

# INTRODUCING THE LIFE SCIENCES INNOVATION CASE STUDY PROJECT

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## 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.

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## 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).<sup>1</sup> 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.<sup>2</sup>

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,

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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](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.<sup>3</sup> 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.<sup>4</sup> But

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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 Patent* <https://www.google.com/intl/en/about/products?tab=mh1s> and *Antitrust*,  
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others criticize the extensive use of patents in the pharmaceutical and biotechnology industries. They argue patents increase the price of new drugs during the exclusivity term,<sup>5</sup> clog cumulative innovation, and hinder collaboration (the “tragedy of the anticommons”).<sup>6</sup>

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.<sup>7</sup> 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.<sup>8</sup> 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

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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* note 7; Williams, *supra* note 3.

implementation in the Berkeley Law Life Sciences & Innovation Workshop (“LSI Workshop”) course held during the 2022–23 academic year.

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.<sup>9</sup> Ostrom’s work tackled a problem of similar complexity (water resource management) to understand the governance of finite, common-pool resources.<sup>10</sup> Ostrom successfully used

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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).

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 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.<sup>11</sup> 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.<sup>12</sup> At the same time, many apothecaries began converting into

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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.>



wholesale drug companies.<sup>13</sup> These two changes corresponded to improvements in chemical and laboratory sciences, which permitted isolation of active ingredients,<sup>14</sup> study of the processes by which the human body metabolizes drugs,<sup>15</sup> and chemical analysis of the isolated and synthesized products.<sup>16</sup>

After World War II, pharmaceutical companies in the United States, Europe, and Japan expanded rapidly, with major investments in research, development, and marketing.<sup>17</sup> These companies expanded their in-house R&D capacities significantly, while continuing to collaborate with academic researchers.<sup>18</sup> 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.<sup>19</sup>

American inventors patented very few active pharmaceutical ingredients in the eighteenth and nineteenth centuries.<sup>20</sup> Instead, the pharmaceutical industry

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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 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 19<sup>th</sup> Century*, 6 DRUG METABOLISM REV. 1 (1977) (detailing the significant scientific work of 19<sup>th</sup> 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”<sup>21</sup> with dubious therapeutic properties.<sup>22</sup> 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.<sup>23</sup> Pharmaceutical companies now routinely rely on patents to protect compositions (active ingredient and drug product), formulations, and methods of treatment for their therapeutic products.<sup>24</sup>

## 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.<sup>25</sup> 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.<sup>26</sup>

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

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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 vegetable 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.<sup>27</sup> 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.<sup>28</sup> 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.<sup>29</sup> 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.<sup>30</sup> 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.<sup>31</sup>

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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,<sup>32</sup> 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,<sup>33</sup> 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.<sup>34</sup> 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”).<sup>35</sup> 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;<sup>36</sup> random curative trials;<sup>37</sup> requirements for voluntary informed consent in clinical trials in the 1947 Nuremberg Code;<sup>38</sup> and formal statements of ethical principles guiding human

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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](https://en.wikipedia.org/wiki/Nuremberg_Code) (last visited Jan. 21, 2024).

trials in the 1948 Geneva Declaration,<sup>39</sup> the 1964 Helsinki Declaration,<sup>40</sup> and the 1966 International Covenant on Civil and Political Rights.<sup>41</sup> 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.<sup>42</sup> 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.<sup>43</sup> Finally, in 1996, the International Conference on Harmonization published Good Clinical Practice guidelines, which provide a universal standard for ethical conduct in clinical trials.<sup>44</sup>

### 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.<sup>45</sup> 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](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.<sup>46</sup> 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.<sup>47</sup> 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.<sup>48</sup>

### 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.

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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).

- **Type or Nature of Innovation:**
  - 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,<sup>49</sup> 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.

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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).

- **Transition Across the “Valley of Death”:**<sup>50</sup>
  - What factors motivated funders to help inventors and companies through early-stage development?
  - 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.

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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).



