Notes

THE PROMISING VIRAL THREAT TO BACTERIAL RESISTANCE: THE UNCERTAIN PATENTABILITY OF PHAGE THERAPEUTICS AND THE NECESSITY OF ALTERNATIVE INCENTIVES

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ABSTRACT

Bacteriophages, or "phages," are a category of highly adept and adaptable viruses that can infect and kill bacteria. With concerns over the burgeoning antibiotic-resistance crisis looming in recent years, scientists and policymakers have expressed a growing interest in developing novel treatments for bacterial infections that utilize bacteriophages. Because of the great expense associated with bringing a new drug to market, patents are usually considered the gold standard for incentivizing research and development in the pharmaceutical field. Absent such strong protection for a developer's front end investment, pharmaceutical development remains financially risky and unattractive. Unfortunately, recent Supreme Court jurisprudence analyzing patentable subject matter under 35 U.S.C. § 101 has cast doubt on whether phage therapeutics would be eligible for strong patent protection. In order for the promise of phage therapeutics to become a reality, alternative protections or incentives are likely necessary. Such a framework would likely include trade secrecy, regulatory exclusivities, research support, alternative payment models, or some combination thereof.

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INTRODUCTION

In 2017, headlines across the country praised a miraculous sewer sludge that brought a man back from the brink of death when all else failed.[1] Many months before, sixty-nine-year-old Tom Patterson had developed a bacterial infection caused by an often deadly, multidrug-resistant strain of *Acinetobacter baumannii*.[2] He was admitted to the hospital with intense abdominal pain and a fever, where he began projectile vomiting black bile "like something out of 'The Exorcist.'"[3] After a last resort combination of potent, high-risk antibiotics failed, Mr. Patterson's condition worsened, and he slipped into a coma.[4] Although told to prepare for the worst, Mr. Patterson's wife, infectious disease epidemiologist Dr. Steffanie Strathdee, refused to give up; she began researching alternative treatments.[5] Dr. Strathdee found promising reports of a type of virus known as a bacteriophage ("phage") that can infect and kill bacteria, thereby curing antibiotic-resistant infections.[6] She began contacting countless researchers and labs with the hope of finding a phage that could target *A. baumannii*.[7] Researchers at Texas A&M University and the U.S. Naval Research Laboratory in Maryland responded, identifying a few promising phage candidates that had been isolated from samples taken from a local sewage plant, as well as some that were stored in existing phage libraries and labs.[8] Dr. Strathdee secured emergency FDA approval to use the phages, and Mr. Patterson was injected with two individualized

1. Azeen Ghorayshi, *Her Husband Was Dying From a Superbug. She Turned to Sewer Viruses Collected by the Navy*, BUZZFEED (May 6, 2017), https://www.buzzfeed.com/azeenghorayshi/navy-phage-viruses-for-antibiotics-crisis?utm_term=.dh0aywqDM#.vq8BbMY4a [https://perma.cc/F5X2-PZLS] (detailing how a bacteriophage found in sewage helped cure a man's life-threatening bacterial infection); Lauren Weber, *Sewage Saved This Man's Life. Someday It Could Save Yours*, HUFFINGTON POST (May 11, 2017), https://www.huffingtonpost.com/entry/antibiotic-resistant-superbugs-phage-therapy_us_5913414de4b05e1ca203f7d4 [https://perma.cc/N8NV-DDTB] (same).

2. Scott LaFee & Heather Buschman, *Novel Phage Therapy Saves Patient with Multidrug-Resistant Bacterial Infection*, UC SAN DIEGO HEALTH NEWSROOM (Apr. 25, 2017), https://health.ucsd.edu/news/releases/Pages/2017-04-25-novel-phage-therapy-saves-patient-with-multidrug-resistant-bacterial-infection.aspx [https://perma.cc/AH2E-7EEP].

3. Weber, *supra* note 1.

4. LaFee & Buschman, *supra* note 2.

5. Weber, *supra* note 1.

6. *Id.*

7. *Id.*

8. *Id.*

phage cocktails.[9] After being in a coma for two months, he woke up three days after the phages were administered.[10]

Mr. Patterson's experience illustrates the urgency of the bacterial-resistance crisis. With antibiotic resistance becoming an increasingly lethal and prevalent threat to global public health,[11] innovative antimicrobial products that are capable of treating these dangerous infections are more important now than ever before. Phages have demonstrated their efficacy as highly targeted, potent, and adaptable killers of antibiotic-resistant bacteria. These viruses depend on their ability to infect bacteria in order to proliferate, and as such have evolved diverse mechanisms for breaking through bacterial defenses.[12] However, they remain relatively harmless to humans, leading researchers in recent years to identify phage therapeutics as a possible panacea for the antibiotic-resistance crisis.[13] However, this solution depends on the development of viable phage products, an area that has seen little investment by biotechnology and pharmaceutical companies, regardless of its medical promise.[14] This lack of innovation is likely due in large part to the dubious patentability of phages and phage therapies following the Supreme Court's decision in *Association for Molecular Pathology v. Myriad Genetics, Inc.*,[15] which held that naturally occurring products are not patent-eligible subject matter.[16] This Note is the first to closely analyze the patentability of phage therapies, to discuss the impact of uncertain patentability on innovation in the phage therapeutics field, and to suggest possible nonpatent alternatives.

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9. LaFee & Buschman, *supra* note 2.

10. *Id.*

11. *See* C. Lee Ventola, *The Antibiotic Resistance Crisis, Part 1: Causes and Threats*, 40 PHARMACY & THERAPEUTICS 277, 283 (2015) ("Rapidly emerging resistant bacteria threaten the extraordinary health benefits that have been achieved with antibiotics." (citation omitted)).

12. Derek M. Lin, Britt Koskella & Henry C. Lin, *Phage Therapy: An Alternative to Antibiotics in the Age of Multi-Drug Resistance*, 8 WORLD J. GASTROINTESTINAL PHARMACOLOGY & THERAPEUTICS 162, 164 (2017), https://www.ncbi.nlm.nih.gov/pmc/articles/PMC5547374 [https://perma.cc/AAZ4-KAWB] ("Bacteria have evolved numerous mechanisms to resist infection by lytic phages, and phages have an equally impressive diversity of mechanisms for breaking this resistance.").

13. Sara Reardon, *Modified Viruses Deliver Death to Antibiotic-Resistant Bacteria*, NATURE: NEWS (June 21, 2017), https://www.nature.com/news/modified-viruses-deliver-death-to-antibiotic-resistant-bacteria-1.22173 [https://perma.cc/4NCQ-5JEA].

14. *See id.* (explaining that the "development of phage therapy has been slow").

15. Ass'n for Molecular Pathology v. Myriad Genetics, Inc., 569 U.S. 576 (2013).

16. *Id.* at 580.

