer/research.html (last visited Sept. 23, 2022) (estimating that Illumina NGS and microarray technologies "account for ~90% of the world's sequence data").

342. *Illumina and Pacific Biosciences Announce Termination of Merger Agreement*, PACBIO (Jan. 2, 2020), https://www.pacb.com/press_releases/Illumina-and-pacific-biosciences-announce-termination-of-merger-agreement/.

343. Conor Hale, *Illumina to pay $8B to reacquire cancer blood test maker Grail, with all eyes on 2021*, FIERCE BIOTECH (Sept. 21, 2020), https://www.fiercebiotech.com/medtech/Illumina-to-pay-8b-to-reacquire-cancer-blood-test-maker-grail-all-eyes-2021.

344. Steve Lohr, *F.T.C. Orders Gene-Sequencing Company Illumina to Divest Acquisition*, N.Y. TIMES (Apr. 3, 2023), https://www.nytimes.com/2023/04/03/business/ftc-illumina-grail-divest.html.

345. Complaint, Illumina, Inc. and Grail, Inc., In the Matter of, FTC Matter No. 2010144 (Mar. 30, 2021), https://www.ftc.gov/legal-library/browse/cases-proceedings/201-0144-illumina-inc-grail-inc-matter.

346. *FTC Orders Illumina to Divest Cancer Detection Test Maker GRAIL to Protect Competition in Life-Saving Technology Market*, FED. TRADE COMM'N (Apr. 3, 2023), https://www.ftc.gov/news-events/news/press-releases/2023/04/ftc-orders-illumina-divest-cancer-detection-test-maker-grail-protect-competition-life-saving.

V. STATE OF THE ART

Although Illumina has dominated the NGS market for over a decade, several alternative DNA sequencing approaches have proliferated on the sidelines. This Part discusses the modern state of DNA sequencing, focusing on the three generations: (1) the continued use of first-generation Sanger sequencing; (2) alternative strategies within the NGS approach; and (3) the development of long-read third-generation sequencing.

A. FIRST-GENERATION SEQUENCING AND TARGETED STUDIES

NGS provides advantages over first-generation sequencing techniques, including reduced speed and cost. Specifically, NGS increases the capacity to detect rare variants, achieves high coverage across entire genomes, and multiplexes several DNA libraries for parallelized analysis.[347] But, in many contexts, researchers prefer first-generation Sanger technology over NGS. For example, Illumina's NGS platform is less accurate for small-scale DNA sequencing for individual genes in low numbers.[348] For this purpose, Sanger sequencing remains the gold standard. And, even in diagnostic settings, NGS technologies have downsides. Many diseases are diagnosed based on the detection of chromosomal abnormalities in localized regions, integrating genetic and positional (*in situ*) data. In these diagnoses, targeted, low-throughput Sanger sequencing, often paired with assays such as fluorescence *in situ* hybridization, is more effective than whole-genome sequencing.[349]

As discussed in Section III.A, *supra*, Hood's research at Caltech catalyzed the early leap into automated Sanger sequencing. His company, Applied Biosystems (now Life Technologies), brought the first automated Sanger sequencing machine to market. Life Technologies, now a subsidiary of Thermo Fisher Scientific (Thermo),[350] remains a leader in the Sanger sequencing market.[351] Many core sequencing facilities around the world specialize in running Sanger sequencing reactions on Life Technologies and other automated sequencer machines. These Sanger sequencing methods support

347. Illumina on NGS vs Sanger, *supra* note 37.

348. *Id.* (describing that NGS is "less cost-effective" and "time-consuming" for researchers looking to "sequenc[e] low numbers of targets (1–20 targets)").

349. Behjati & Tarpey, *supra* note 76, at 236.

350. *Life Technologies*, THERMOFISHER SCI., https://www.thermofisher.com/us/en/home/brands/life-technologies.html (last visited Nov. 24, 2022).

351. *See* Cook-Deegan & Heaney, *supra* note 239, at 404–5; *Instruments for Sanger Sequencing and Fragment Analysis by Capillary Electrophoresis*, THERMOFISHER SCI., https://www.thermofisher.com/us/en/home/life-science/sequencing/sanger-sequencing/sanger-sequencing-technology-accessories.html (last visited Oct. 24, 2022).

basic research in the life sciences, where small-scale confirmation of individual genomic regions is often an essential component of experiments.

B. ALTERNATIVE NGS METHODS

Many other companies have developed NGS technology with similar functionality as the Illumina platform. As discussed in Section II.B *supra*, there are four conserved steps in all NGS pipelines: library preparation, amplification, read generation, and data analysis. While most NGS methods carry out the first and final steps (library preparation and data analysis) similarly, the methods vary in the amplification and read generation steps.