- **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<sup>51</sup> 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?

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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](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).

- 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 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.<sup>52</sup> 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.<sup>53</sup> 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

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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.



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

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).

## 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 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*,<sup>60</sup> 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.<sup>61</sup> Lyrica's development came at a time when significant unmet medical needs existed for new treatments for fibromyalgia,<sup>62</sup> neuropathic pain,<sup>63</sup> and epilepsy.<sup>64</sup> Zhang identifies the key role that U.S. and international public

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/2024/021446s041,022488s018,209501s0051bl.pdf](https://www.accessdata.fda.gov/drugsatfda_docs/label/2024/021446s041,022488s018,209501s0051bl.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](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](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).

health organizations played in reducing stigma surrounding epilepsy and promoting epilepsy treatment research in the late twentieth century.<sup>65</sup>

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.<sup>66</sup> Pregabalin is one of a class of fourteen 3-alkyl GABA derivatives that Andruszkiewicz synthesized under the direction of Silverman in 1988.<sup>67</sup> Both epileptic seizures and certain neuropathic pain conditions can be traced to diminished GABA levels in the brain.<sup>68</sup> At the time, Silverman thought that the 3-alkyl GABA derivative compounds would increase GABA neurotransmitter levels in the human brain.<sup>69</sup> 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.<sup>70</sup>

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.<sup>71</sup> 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.<sup>72</sup> 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.<sup>73</sup>

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

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

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

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)).

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.<sup>74</sup> In fact, Lyrica was one of the first major pharmaceutical products to arise under the Bayh-Dole regime.<sup>75</sup> Northwestern's technology transfer office marketed pregabalin to pharmaceutical companies, as Northwestern (like other universities) lacked the capacity to conduct clinical trials or engage in large-scale manufacturing of pregabalin.<sup>76</sup>

Lyrica's commercialization pathway also depended on Silverman's strong belief in the value of patenting research outputs.<sup>77</sup> 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."<sup>78</sup>

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.<sup>79</sup> 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.<sup>80</sup> 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.<sup>81</sup> Parke-Davis also focused on effectiveness of pregabalin in a murine model, rather

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

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

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.*

than in *in vitro* testing.<sup>82</sup> Finally, Parke-Davis's concurrent development of gabapentin, another GABA-modulating compound, provided the company with additional insight toward the development of pregabalin.<sup>83</sup>

Later, Parke-Davis pursued an aggressive clinical trial strategy, electing to run Phase II and Phase III trials concurrently for multiple potential pregabalin indications.<sup>84</sup> Although riskier than the conventional clinical trial strategy of pursuing one type of study and one indication at a time, Parke-Davis saved significant development time and costs with concurrent trials.<sup>85</sup> Parke-Davis's riskier strategy paid off: the FDA approved pregabalin for multiple indications in short succession.<sup>86</sup>

Finally, Zhang's case study briefly details Pfizer's later development of Lyrica CR,<sup>87</sup> 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*,<sup>88</sup> 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.<sup>89</sup> Truvada is comprised of two small molecule active ingredients: tenofovir (formulated as the prodrug tenofovir disoproxil fumarate) and emtricitabine.<sup>90</sup>

Kasper describes the critical role that the HIV/AIDS public health crisis played in shaping Truvada's development path. This crisis reached lethal

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82. *Id.*

83. *Id.*

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

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 neuralgia 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](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](https://www.accessdata.fda.gov/drugsatfda_docs/label/2023/021752Orig1s063lbl.pdf).

90. *Id.* at 1, 5, 18–19, 36.

pandemic levels in the late twentieth century.<sup>91</sup> 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.<sup>92</sup> 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 governmental agencies and philanthropic organizations also played instrumental roles in pushing HIV/AIDS treatments to the global South.<sup>93</sup>

University scientists first discovered both active ingredients in Truvada.<sup>94</sup> 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.<sup>95</sup> Gilead Sciences, a startup company focused on antiviral therapeutics, stepped in to pursue development of both compounds to commercialization<sup>96</sup> (Viread for the prodrug form of tenofovir;<sup>97</sup> Coviracil for the single compound form of emtricitabine<sup>98</sup>). 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.<sup>99</sup>

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.<sup>100</sup> 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.<sup>101</sup>

As with many synthetic chemistry endeavors, brute force also played a role in development efforts for tenofovir and emtricitabine. For tenofovir, the

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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.