This Note argues that to bring about the promise of phage therapies for the treatment of antibiotic-resistant infections, the traditional patent-centric model for stimulating drug innovation is insufficient. Alternative protections or incentives, such as trade secrecy, regulatory exclusivities, research support, alternative payment models, or some combination thereof, are likely necessary to spur phage therapy innovation. Part I explains the development of antibiotic resistance in bacteria and the growing threat it poses to global health. Part II discusses the unique characteristics of phages and the benefits and challenges of creating phage-based treatments. Part III analyzes the murkiness of recent patent-eligibility jurisprudence and the weak protection it offers for phage therapies. Finally, Part IV goes on to address the availability of and need for alternative protections and incentives that stimulate phage therapy innovation, including trade secrecy, regulatory exclusivities, governmental research support and funding, and alternative payment models.

I. THE GLOBAL ANTIBIOTIC RESISTANCE CRISIS

Like war, religion, and technology, humanity has been inextricably intertwined with, and shaped by, bacterial disease. Though modern antibiotics have provided the human race with great relief from bacterial onslaught, these simple microorganisms have recently begun developing ways to slip through the chinks in our antibiotic armor.

A. Bacterial Diseases and the Discovery of Penicillin

Many highly dangerous infectious diseases are caused by bacteria—a group of microscopic, unicellular prokaryotes that are defined by their lack of a membrane-bound nucleus and other specialized organelles that are found in plant and animal cells.[17] Bacteria's small size and flexible metabolic capabilities promote fast replication and adaptability, allowing these organisms to rapidly establish a presence in a wide variety of environmental conditions.[18]

17. Kara Rogers & Robert J. Kadner, *Bacteria*, ENCYCLOPEDIA BRITANNICA, https://www.britannica.com/science/bacteria [https://perma.cc/XV2K-4TK8].

18. *See, e.g.*, Robin Andrews, *Living in Hell: The Possibility of Life Inside a Volcano*, FORBES (Apr. 15, 2017), https://www.forbes.com/sites/robinandrews/2017/04/15/living-in-hell-the-possibility-of-life-inside-a-volcano/#56725cc51c1d [https://perma.cc/VD7E-EQF4] (noting that bacterial life is capable of surviving even in "Yellowstone's superheated, anoxic, acidic hot springs"); Olivia U. Mason et al., *First Investigation of the Microbiology of the Deepest Layer of Ocean Crust*, PLOS ONE, Nov. 2010, http://journals.plos.org/plosone/article?id=10.1371/

Their adaptability and symbiotic coevolution with life and the environment has aided the proliferation of the estimated five million trillion trillion bacteria existing today.[19] According to Andrew H. Knoll, professor of biology at Harvard University, "[w]e definitely live in a bacterial world."[20]

While most bacterial strains have either a neutral or beneficial impact on humans, less than one percent are pathogenic.[21] Bacterial infections cause an array of symptoms and can result in death.[22] Many profound episodes of human loss throughout history can be attributed to bacterial infections. One of the most infamous catastrophes, the Black Death of 1347–1351, was caused by the bacterium *Yersinia pestis* and resulted in the death of an estimated 30–50 percent of the European population, and up to 100 million people worldwide.[23] During humanity's earlier days, similar epidemics of leprosy, plague, syphilis, cholera, and typhoid fever were the norm,[24] profoundly impacting the development of the world's habits, commerce, and culture.[25]

A monumental turning point came in 1928, when an accidentally contaminated petri dish led to the discovery of penicillin.[26] By 1942, penicillin was deployed to save the life of a young woman dying of

journal.pone.0015399 [https://perma.cc/UV3B-KM7D] (describing the bacterial communities found in the deepest layer of the oceanic crust); Arie Nissenbaum, *The Microbiology and Biogeochemistry of the Dead Sea*, 2 MICROBIAL ECOLOGY 139 (1975) (discussing bacterial cultures found in the hypersaline Dead Sea).

19. *Planet Bacteria*, BBC NEWS (Aug. 25, 1998), http://news.bbc.co.uk/2/hi/science/nature/158203.stm [https://perma.cc/H5LY-BZ4V].

20. NOVA, *How Did Life Begin?*, PBS (July 1, 2004), http://www.pbs.org/wgbh/nova/evolution/how-did-life-begin.html [https://perma.cc/R8EM-CVUZ].

21. *Bacterial Infections*, PUBMED HEALTH, https://www.ncbi.nlm.nih.gov/pubmedhealth/PMHT0024516 [https://perma.cc/J4WJ-VQK8].

22. *Id.*

23. Kirsten I. Bos et al., *A Draft Genome of* Yersinia Pestis *from Victims of the Black Death*, 478 NATURE 506, 506 (2011); TEXTBOOK EQUITY, 2 COLLEGE BIOLOGY 602–03 (2014) (ebook).

24. Philip S. Brachman, Editorial, *Infectious Diseases – Past, Present, and Future*, 32 INT'L J. EPIDEMIOLOGY 684, 684 (2003).

25. *See* Maxine Whittaker, *How Infectious Diseases Have Shaped Our Culture, Habits and Language*, THE CONVERSATION (July 12, 2017), https://theconversation.com/how-infectious-diseases-have-shaped-our-culture-habits-and-language-75061 [https://perma.cc/H38Y-E4E6] (describing how these bacterial diseases "have changed the structure and numbers of people living in communities").

26. Tim Newman, *How Do Penicillins Work?*, MED. NEWS TODAY, https://www.medicalnewstoday.com/articles/216798.php [https://perma.cc/T5L8-8BJB].

streptococcal septicemia following a miscarriage.[27] The success of the discovery provoked interest in antibiotic research, which has led to the development of the over 150 types of antibiotics on the market today.[28] Antibiotic drugs have greatly decreased the number of individuals dying from standalone bacterial diseases, and have vastly improved the safety of medicine.[29] Antibiotics have changed the course of history by saving what is estimated to be hundreds of millions of lives over the course of the past century.[30] In recognition of their great impact, the BBC announced in 2017 that antibiotics had been voted "Britain's Greatest Invention."[31]

B. The Development of Antibiotic Resistance in Bacteria

While current antibiotics have undoubtedly benefitted global health, there is still room for improvement. Regardless of the availability and affordability of these drugs, "[b]acterial infection remains a leading cause of death in both the Western and developing world."[32] Research on the subject suggests that multiple factors may be contributing to our inability to reign in infectious diseases. Chief among these concerns is the waning efficacy of existing antibiotics. As small, simple organisms with the proven ability to adapt to new environments and rapidly regenerate, bacteria are able to quickly generate new populations of stronger, better-suited pathogens when

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27. John Curtis, *Fulton, Penicillin and Chance*, 34 YALE MED. MAGAZINE, no. 1, 1999, http://ymm.yale.edu/autumn1999/features/capsule/55396 [https://perma.cc/F6PL-E92Y]; Newman, *supra* note 26.