As described in Section II.B.1.a, *supra*, Illumina carries out amplification with strands anchored to a solid support, leveraging bridge clustering and PCR amplification to generate sufficient substrate quantity for a strong fluorescent signal. The PCR step is unavoidable for NGS pipelines, but other companies replace solid support bridge clustering PCR with emulsion PCR.[352] Emulsion PCR maintains the physical immobilization of DNA strands by fixing template strands to beads, rather than a solid support array.[353] The PCR amplification step occurs on the beads, which are later immobilized by deposition on a different surface.[354] Multiple companies, including 454 Life Sciences and Applied Biosystems, adopted the emulsion PCR approach. 10x Genomics—although perceived by some to be a third-generation sequencing company—also relies on a bead-based immobilization step for their Chromium product line, feeding ultimately into an Illumina sequencing pipeline.[355] From a technical perspective, it remains unclear whether bridge PCR or emulsion PCR is more advantageous when integrated into NGS pipelines. While Illumina dominates the NGS market with a bridge PCR approach, emulsion PCR may achieve equally or even more better results—but the technique failed to take off due to Solexa's early market entry.

Companies in the NGS space have also explored modifications to the read generation step. Illumina uses SBS for read generation, with 3'-*O*-blocked nucleotides that emit fluorescent signals during sequencing. However, other SBS and non-SBS forms of read generation, distinct from the Illumina platform, may fit into the NGS protocol. For example, the first NGS machine on the market, 454 Life Sciences GS20, used a read generation method based on Melamede and Nyrén's early pyrosequencing work. As discussed in Section

352. *See* Metzker, *supra* note 42, at 32.

353. *Id.*

354. *Id.* (listing examples of emulsion PCR post-bead immobilization strategies, such as polyacrylamide gel on microscope sides, amino-coated glass surfaces, or PicoTiterPlate wells).

355. *Chromium Instrument Family*, 10X GENOMICS, https://www.10xgenomics.com/instruments/chromium-family (last visited Nov. 24, 2022).

II.B.1.c, *supra*, pyrosequencing is another form of SBS; it leverages the natural process of DNA strand elongation and the production of inorganic pyrophosphate to monitor luminescence as an alternative signal to the fluorescence of the Illumina platform. Roche Diagnostics acquired 454 Life Sciences, but has since been shut down.[356] In addition to their Sanger sequencing machines, Thermo also manufactures NGS systems that use yet another type of SBS, called Ion Torrent sequencing.[357] This approach, similar to pyrosequencing, leverages a natural byproduct released during DNA polymerization (hydrogen ions) to monitor pH as a "light-free" method of SBS.[358] Finally, an entirely non-SBS based form of NGS, called sequencing-by-ligation, substitutes DNA ligase for DNA polymerase. Applied Biosystems (later Life Technologies and, then, Thermo), previously marketed a version of this platform known as SOLiD (sequencing by oligonucleotide ligation and detection).[359]

C. THIRD-GENERATION SEQUENCING (TGS)

Despite completion of the HGP, for many years, the *complete* human genome sequence remained elusive. At least 5% of the human genome is littered with copy number variations, regions with atypical GC content, and repeats.[360] These genomic areas pose a unique technical challenge, even for NGS technologies, because repetitive regions are difficult to "read" accurately. So, 8% of the human genome was left unknown even after the HGP was completed, only to become accessible with the development of TGS technology.[361]

---

356. Mark Hollmer, *Roche to Close 454 Life Sciences as It Reduces Gene Sequencing Focus*, FIERCE BIOTECH (Oct. 17, 2013), https://www.fiercebiotech.com/medical-devices/roche-to-close-454-life-sciences-as-it-reduces-gene-sequencing-focus.

357. *Ion Torrent Next-Generation Sequencing Systems and Support*, THERMOFISHER SCI., https://www.thermofisher.com/us/en/home/life-science/sequencing/next-generation-sequencing/ion-torrent-next-generation-sequencing-products-services/ion-torrent-next-generation-sequencing-systems-support.html (last visited Nov. 24, 2022).

358. *Ion Torrent Next-Generation Sequencing Technology*, THERMOFISHER SCI., https://www.thermofisher.com/us/en/home/life-science/sequencing/next-generation-sequencing/ion-torrent-next-generation-sequencing-technology.html (last visited Nov. 24, 2022).