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.

scientific team synthesized many derivatives to find the optimal compound.<sup>102</sup> And, for emtricitabine, the inventors tested many synthetic methods to find the optimal synthetic route to the final compound.<sup>103</sup>

Efficient transfer of the tenofovir and emtricitabine small molecule inventions to private company partners also played a critical role in bringing Truvada to market.<sup>104</sup> The development stories for both compounds followed similar paths.<sup>105</sup> 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).<sup>106</sup> 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.<sup>107</sup> Third, the private company abandoned the compound due to a deprioritization in various merger & acquisition (M&A) deals.<sup>108</sup> Fourth, Gilead eventually licensed or acquired patents covering both active ingredients<sup>109</sup> and received FDA approval to market each compound as a separate therapeutic product.<sup>110</sup> 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.<sup>111</sup>

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

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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.

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.



Gilead pursued PrEP to significantly expand its patient base (and its potential profit margin) with a HIV-preventative treatment.<sup>116</sup> Public health agencies including the CDC strongly encouraged Gilead to develop a PrEP product.<sup>117</sup> 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.<sup>118</sup>

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,<sup>119</sup> patented tenofovir prodrugs,<sup>120</sup> and acquired the patent rights to emtricitabine from Emory University.<sup>121</sup> Finally, Gilead received several patents directed to methods of treatment for HIV using Truvada.<sup>122</sup>

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.<sup>123</sup> Second, as noted *supra*, the CDC unsuccessfully attempted to assert its PrEP patent claims against Gilead.<sup>124</sup>

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.<sup>125</sup> 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.<sup>126</sup>

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

116. *Id.* at Section IV.C.2.b.

117. *Id.*

118. *Id.* at Sections III.C, IV.C.1.a.

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.

governmental support of HIV therapeutic development.<sup>127</sup> 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.<sup>128</sup>

### 3. *Spravato*

In *How Ketamine Became an Antidepressant*,<sup>129</sup> 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 disorder with acute suicidal ideation and/or behavior.<sup>130</sup> 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.<sup>131</sup>

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).<sup>132</sup> 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.<sup>133</sup> To tackle this problem, scientists at Yale School of Medicine identified glutamate-modulating compounds as a class of promising new depression therapeutics.<sup>134</sup> With increased scientific understanding of the science underlying development of glutamate-modulating antidepressants,<sup>135</sup> government scientists at the National Institute of Mental Health (NIMH) began collaborations with the Yale scientists and teams from other institutions.<sup>136</sup> NIMH funded most early-stage glutamate-targeted antidepressant investigations.<sup>137</sup>

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127. *Id.* at Section III.A.3.b.

128. *Id.* at Section IV.C.2.a.

129. Joralemon, *supra* note 56.

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](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-3 $\beta$* , 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.

After promising early-stage clinical results,<sup>138</sup> Hussein Manji, the director of the Mood and Anxiety Disorders program at NIMH, moved to Janssen's Neuroscience Research & Development program in 2008.<sup>139</sup> 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.<sup>140</sup> 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-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.<sup>141</sup>

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.<sup>142</sup> 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.<sup>143</sup> 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.<sup>144</sup> 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.<sup>145</sup> 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).<sup>146</sup>

*How Ketamine Became an Antidepressant* suggests several instances of serendipity in the discovery and development process of Spravato. For

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.

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.

