SERENDIPITOUS LAB DISCOVERY TO COMMERCIAL BLOCKBUSTER: THE INVENTION OF LYRICA

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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.

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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.

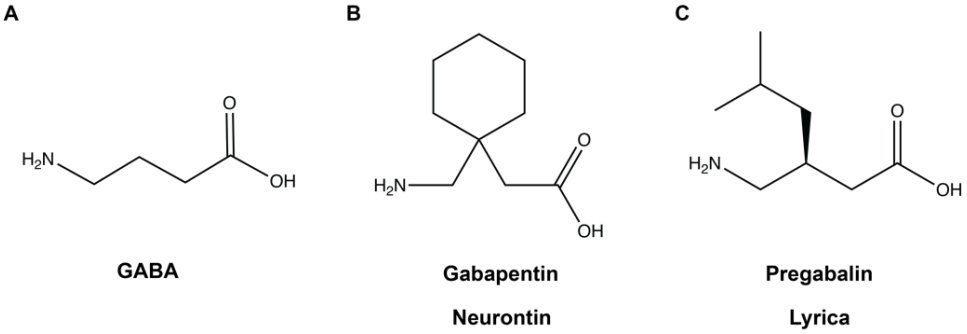
7. NIH Epilepsy Information, *supra* note 3.

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]

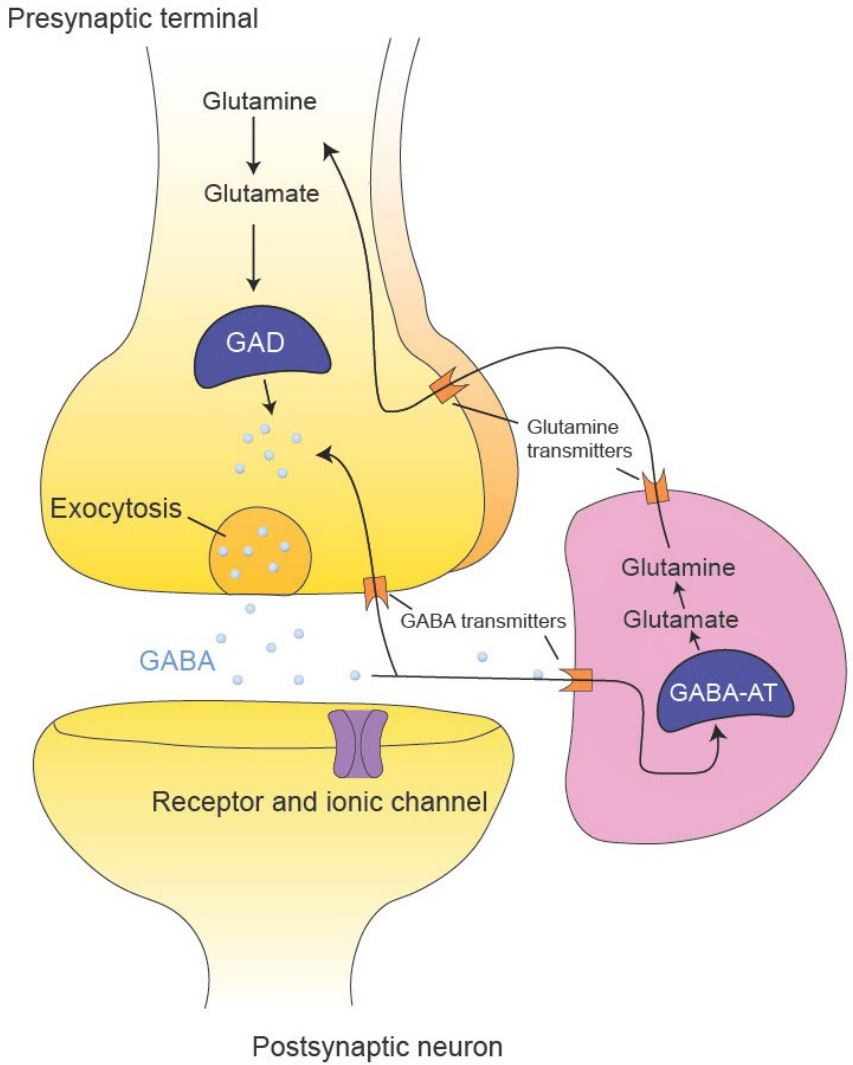
11. Silverman, *supra* note 2, at 3500.

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.*

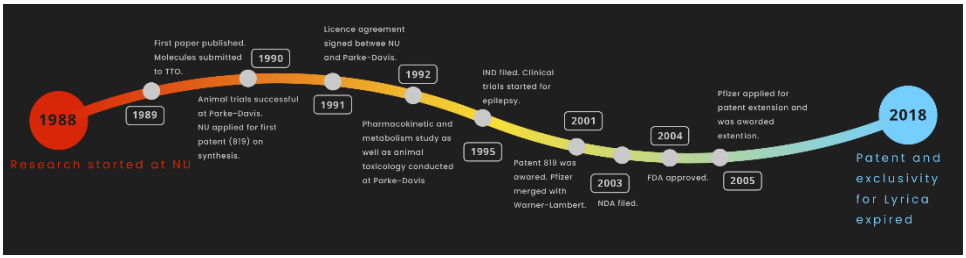
60. LI XU ET AL., TRANSLATIONAL RESEARCH IN PAIN AND ITCH 118–25 (2016).

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]

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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]

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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]

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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.