359. Anton Valouev et al., *A High-Resolution, Nucleosome Position Map of C. elegans Reveals a Lack of Universal Sequence-Dictated Positioning*, 18 GENOME RSCH. 1051 (2008).

360. Hood & Rowen, *supra* note 105, at 5.

361. Sarah Zhang, *The Human Genome Is—Finally!—Complete*, ATLANTIC (June 11, 2021), https://www.theatlantic.com/science/archive/2021/06/the-human-genome-is-finally-complete/619172/. The article reporting the truly complete sequence of the human genome was published in 2022. Nurk et al., *supra* note 35 (using a combination of technologies from PacBio, Oxford Nanopore, and Illumina, but predominantly long-read shotgun sequencing, to resolve the remaining 8% of the human genome sequence).

There are a few key differences between TGS and NGS technologies, although a precise definition of what constitutes a TGS platform remains in flux. A hallmark of NGS is the production of short reads (hundreds of base pairs in length).[362] TGS, on the other hand, typically produces reads over 10,000 base pairs in length.[363] Longer reads offer advantages in the context of genome assembly, where piecing together an organism's entire genome benefits from large regions of overlap between individual reads.[364] This difference highlights the complexity of assembly and data analysis at the end of the sequencing pipeline: short-read technologies only generate complete human genome sequences when they have a reference sequence for assembly; long-read technologies assemble genome sequences *de novo*.[365]

Another difference is that TGS methods omit the PCR amplification step of NGS. NGS relies on PCR amplification to generate an abundance of template DNA, so that the resulting fluorescent signal from SBS read generation is strong enough for detection. However, PCR is "cumbersome to implement" in the context of high-throughput DNA sequencing.[366] The PCR amplification step makes NGS vulnerable to erroneous introduction of mutations (which show up as false positive variants) and amplification bias (which arbitrarily alters the relative abundance of sequence fragments).[367] For highly quantitative applications, such as rare variant analysis, these PCR-inherent qualities can pose a serious issue.[368]

Unlike Illumina's dominance in the NGS space, there are several central players with currently or previously successful TGS platforms, including Helicos Biosciences (Helicos), PacBio, and Oxford Nanopore Technologies (Oxford). Researchers tend to prefer these platforms over NGS for *de novo* genome assembly, which benefits from longer reads.[369] All, however, are currently hindered by much higher error rates than other types of sequencing technologies. The biochemical basis of TGS (i.e., long DNA strands) is inherently less stable than the shorter strands used by NGS technology; as

362. Jade L. L. Teng et al., *PacBio but not Illumina Technology can Achieve Fast, Accurate and Complete Closure of the High GC, Complex Burkholderia pseudomallei Two-Chromosome Genome*, 8 FRONTIERS MICROBIOLOGY 1, 2 (2017).

363. Alice McCarthy, *Third Generation DNA Sequencing: Pacific Biosciences' Single Molecule Real Time Technology*, 17 CHEMISTRY & BIOLOGY INNOVATIONS 675, 675–76 (2010).

364. Teng et al., *supra* note 362, at 11 (noting that "long reads have greatly enhanced the accuracy of genome assembly").

365. Hood & Rowen, *supra* note 105, at 6.

366. Metzker, *supra* note 42, at 32.

367. *Id.*

368. *See id.*

369. *See* Metzker, *supra* note 42, at 37.

reads increase in length, the quality of sequencing data gradually deteriorates.[370] This is unacceptable for many of the more sensitive applications of NGS, but permissible for more crude purposes, such as structural variant calling.[371]

Several companies pursuing TGS instead use a *single-molecule*, amplification-free sequencing approach. Recall that the Solexa team was initially working with a single-molecule platform, before licensing the bridge PCR cluster technology from Manteia—this pushed them from single-molecule sequencing into the conventional NGS amplification approach. Helicos stuck with this single-molecule strategy and immobilized strands to a solid support without amplifying them.[372] And for Helicos, this worked—their platform was the first to successfully implement the single-molecule strategy to sequence DNA, building on preliminary research conducted by Stephen Quake at Caltech. Helicos has since filed for bankruptcy, having stepped out of the DNA sequencing space in 2010.[373] PacBio adopted a different approach, using polymerase molecules (themselves immobilized on a solid support) to immobilize single strands of DNA.[374] In the PacBio process, a single molecule passes through the polymerase as sequencing occurs in real-time. PacBio remains a leader in the TGS space, with Illumina recently (unsuccessfully) attempting to acquire the company due to an FTC complaint.[375] And Oxford uses yet another approach: it distinctively achieves template immobilization using biological protein nanopores and sequences single DNA molecules as they pass through the pore.[376] With the transition away from a solid support array, the Oxford platform is miniaturized and portable. Notably, many of the original Solexa team members, including Milton, Brown, and McCooke, now work at Oxford.