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.<sup>147</sup> And, when scientists struggled with the limited bioavailability of intranasal ketamine formulations, the S-enantiomer of ketamine provided the necessary potency boost.<sup>148</sup>

Accelerated regulatory approval and marketing exclusivity also incentivized Spravato development. The FDA had previously approved racemic ketamine formulations for anesthetic indications.<sup>149</sup> But, the FDA approved Spravato as the first (and currently only) ketamine product approved for use in treating depression (in conjunction with one or more traditional antidepressants).<sup>150</sup> 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.<sup>151</sup> The FDA also granted Janssen five years of new chemical entity marketing exclusivity for use of an enantiomer of a previously approved racemic mixture.<sup>152</sup> 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.<sup>153</sup> Although there is some evidence that clinicians have used ketamine formulations for depression off-label since the early 2000s,<sup>154</sup> 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.<sup>155</sup>

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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.

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](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\(tradename,and%20maintenance%20of%20general%20anesthesia\)](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))).

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.<sup>156</sup> 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.<sup>157</sup>

#### 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*,<sup>158</sup> 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.<sup>159</sup> 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.<sup>160</sup>

Thus far, the FDA has approved six CAR-T cell therapy treatments for blood cancers.<sup>161</sup> 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.<sup>162</sup>

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

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

157. *Id.*

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)).

institutions.<sup>163</sup> 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.<sup>164</sup> 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 production.<sup>165</sup> This manufacturing expense required significant funding even for early-stage, small clinical trials (and compounded the costs of later-stage, larger trials).<sup>166</sup>

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.<sup>167</sup> 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.<sup>168</sup>

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.<sup>169</sup> Multiple startups arose in the CAR-T cell therapy space to access private sector funding throughout the development process.<sup>170</sup> In transitioning to the clinical phase, manufacturers required substantial funding to scale CAR-T cell therapy manufacturing.<sup>171</sup> 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).<sup>172</sup> Private sector funding from large pharmaceutical and

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

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

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.

biotech companies funded larger, later-stage clinical trials necessary for FDA approval.<sup>173</sup>

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.<sup>174</sup> The case study also identifies the key role of scientific curiosity as a driver for early-stage university and government inventors.<sup>175</sup> For some early-stage scientists in the CAR-T cell therapy space, the possibility of financial rewards through patenting, royalties, and potential commercialization served as a major driver;<sup>176</sup> for others, potential financial incentives did not play a role<sup>177</sup> (and, in some cases, these financial benefits only became evident in hindsight<sup>178</sup>). 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.<sup>179</sup>

The CAR-T cell therapy IP landscape is complex, as reflected in the various licensing schemes between university, government, and private innovators.<sup>180</sup> 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;<sup>181</sup> (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.<sup>182</sup> 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.<sup>183</sup>

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

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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.

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.

Breakthrough Therapy designation in July 2015,<sup>184</sup> 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.<sup>185</sup> Second, regulatory exclusivities motivated CAR-T cell therapy development. New biological therapeutics like Yescarta receive twelve years of marketing exclusivity upon approval.<sup>186</sup> And, all FDA-approved CAR-T cell therapies have received at least one orphan drug exclusivity designation, granting seven additional years of marketing exclusivity.<sup>187</sup> The purpose of orphan drug exclusivity is to incentivize development of therapeutics for diseases affecting small patient populations (where a pharmaceutical company may not expect to recoup its R&D investment without extended exclusivity).<sup>188</sup>

### 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*,<sup>189</sup> Caressa N. Tsai explains the development story of Illumina's "next-generation sequencing" (NGS) technology.<sup>190</sup> 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).<sup>191</sup> In the early 2000s, scientists developed NGS platforms, which allowed for "massively parallel" DNA sequencing.<sup>192</sup> Tsai notes that, "[w]ith NGS [technology], it is now possible to sequence the entire human genome in one day, for approximately \$1,000."<sup>193</sup> And, Tsai outlines the significant improvements that commercial NGS

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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.