28. *Antibiotics*, NEW MED. INFO. & HEALTH INFO., http://drugs.nmihi.com/antibiotics.htm [https://perma.cc/CTQ2-4TWL].

29. CTRS. FOR DISEASE CONTROL & PREVENTION, ANTIBIOTIC RESISTANCE THREATS IN THE UNITED STATES, 2013, at 41 (2013), https://www.cdc.gov/drugresistance/threat-report-2013/pdf/ar-threats-2013-508.pdf [https://perma.cc/Q2ZG-BHJY] ("Antibiotics were first used to treat serious infections in the 1940s. Since then, antibiotics have saved millions of lives and transformed modern medicine."). Prior to the discovery of penicillin, women were 50 times more likely to die in childbirth due to infection. *Which Invention Won Britain's Greatest Invention?*, BBC, http://www.bbc.co.uk/programmes/articles/5QRlT3MhZLnsTjrGswV2FlJ/which-invention-won-britains-greatest-invention [https://perma.cc/ZGB2-98DX]. Penicillin also greatly improved the recovery rate of soldiers who incurred traumatic injuries in battle. *Id.*

30. CTRS. FOR DISEASE CONTROL & PREVENTION, *supra* note 29, at 41 ("Without [antibiotics], 200 million of us wouldn't be here, and that's a very conservative calculation.").

31. *Id.*; *Antibiotics Win Greatest British Invention in Live TV Broadcast*, U. OXFORD MED. SCI. DIVISION (June 16, 2017), https://www.medsci.ox.ac.uk/news/antibiotics-win-greatest-british-invention-in-live-tv-broadcast [https://perma.cc/DVG8-92L3].

32. 77 ADVANCES IN ENZYMOLOGY & RELATED AREAS OF MOLECULAR BIOLOGY xi (Eric J. Toone ed., John Wiley & Sons, Inc. 2011).

faced with a threat.[33] When that threat is an antibiotic, bacteria may develop ways to resist that drug.[34]

Today, strains of antibiotic-resistant bacteria have emerged for each class of antibiotic; some of these bacteria have shown resistance to multiple drugs.[35] Because resistance to an antibiotic drug within one class may confer to a bacterium some resistance to other drugs within the same class, this is particularly troubling.[36] Infection by antibiotic-resistant bacteria greatly limits the number of treatment options that are available, and the drugs that remain often have decreased efficacy, making it harder—and sometimes even impossible—to treat the infection.[37] A recent report by the Center for Disease Control ("CDC") estimates that at least two million people in the United States become infected with antibiotic-resistant bacteria each year, with 23,000 dying as a direct result of the infection.[38] By 2050, some experts predict that the annual number of deaths due to antibiotic-resistant infections will reach ten million if efforts are not made to curtail bacterial resistance.[39]

Bacterial resistance to existing antibiotics has been further exacerbated by a number of factors. First, humans, and their pathogen hitchhikers, are able to travel faster and farther than ever before; this modern development has been linked to the proliferation of uncommon pathogenic infections in unprepared communities.[40] As more pathogens circulate worldwide, the urbanization of modern

33. Newman, *supra* note 26.

34. Kimberly Buckmon, *BARDA Seeks to Launch a Novel Partnership, a Product Accelerator to Address Antimicrobial Resistance*, OFF. ASSISTANT SEC'Y PREPAREDNESS & RESPONSE: BLOG (Feb. 19, 2016), https://www.phe.gov/ASPRBlog/Lists/Posts/Post.aspx?ID=176 [https://perma.cc/CLQ4-HXEB] (discussing the increase in and deadliness of bacterial infections that are resistant to existing antibiotics).

35. *Id.*

36. *Antibiotics: An Overview*, KHAN ACAD., https://www.khanacademy.org/science/health-and-medicine/current-issues-in-health-and-medicine/antibiotics-and-antibiotic-resistance/a/antibiotics-an-overview [https://perma.cc/N36K-CURR].

37. *Antibiotic Resistance*, WHO (Feb. 5, 2018), http://www.who.int/mediacentre/factsheets/antibiotic-resistance/en [https://perma.cc/U99F-UZ36].

38. *Antibiotic/Antimicrobial Resistance*, CTRS. DISEASE CONTROL & PREVENTION (last updated Mar. 29, 2018), https://www.cdc.gov/drugresistance [https://perma.cc/V9U8-HH33].

39. Cassandra Willyard, *The Drug-Resistant Bacteria that Pose the Greatest Health Threats*, NATURE: NEWS (Feb. 28, 2017), https://www.nature.com/news/the-drug-resistant-bacteria-that-pose-the-greatest-health-threats-1.21550 [https://perma.cc/U5WT-ZMEC].

40. *See* A.J. Tatem, D.J. Rogers & S.I. Hay, *Global Transport Networks and Infectious Disease Spread*, 62 ADVANCES PARASITOLOGY 293, 295 (2006) ("[T]he global growth of economic activity, tourism and human migration is leading to ever more cases of the movement of both disease vectors and the diseases they carry.").

societies has created perfect conditions for a bacterial infection to quickly and rampantly make its way through the dense populace,[41] while the warming climate fuels the expansion of vector-borne diseases.[42] Second, poverty, war, weakened health systems, and poor infrastructure all likely play a strong role in infectious disease outbreaks.[43]

As antibiotic-resistant bacteria continue to proliferate, new treatments are needed to meet this growing threat. However, research and development ("R&D") investments by the pharmaceutical industry into innovative antibiotics have been sorely lacking. Following the "golden" pipeline of antibiotic development in the 1960s and '70s, the majority of pharmaceutical manufacturers abandoned the field to pursue more lucrative therapeutics.[44] Low-hanging therapies have already been discovered, and the costs associated with conducting highly intensive, complex research have risen to astronomical heights. As a result, by the turn of the twenty-first century, the number of new antibiotics in development dropped from dozens to just three.[45]

The World Health Organization ("WHO") has identified 12 classes of pathogens that are highly resistant and thus in urgent need of new treatments.[46] While a number of domestic and international

41. Ronak B. Patel & Thomas F. Burke, *Urbanization – An Emerging Humanitarian Disaster*, 361 NEW ENG. J. MED. 741, 741 (2009).

42. *See* Nick Watts et al., *The 2017 Report of the Lancet Countdown: From 25 Years of Inaction to a Global Transformation for Public Health*, LANCET, Oct. 2017, at 3 (identifying that "altered climactic conditions are contributing to growing vectorial capacity for the transmission of dengue fever by *Aedes aegypti*").