Another key difference between TGS and NGS technologies is in the read generation step. Illumina's NGS uses reversible terminator chemistry as part

370. Sara Goodwin et al., *Coming of Age: Ten Years of Next-Generation Sequencing Technologies*, 17 NATURE REVS. GENETICS 333 (2016).

371. Structural variants are genomic changes involving regions greater than 50 base pairs in length. TGS methods have been shown to outperform NGS technologies in structural variant calling. *See* Jason D. Merker et al., *Long-Read Genome Sequencing Identifies Causal Structural Variation in a Mendelian Disease*, 20 GENETICS MED. 159 (2018); Fritz J. Sedlazeck et al., *Accurate Detection of Complex Structural Variations Using Single-Molecule Sequencing*, 15 NATURE METHODS 461 (2018).

372. Metzker, *supra* note 42, at 33.

373. Helicos Biosciences Corp. (Form 8-K) (Nov. 15, 2012), https://web.archive.org/web/20121121065028/http://biz.yahoo.com/e/121115/hlcs8-k.html.

374. Metzker, *supra* note 42, at 33.

375. *See* discussion *supra* Section IV.B.5.

376. Daniel Branton et al., *The Potential and Challenges of Nanopore Sequencing*, 26 NATURE BIOTECHNOLOGY 1146 (2008).

of SBS, with 3'-*O*-blocked nucleotides that both transiently pause chain elongation and fluoresce as an approximation of nucleotide identity. The Illumina nucleotides contain a blocking group attached to the ribose sugar, and a fluorescent label attached to the nucleobase. Helicos, PacBio, and Oxford all adopted different nucleotide chemistry for this step of their TGS platforms. Helicos used 3'-*O-unblocked* nucleotides, with both a blocking group and a fluorescent label attached to the nucleobase.[377] PacBio uses yet another distinct nucleotide type, which omits the blocking group and includes a fluorescent label alone, attached instead to the phosphate groups.[378] Finally, Oxford distances itself entirely from the SBS chemistry concept; it monitors changes in electric current as single DNA strands pass through the nanopores, rather than monitoring fluorescent signals.[379]

VI. CONCLUSION

NGS technology has been one of the most important developments in molecular biology since the 1970s. NGS platforms revolutionized the ways in which scientists and clinicians approached the analysis and treatment of disease. The technology continues to break new ground in bringing research from bench to bedside. This Article focused on the Illumina NGS platform as the dominant technology of the DNA sequencing market for over a decade.

As of 2023, Illumina maintains control over an estimated 80% of the sequencing market.[380] But, given the recent—and imminent—expiry of some of Illumina's major SBS patents, this dominance may falter soon.[381] Illumina also increasingly faces competition from TGS companies. And the price of sequencing a human genome continues to fall below even the level HGP researchers targeted. Certainly, however, Illumina's work has laid a remarkable base for future development in DNA sequencing.

The history of Illumina's success took place over several decades, across multiple countries and institutions. It occurred in two distinct stages—one dedicated to scientific discovery, the other to business development. Many different sources of motivation, features of scientific research, and characteristics of intellectual property protection all came together to propel the Illumina NGS platform forward. This development story suggests that an

377. Timothy D. Harris et al., *Single-Molecule DNA Sequencing of a Viral Genome*, 320 SCI. 106 (2008); Metzker, *supra* note 42, at 34–35.

378. Paul M. Lundquist et al., *Parallel Confocal Detection of Single Molecules in Real Time*, 33 OPTICS LETTERS 1026 (2008); Metzker, *supra* note 42, at 35.

379. Branton et al., *supra* note 376.

380. Eisenstein, *supra* note 332, at 3.

381. *Id.*

initial era of scientific curiosity, altruism, public funding sources, academic recognition, and serendipity established an initial foundation from which the Solexa team grew. Then, as research and development costs increased, a secondary era driven by private funding sources, a rigorous patent portfolio, well-timed licensing, dedication to commercialization potential, and aggressive litigation brought the technology to market. For this platform technology—and perhaps for many other areas of science—it does seem true that "so much progress depends on the interplay of techniques, discoveries and new ideas, probably in that order of decreasing importance."[382]

382. Sydney Brenner, Symposium Talk at the Friedrich Miescher Institute, Basel, Switzerland (Mar. 20, 1980), https://www.ncbi.nlm.nih.gov/pmc/articles/PMC139404/.