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)).



technology has provided to three important life sciences applications: (1) diagnostic testing for genetic variants that may indicate disease;<sup>194</sup> (2) personalized medicine applications to guide physician treatment strategies;<sup>195</sup> and (3) direct-to-consumer genomics applications such as personalized genetic testing kits.<sup>196</sup>

*The Invention of Next-Generation Sequencing* tells the story of how Illumina came to dominate the NGS market.<sup>197</sup> Tsai describes two major phases of development: (1) a foundational phase, driven by university research and 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.<sup>198</sup>

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.<sup>199</sup> Instead, the scientists sought to understand the enzyme kinetics of DNA polymerase and were struggling to capture the exact timing of nucleotide incorporation.<sup>200</sup> 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.<sup>201</sup> There, the team developed the idea of using a parallelized approach to overcome the nucleotide incorporation visualization issue.<sup>202</sup> But, the scientists also realized that parallelization might also dramatically improve DNA sequencing applications.<sup>203</sup> 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

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)).

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.*

or IP acquisition goals.<sup>204</sup> 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.<sup>205</sup> 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.<sup>206</sup> 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.<sup>207</sup> Tsai notes that academic recognition likely drove many researchers as DNA sequencing publications consistently received publication offers from high-impact journals.<sup>208</sup>

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.<sup>209</sup> Most key innovators in the Illumina NGS story worked at universities or in other academic settings and spun their work out into startups.<sup>210</sup> 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.<sup>211</sup>

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).<sup>212</sup> 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

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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.*

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.

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.<sup>213</sup> 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.<sup>214</sup> The altruistic perspective of the Human Genome Project scientists eventually won out. Coincidentally, later case law restricted patent eligibility for biological inventions, including genes.<sup>215</sup> Third, during the Solexa (now Illumina) era, companies focused on obtaining a broad patent portfolio to support commercialization efforts.<sup>216</sup> Tsai notes that Illumina now holds patents on “virtually every eligible aspect of their [NGS] technology.”<sup>217</sup> Tsai traces the development of the patented technology for the three key elements of NGS (the use of a solid support array,<sup>218</sup> bridge PCR clustering for read amplification,<sup>219</sup> and sequencing-by-synthesis<sup>220</sup>), including strategic in-licensing deals (most notably for the bridge PCR clustering technology).<sup>221</sup>

Solexa and other startup companies competed to reach the market first with an NGS machine.<sup>222</sup> In effect, Solexa “won” because it reached the market first.<sup>223</sup> Later, Illumina essentially sought a monopoly on all macromolecule sequencing markets by acquiring Solexa.<sup>224</sup> 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.<sup>225</sup> And, Illumina has continued a merger and acquisition campaign in the sequencing

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213. *Id.* at Sections III.B, IV.A.2.

214. *Id.* at Section IV.A.2.

215. *Id.*

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.

space, encountering scrutiny from the Federal Trade Commission for potentially anticompetitive practices.<sup>226</sup>

#### 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.

##### 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.<sup>227</sup> 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

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226. *Id.*

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.

commercialization process.<sup>228</sup> 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.<sup>229</sup> These startup 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.<sup>230</sup> 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.

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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.

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

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.<sup>231</sup> 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;<sup>232</sup> (2) avoidance of compulsory licensing through voluntary licensing procedures;<sup>233</sup> (3) strategic patent filing to exploit available IP space but avoid prior art and potential subject matter patentability issues;<sup>234</sup> and/or (4) defense of their IP rights through litigation.<sup>235</sup> 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.<sup>236</sup> 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

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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.

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.

cases.<sup>237</sup> In that example, insurers required FDA approval for esketamine as a treatment-resistant depression therapeutic to obtain insurance coverage and reimbursement.<sup>238</sup> 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.<sup>239</sup> 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 Truvada (for HIV treatment and prevention)<sup>240</sup> and Lyrica (for, among other indications, epilepsy).<sup>241</sup> 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

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

238. See *id.*

239. See *id.*

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.

promote biomedical advances, particularly in light of the new technological challenges such as the emergence of big data and artificial intelligence.