43. *See* Waleed Al-Salem, Jennifer R. Herricks & Peter J. Hotez, *A Review of* Visceral Leishmaniasis *During the Conflict in South Sudan and the Consequences for East African Countries*, 9 PARASITES & VECTORS, Aug. 22, 2016, at 2 ("Visceral leishmaniasis . . . , also known as kala-azar, is a serious and often fatal neglected tropical disease . . . that is highly correlated with war, poverty and failed health systems . . . ."); Julia Belluz, *Why is Ebola Less Deadly in America than in Africa?*, VOX (Oct. 28, 2014), https://www.vox.com/2014/10/24/7059743/why-is-ebola-virus-outbreak-american-africa-nina-pham [https://perma.cc/GL74-4C5N] (noting that deficient health care systems have led to higher rates of death from Ebola in Africa than in the United States).

44. Jose M. Munita & Cesar A. Arias, *Mechanisms of Antibiotic Resistance*, 4 MICROBIOLOGY SPECTRUM, Apr. 2016, at 25; *see also* Ventola, *supra* note 11, at 279 (discussing that 15 of the 18 largest pharmaceutical companies have completely abandoned the antibiotic field).

45. Maryn McKenna, *We Need Antibiotics. They're Not Profitable to Make. Who Pays?*, NAT'L GEOGRAPHIC: SCI. & INNOVATION: GERMINATION (May 23, 2015), http://phenomena.nationalgeographic.com/2015/05/23/oneill-amr-3 [https://perma.cc/LK76-DNJW].

46. WHO, PRIORITIZATION OF PATHOGENS TO GUIDE DISCOVERY, RESEARCH AND DEVELOPMENT OF NEW ANTIBIOTICS FOR DRUG-RESISTANT BACTERIAL INFECTIONS,

efforts have been made to incentivize pharmaceutical manufacturers to invest in the field,[47] the vast majority of antimicrobials developed in conjunction with these programs are small, low-risk improvements to existing therapeutics.[48] Only eight were identified by the WHO as innovative treatments that may actually add value to the current treatment arsenal.[49]

II. PHAGES: USING THE NATURAL ENEMY OF BACTERIA IN NEW TREATMENTS

Increasing bacterial resistance and the urgent need for novel antimicrobial therapeutics has reignited interest within the scientific community about phage therapy.[50] This Part introduces phages, their therapeutic possibilities, and some of the challenges phage therapeutic manufacturers face.

A. What Are Phages?

Phages, the most abundant biological grouping on earth, are a category of viruses that are able to infect bacteria.[51] The term "bacteriophage" can be literally translated to "bacteria eater," in reference to the virus's bactericidal capabilities.[52] Like most viruses, phages generally consist of a protein coat that surrounds a core

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INCLUDING TUBERCULOSIS 79 (2017), http://www.who.int/medicines/areas/rational_use/PPLreport_2017_09_19.pdf?ua=1 [https://perma.cc/T5UE-RAYY]. The WHO's list includes and prioritizes bacterial infections based on their mortality, their burden on healthcare systems and communities, antibiotic-resistance prevalence and trends, their transmissibility, their preventability, their treatability, and existing antibiotics in the pipeline. *Id.* at 78. The top-priority pathogens are strains of *Pseudomonas aeruginosa*, a common cause of sepsis and pneumonia; *Enterobacteriaceae*, a family of bacteria causing urinary tract and bloodstream infections and pneumonia; and *A. baumannii*, which is commonly associated with bloodstream infections and pneumonia. *Id.* at 41–42.

47. *See infra* Part IV.

48. Zosia Kmietowicz, *Few Novel Antibiotics in the Pipeline, WHO Warns*, BRIT. MED. J. (Sept. 19, 2017), https://www.bmj.com/content/358/bmj.j4339 [https://perma.cc/MV9N-85LJ].

49. *Id.*

50. *See* Dwayne R. Roach et al., *Synergy Between the Host Immune System and Bacteriophage is Essential for Successful Phage Therapy Against an Acute Respiratory Pathogen*, 22 CELL HOST & MICROBE 38, 38–39 (2017).

51. James MacDonald, *Fighting Bacterial Infection with . . . Viruses?*, JSTOR: DAILY (Apr. 2, 2018), https://daily.jstor.org/fighting-bacterial-infection-with-viruses/ [https://perma.cc/R57G-JX3E].

52. *Bacteriophage*, NATURE EDUC.: SCITABLE, https://www.nature.com/scitable/definition/bacteriophage-phage-293 [https://perma.cc/V83Q-5YB6] [hereinafter *Bacteriophage*, SCITABLE].

containing viral DNA or RNA.[53] While other forms exist, the most recognizable phage shape houses the viral genetic material in a spherical, twenty-sided—or icosahedral—protein shell that is connected by a tube to a set of spider-like legs.[54]

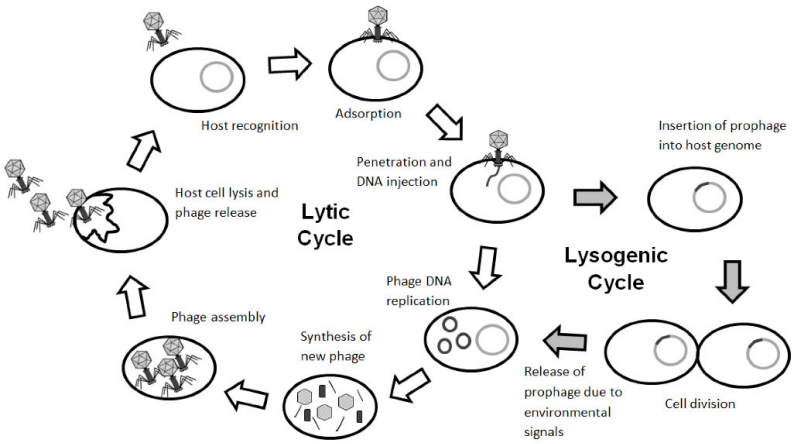

Figure 1. Bacteriophage Lytic and Lysogenic Cycles.

As seen in *Figure 1. Bacteriophage Lytic and Lysogenic Cycles*,[55] phages infect their hosts by binding to a bacterium's cell wall, perforating the wall through enzymatic action, and injecting viral genetic material into the bacterium.[56] A phage's genetic material then effectively "hijacks" the host cell and causes it to produce viral components that assemble into new phages.[57] Eventually, the pressure of the numerous new viruses within the cell cause the infected bacterium to rupture and die, and the new phages burst forth to continue the cycle.[58] This, notably, is the only method through which

53. *Bacteriophage – Bacteriophage Structure*, JRANK, http://science.jrank.org/pages/715/Bacteriophage-Bacteriophage-structure.html [https://perma.cc/K7SG-PEDQ].

54. *See id.* ("Bacteriophage have different three-dimensional shapes (or morphologies). T-even phages . . . have a head that has a slightly spherical shape called an icosahedron. A tube connects the head to spider-like supporting legs.").

55. Janis Doss et al., *A Review of Phage Therapy Against Bacterial Pathogens of Aquatic and Terrestrial Organisms*, 9 VIRUSES 50, fig. 2 (2017).

56. *Bacteriophage – Bacteriophage Structure*, *supra* note 53.

57. *Bacteriophage*, SCITABLE, *supra* note 52.

58. *Id.* (describing the process of lysis).

phages can multiply.[59] Some phages also undergo lysogenic cycles, whereby the phage invades a host nonlethally by injecting it with viral DNA that is then incorporated into the bacterial DNA and passed down to subsequent bacterial generations.[60] Certain conditions can cause the dormant prophage DNA to reactivate and initiate a lytic cycle.[61]

Like the bacteria they infect, phages can flourish in almost any environment,[62] as they are highly adaptable.[63] Researchers hypothesize that the coevolution of bacteria and phages has been crucial in shaping the microbial communities that are essential to defining life on Earth.[64] As bacteria adapt and change, phages quickly respond, keeping bacterial populations in check.[65] This coevolution makes phages highly specialized to just one or a few strains of bacteria.[66] While a certain phage strain may only be able to infect one strain of bacteria, a single strain of bacteria may have multiple types of phages that have adapted to infect it.[67] Studies suggest that this relationship has led to a vast continuum of genetic variation in the phage world.[68]

Because the continued existence of a specific phage strain is conditioned on phages of those type finding a proper bacterial host, phages targeted to infecting specific strains of bacteria are found

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59. *See* Beata Weber-Dabrowska et al., *Bacteriophage Procurement for Therapeutic Purposes*, 7 FRONTIERS MICROBIOLOGY, Aug. 12, 2016, at 2 ("Bacteriophages are viruses which have the ability to multiply only in bacterial cells . . . .").

60. *Bacteriophages*, KHAN ACAD., https://www.khanacademy.org/science/biology/biology-of-viruses/virus-biology/a/bacteriophages [https://perma.cc/PDR8-2S28].

61. *Id.*

62. Howard Hughes Med. Inst., *Understanding Genetic Diversity of Bacteriophage*, PHYS.ORG (Apr. 29, 2015), https://phys.org/news/2015-04-genetic-diversity-bacteriophages.html [https://perma.cc/SC4V-M8U3].

63. Britt Koskella & Michael A. Brockhurst, *Bacteria-Phage Coevolution as a Driver of Ecological and Evolutionary Processes in Microbial Communities*, 38 FEMS MICROBIOLOGY REV. 916, 924 (2014).

64. *Id.* at 920.

65. *Id.* at 923.

66. *Id.* at 925 (discussing the coevolution of phages and bacteria, the variety of phage genotypes it produces, and suggesting that this genetic mosaicism means there is "some constraint upon host range even among the most broadly infectious phages").

67. Julianne H. Grose & Sherwood R. Casjens, *Understanding the Enormous Diversity of Bacteriophages: The Tailed Phages that Infect the Bacterial Family* Enterobacteriaceae, VIROLOGY, Sept. 19, 2014, at 421–22.

68. *See* Howard Hughes Med. Inst., *supra* note 62 ("The study compared the genomes of 627 bacteriophages isolated from a single species of bacteria, and found a continuum of genetic diversity, rather than discrete groups within the population.").

wherever that bacterium is.[69] For example, phages exist as highly specified and highly effective killers in lakes, soil, sludge, fecal matter, and other bacteria-rich environments.[70] Human-altered environments, such as areas with hospital waste and sewage, therefore offer rich supplies of phages that are capable of infecting bacteria that are pathogenic in humans.[71]

B. Developing Therapeutic Interventions that Utilize Phages

After phages were officially discovered in the early twentieth century, scientists quickly identified their possible therapeutic potential.[72] In 1917, approximately one year after the first phages were isolated, microbiologist Felix d'Herelle tested a phage cocktail on a number of patients suffering from severe dysentery.[73] All four patients recovered within 24 hours after receiving a single dose of phages.[74] By the 1940s, several companies had begun developing and producing phage therapies targeted at bacterial pathogens such as staphylococci, streptococci, and *Escherichia coli*.[75]

Despite some initial success, the efficacy of these early phage therapeutics remained controversial within the scientific community.[76] Around the same time, antibiotics came bursting onto the scene with the discovery of penicillin.[77] Not long afterwards, the Western world

69. *See* Dipali Pathak, *Bacteriophages, Natural Drugs to Combat Superbugs*, PHYS.ORG (Apr. 18, 2017), https://phys.org/news/2017-04-bacteriophages-natural-drugs-combat-superbugs.html [https://perma.cc/2W9F-3YSM] (noting that birds and dogs carrying a particular *Escherichia coli* bacteria strain also carry the phages specific to that strain).

70. Weber-Dabrowska et al., *supra* note 59, at 2, 6.

71. Roja Rani Pallavali et al., *Isolation and* In Vitro *Evaluation of Bacteriophages Against MDR-Bacterial Isolates from Septic Wound Infections*, 12 PLOS ONE, July 18, 2017, at 3, https://journals.plos.org/plosone/article?id=10.1371/journal.pone.0179245 [https://perma.cc/475C-EMG7].

72. *See* Alexander Sulakvelidze, Zemphira Alavidze & J. Glenn Morris, Jr., *Bacteriophage Therapy*, 45 ANTIMICROBIAL AGENTS & CHEMOTHERAPY 649, 649–50 (2001) (discussing the official discovery of phages by Felix d'Herelle and his subsequent use of phages to treat dysentery in 1919).

73. Zhabiz Golkar, Omar Bagasra & Donald Gene Pace, *Bacteriophage Therapy: A Potential Solution for the Antibiotic Resistance Crisis*, 8 J. INFECTION DEVELOPING COUNTRIES 129, 131 (2014).

74. *Id.*

75. Sulakvelidze et al., *supra* note 72, at 650.

76. *Id.*

77. *Id.*; Newman, *supra* note 26.

abandoned its pursuit of effective phage therapeutics in favor of these easier-to-produce, cheaper, and more consistent drugs.[78]

1. *Creating Phage-Based Therapeutic Products.* With the potentially catastrophic effects of antibiotic resistance looming in the near future, physicians' and researchers' interests in phage therapy have been reinvigorated.[79] Mr. Patterson's sensational story is just one example of the scientific community testing the waters of phage therapeutics.[80] Phage therapies present a number of observed and theoretical benefits over traditional antibiotics. Unlike antibiotics, bacterial resistance to phages is not generally a threat; even the toughest multidrug-resistant bacteria are fully vulnerable to the right phage.[81] If a bacterial strain exposed to phage therapy does develop some defense mechanism against phage infection, true resistance is unlikely to develop.[82] Unlike the static chemical compounds that make up antibiotics, phages are *living things*. As naturally occurring organisms with many millennia of natural selection ingrained in their evolutionary past, phages likely have the innate ability to counter almost any phage-resistant bacterial adaptations.[83] This would allow physicians to alter phage treatments in real time to kill bacteria, should resistance develop.[84]

Unlike traditional antibiotics that may target and destroy good or neutral systemic bacteria, phages are also highly specified to certain

78. Sulakvelidze et al., *supra* note 72, at 650. Some research on, and therapeutic use of, phages continued in a number of Eastern European countries and the Soviet Union; this work has yielded a fair amount of international literature supporting the safety and efficacy of various phage therapies. *Id.*

79. *See* LaFee & Buschman, *supra* note 2 (describing the possibilities of phage therapy for multidrug-resistant infections and personalized medicine).

80. *See* Carl Zimmer, *A Virus, Fished Out of a Lake, May Have Saved a Man's Life – And Advanced Science*, STAT (Dec. 7, 2016), https://www.statnews.com/2016/12/07/virus-bacteria-phage-therapy/ [https://perma.cc/B2UL-EPDF] (describing another successful use of phage therapy in the United States).

81. *See* Joanna Urban, *Advancing Phage Therapy*, AM. SOC'Y MICROBIOLOGY: MBIOSPHERE (Jan. 17, 2017), https://www.asm.org/index.php/mbiosphere/item/5471-advancing-phage-therapy [https://perma.cc/332W-2ZNP] ("Antibiotic-resistant bacteria are usually fully sensitive to phages, and because phages are so abundant in nature, multiple phages can be used together or combined with antibiotics to maximize treatment outcomes.").

82. Golkar et al., *supra* note 73, at 131. However, that is not to say that a *specific* strain of bacteria cannot become fully resistant to a *specific* phage strain.

83. *See id.* ("Like bacteria, phages mutate and therefore can evolve to counter phage-resistant bacteria.").

84. *See* Pathak, *supra* note 69 (quoting a scientist working with phages: "Should resistance develop again, we will evolve another phage - right back at them!").

hosts, which limits their ability to bind to off-target sites.[85] This makes them particularly safe therapeutics, with low toxicity and a much lower risk of negative side effects than traditional antibiotics.[86] The relatively benign systemic effects of phages on humans allow physicians to safely combine multiple phage strains into therapeutic cocktails when it is unclear which strain will be effective against a certain bacterium, or when doing so will synergistically increase the strength of the therapy.[87] Finally, a particularly salient strength of phage therapeutics is the mechanism by which they kill bacteria. Because phages destroy bacterial cells by reproducing within them, the therapeutic agent itself, the phage, multiplies at the site of the infection, thus concentrating and strengthening the treatment where it is needed most.[88]

2. *Biotechnology Companies Currently Researching Phage Therapies.* Reinvigorated interest in phage therapy has prompted both governmental bodies and a few private biotechnology companies to begin investigating phage therapeutics. In the United States, the National Institute of Allergy and Infectious Diseases ("NIAID") has identified phage therapy as one of seven prongs in its plan to combat antibiotic resistance, and has awarded grants to a number of universities studying phage therapies.[89] Although no phage therapeutics are currently approved for use in humans in the United States, the Food and Drug Administration ("FDA") announced in 2017 that it will allow compassionate use.[90] The European Commission expressed its approval in 2014 by funding Phagoburn, the first large,

85. Golkar et al., *supra* note 73, at 131.

86. Weber-Dabrowska et al., *supra* note 59, at 2.

87. *See id.* at 3. Studies have recorded synergistic effects when combining multiple phages that are each effective against the same host. *Id.*

88. *Id.* at 2.

89. Sara Reardon, *Phage Therapy Gets Revitalized*, NATURE: NEWS (June 3, 2014), https://www.nature.com/news/phage-therapy-gets-revitalized-1.15348 [https://perma.cc/3UL9-UJJP]; Press Release, Nat'l Inst. Health, New NIH Awards Will Support Development of Therapeutic Alternatives to Traditional Antibiotics (Jan. 12, 2016) [hereinafter New NIH Awards], https://www.nih.gov/news-events/news-releases/new-nih-awards-will-support-development-therapeutic-alternatives-traditional-antibiotics [https://perma.cc/Z9P6-4H9B].

90. Julie Odland, *Everything Old is New Again: Bacteriophage Therapy*, CLARIVATE ANALYTICS (Dec. 14, 2017), https://clarivate.com/blog/life-sciences-connect/everything-old-new-bacteriophage-therapy/ [https://perma.cc/Z433-VXQB]. "Compassionate use" refers to the use of investigational, non-FDA-approved therapeutic products for treatment purposes; it is generally only available in serious or life-threatening situations when all available treatment options have been exhausted. *Expanded Access (Sometimes Called Compassionate Use)*, U.S. FOOD & DRUG ADMIN., https://www.fda.gov/NewsEvents/PublicHealthFocus/ExpandedAccessCompassionateUse/default.htm [https://perma.cc/YR3C-MQNU] (last updated June 19, 2018).

multicenter, multiyear clinical trial testing phage therapies for human infections.[91]

Three private sector companies have taken the lead in investigating phage therapeutics in the United States. While not geared toward treating bacterial infections, Intralytix has brought to market a number of FDA-approved phage products that address food safety issues.[92] On February 15, 2018, Intralytix announced that the FDA cleared Intralytix's phage treatment for Crohn's disease for Phase I/II clinical trials, making it one of the first phage therapies to begin clinical testing in the United States.[93] Another company, AmpliPhi Biosciences, was on the team that helped treat Tom Patterson.[94] AmpliPhi is currently developing multiphage therapeutics aimed at treating infections caused by *Staphylococcus aureus* and *Pseudomonas aeruginosa*, both of which are on the WHO's 2017 Priority Pathogens List.[95] Finally, EpiBiome has developed and brought to market a superior bacterial profiling service,[96] and has developed partnerships with a number of organizations to leverage this technology in developing highly targeted phage therapeutics.[97]

While these ongoing efforts suggest a percolating interest in phage therapeutics, progress and investment in the field remains minimal in Western countries.

3. *Challenges in Developing Phage Therapeutics.* The road to creating phage therapeutics is not smoothly paved, and many

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91. Reardon, *supra* note 89.

92. *Frequently Asked Questions*, INTRALYTIX, http://www.intralytix.com/index.php?page=faq [https://perma.cc/CBC8-D5AP].

93. *Intralytix Receives FDA Clearance to Initiate Phase I/IIa Clinical Trials*, INTRALYTIX (Feb. 15, 2018), http://www.intralytix.com/index.php?page=news&id=87 [https://perma.cc/6WLE-835P].

94. Marlene Cimons, *This Man Should Have Died, But Unusual Infusions Saved His Life*, WASH. POST (July 2, 2017), https://www.washingtonpost.com/national/health-science/this-man-should-have-died-but-unusual-infusions-saved-his-life/2017/06/30/503585b6-4aec-11e7-9669-250d0b15f83b_story.html?utm_term=.7fa3b6edc736 [https://perma.cc/4SEP-2REJ].

95. *Pipeline*, AMPLIPHI BIOSCIENCES CORP., http://www.ampliphibio.com/pipeline/ [https://perma.cc/F4GB-KWH6].

96. *See Bacterial Profiling: Why Do We Need to Profile Bacteria?*, EPIBIOME, https://www.epibiome.com/products-services/bacterial-profiling/ [https://perma.cc/VQ58-R4A8] (describing this profiling service as "breakthrough technology that enables the most reliably accurate biogram results").

97. *Phage Based Technologies: What Are Bacteriophages?*, EPIBIOME, https://www.epibiome.com/products-services/phage-based-technologies/ [https://perma.cc/AMW2-GLYQ].

challenges stand in the way of companies developing these products. As previously mentioned, the adaptability of phages has produced a great variety of phages in the natural world.[98] Sifting through this vast number of phages to identify a strain capable of targeting a specific pathogen involves significant time, effort, and collaboration.[99] Further complicating phage screening and selection are the instability of certain phage strains when in isolated storage, as well as the risk of a strain having lysogenic capabilities that can transfer genetic information that dangerously alters bacterial virulence or resistance.[100] Phage-based product developers also face a number of manufacturing challenges when isolating, culturing, purifying, sterilizing, preparing, and storing phages.[101] Phage purification and sterilization are particularly delicate tasks. Because phages must be cultured *within* bacteria, the resulting products must be thoroughly filtered to remove any remnants of hazardous bacterial endotoxins.[102] The manufacturing expenses for phage products likely match the high costs seen elsewhere in the pharmaceutical industry.[103]

Importantly, phage products are subject to arguably ill-suited FDA regulation.[104] The clinical trials required by the FDA will likely be complicated by the immediacy with which treatment is often required for bacterial infections, the degree of specificity required

98. *See* Mikael Skurnik, Maria Pajunen & Saija Kiljunen, *Biotechnological Challenges of Phage Therapy*, 29 BIOTECHNOLOGY LETTERS 995, 1001 (2007) (reporting a high rate of genetic novelty among phages sequenced as part of a study of the extensive mosaicism of phage genomes); *see also supra* Part II.A.

99. *About*, PHAGE DIRECTORY, https://phage.directory/about [https://perma.cc/Z5M6-AQAV].

100. *See* Hans-W. Ackermann, Denise Tremblay & Sylvain Moineau, *Long-Term Bacteriophage Preservation*, WORLD FED'N FOR CULTURE COLLECTIONS NEWSL., Issue no. 38, Jan. 2004 (noting difficulties in the long-term storage of phages); Franklin L. Nobrega, Ana Rita Costa, Leon D. Kluskens & Joana Azeredo, *Revisiting Phage Therapy: New Applications for Old Resources*, 23 TRENDS MICROBIOLOGY 185, 185–86 (2015) (noting lysogenic capabilities that risk transferring new genes to bacteria).

101. *See* Stephen T. Abedon, Sarah J. Kuhl, Bob G. Blasdel & Elizabeth Martin Kutter, *Phage Treatment of Human Infections*, 1 BACTERIOPHAGE 66, 74, 81 (2011) (describing some steps of the phage manufacturing process).

102. Skurnik et al., *supra* note 98, at 999.

103. *See* Catherine Loc-Carrillo & Stephen T. Abedon, *Pros and Cons of Phage Therapy*, 1 BACTERIOPHAGE 111, 113 (2011) ("Generally these costs of phage production, per unit, are not out of line with the costs of pharmaceutical production while the costs of discovery (isolation) and characterization can be relatively low.").

104. Callum J. Cooper, Mohammadali Khan Mirzaei & Anders S. Nilsson, *Adapting Drug Approval Pathways for Bacteriophage-Based Therapeutics*, 7 FRONTIERS MICROBIOLOGY, Aug. 2016, at 11.

when matching a phage product and a bacterial strain, comorbidities, and the small number of patients that suffer from the most aggressive antibiotic-resistant bacterial infections.[105] Furthermore, one of the biggest strengths of phage-based products is the potential to create precision cocktails or to adapt a cocktail to target an adapting bacterium.[106] It remains unclear whether each altered cocktail would require full FDA approval as a new therapeutic product.[107] Acquiring FDA approval in advance for each *individual* phage that may be used in a cocktail would also be prohibitively expensive, as phage libraries can include thousands of distinct phages.[108] While the FDA has indicated an interest in addressing these regulatory challenges, the status of the regulatory pathway for phage therapeutics remains unclear.[109]

III. THE PATENTABILITY OF PHAGE THERAPIES

It has long been understood that the unique economic characteristics of the pharmaceutical industry are largely to blame for the exceedingly high price associated with bringing a new drug to market.[110] Though there is heated debate surrounding the issue, most scholars estimate the cost of developing a new drug to be between $1.5 and $2.6 billion.[111] The two factors that have emerged as particularly responsible for the high cost of drug development are the expense of clinical testing and the high risk of product failure.[112]

To offset R&D costs, patent protection and other regulatory exclusivities have proven to be highly important for incentivizing

105. *Id.* at 2.

106. *See supra* Part II.B.1.

107. Cooper et al., *supra* note 104, at 6.

108. *Id.*

109. *See AmpliPhi Biosciences Provides Corporate and Strategic Update*, BUS. WIRE (Dec. 14, 2017), https://www.businesswire.com/news/home/20171214006331/en/AmpliPhi-Biosciences-Corporate-Strategic-Update [https://perma.cc/2EZW-TK26] (stating that the FDA has "expressed a commitment to addressing the unique regulatory challenges that might arise during product development").

110. Iain Cockburn & Genia Long, Editorial, *The Importance of Patents to Innovation: Updated Cross-Industry Comparisons with Biopharmaceuticals*, 25 EXPERT OPINION ON THERAPEUTIC PATS. 739, 740 (2015).

111. Rachel E. Sachs, *Innovation Law and Policy: Preserving the Future of Personalized Medicine*, 49 U.C. DAVIS L. REV. 1881, 1889 n.28 (2016).

112. Cockburn & Long, *supra* note 110, at 739.

pharmaceutical innovation.[113] Patents and other types of exclusivity allow pharmaceutical manufacturers to extract significant value from their inventions by granting a limited monopoly during which competition is prohibited and pricing is discretionary.[114] Extracting sufficient profits from a product during this initial period of exclusivity is highly important to pharmaceutical manufacturers, as an innovator drug's share of market sales drops to near nothing as soon as a less expensive, generic version is introduced.[115] This dynamic has caused patents to become highly valued in the pharmaceutical industry.[116] Numerous studies provide empirical support for the importance of commercial exclusivities in pharmaceuticals; they report that patents are used more often, that they are more heavily relied on, and that they are considered more valuable for innovation in the pharmaceutical industry than in other comparable industries.[117] Many statutory schemes, such as the Drug Price Competition and Restoration Act of 1984, rely heavily on patent rights to encourage drug manufacturers to take on challenging R&D by providing a means for them to recoup those costs in the market.[118]

A. The Problem of Weak Patent Protection for Phage Therapies

Dubious or categorically excluded patent protection for phage therapies could have highly negative implications for the development of phage therapeutics. Because of the unique challenges associated with developing phage-based therapies, the cost associated with bringing a phage therapy to market is likely to match, if not exceed, the multibillion-dollar price tag associated with bringing a new small-molecule drug to market.[119] As previously discussed, phages are numerous, highly variable, highly specialized, and unlikely to traipse smoothly through the FDA's existing regulatory pathway.[120] Bacteria

113. *See id.* (explaining that R&D must be funded by profits from successful, on-market medicines and that typically, once patent protection lapses, generics launch and their share-value increases).

114. Frederick M. Abbott, *Excessive Pharmaceutical Prices and Competition Law: Doctrinal Development to Protect Public Health*, 6 U.C. IRVINE L. REV. 281, 286–87 (2016).

115. Cockburn & Long, *supra* note 110, at 740. One study suggests that an innovator drug's market share drops to about 16 percent within a year of generic entry. *Id.*

116. *Id.* at 739.

117. *Id.* at 740–41.

118. *Id.*

119. *See supra* Part II.B.3.

120. *See supra* Parts II.A, B.3.

can also mutate quickly, meaning there is a risk of a specific phage therapy that is invested in today being rendered worthless tomorrow.[121] While one of the strengths of phages is that they can evolve to meet bacterial resistance, the regulatory roadblocks discussed *supra* in Part II.B.3 present a challenge for addressing this resistance in real time.

Bringing new treatments for bacterial infections to market involves an additional set of challenges for developers that are not as prevalent for developers of drugs targeting other diseases or illnesses. Bacterial infections lack a strong array of diagnostics that are able to quickly and cost-effectively identify specific pathogenic infections against which an antimicrobial can be tested.[122] Because bacterial infections often require immediate treatment, the lack of good diagnostic options would likely complicate and lengthen the already extensive clinical trial process by making it more difficult to identify proper participants and control for confounding factors.[123] Antimicrobials are also taken only for short periods of time and therefore generate a smaller volume of sales than treatments for chronic conditions.[124] Those sales are unlikely to be recoupable through high prices due to the public perception associating the historically high prevalence and low costs of antibiotics with low value.[125] Sales of new antibiotics are further inhibited by medical and public health policies that encourage the sparing use of newer antibiotics to preserve their novelty in order to delay the development of resistance.[126] Insufficiently protecting the front end investment of phage product developers may discourage interest, investment, and innovation in the field.[127]

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121. *See* Andrej Godány, Gabriela Bukovská, Jarmila Farkašovská & Ivan Mikula, *Phage Therapy: Alternative Approach to Antibiotics*, 58 BIOLOGIA 313, 316 (2003) (explaining how bacterial strains develop phage resistance and outlining five groups of bacterial resistance).

122. GREGORY W. DANIEL ET AL., DUKE-MARGOLIS CTR. HEALTH POL'Y, TRACKING THE PROGRESS OF ECONOMIC INCENTIVES FOR ANTIMICROBIAL DRUG DEVELOPMENT IN THE U.S. AND ACROSS THE GLOBE 6 (2016), https://healthpolicy.duke.edu/sites/default/files/atoms/files/Antimicrobial%20Economic%20Incentives%20Landscape%20Analysisv2.pdf [https://perma.cc/DPB6-6D2K].

123. *Id.*

124. *Id.* at *6–7.

125. *See* Ventola, *supra* note 11, at 279 ("Newer antibiotics are generally priced at a maximum of $1,000 to $3,000 per course compared with cancer chemotherapy that costs tens of thousands of dollars. The availability, ease of use, and generally low cost of antibiotics has . . . led to a perception of low value among payers and the public.").

126. *Id.* at 279–80.

127. *See supra* Part II.B.3.

Patents also play an important role in signaling value to potential investors.[128] Removing that signal may therefore decrease the funding opportunities available to companies developing phage therapies to finance their expensive R&D. Intralytix, one of the most active patentees in phage therapy, has already demonstrated the value of their existing portfolio by securing a single investment worth over $17 million.[129]

Failing to properly protect phage therapy patents could have far-reaching implications outside of the field as well. Low levels of innovation may lead to developers abandoning the field as in the 1940s; even if developers stay in the market, lack of competition may inhibit competitive innovation and pricing, or may facilitate the development of natural monopolies that can perpetually charge monopoly prices. Without the guarantee of patent protection, fewer second-comers will be incentivized to enter the market, and competitive pricing will falter. As concerns about healthcare spending in the United States become increasingly panicked, physicians may be hesitant to prescribe expensive phage therapies when traditional antibiotics are currently—and have historically been—so inexpensive.[130] Similar concerns could discourage insurance companies from covering such treatments. Discouraging the use of alternative antibiotics like phages could have the unfortunate effect of exacerbating antibiotic resistance.

B. Mayo*,* Myriad*, and the Changing Patent Landscape*

The patentability of phage therapeutics has been called into question by a number of recent cases that have cast doubt on the patentability of many life sciences products, and have thrown the industry into chaos.[131] In the first of these cases, *Mayo Collaborative*

128. Hanna Hottenrott, Bronwyn H. Hall & Dirk Czarnitzki, *Patents as Quality Signals? The Implications for Financing Constraints on R&D*, 25 J. ECON. INNOVATION & NEW TECH. 197, 199 (2016).

129. *Lesaffre Invests in Intralytix, a US Biotechnology Company*, PRNEWSWIRE (July 24, 2017), https://www.prnewswire.com/news-releases/lesaffre-invests-in-intralytix-a-us-biotechnology-company-300493121.html [https://perma.cc/4QUP-73BR].

130. *See* Carolyn Y. Johnson, *The U.S. Spends More on Health Care than Any Other Country. Here's What We're Buying*, WASH. POST (Dec. 27, 2016), https://www.washingtonpost.com/news/wonk/wp/2016/12/27/the-u-s-spends-more-on-health-care-than-any-other-country-heres-what-were-buying/?utm_term=.4d15fcd5c03e [https://perma.cc/YRR5-S5QL] (discussing the mounting concerns with high levels of health care spending in the United States).

131. Arti K. Rai & Jacob S. Sherkow, *The Changing Life Science Patent Landscape*, 34 NATURE BIOTECHNOLOGY 292, 292 (2016).

Services v. Prometheus Laboratories, Inc.,[132] the Supreme Court held invalid a patent claiming a method of determining the proper dosage of a thiopurine drug.[133] Depending on how a patient metabolizes thiopurine drugs, the same dose may be too high and risk harmful side effects in one patient, while being too low, and likely ineffective, in another.[134] The relevant patent addressed this difficulty in dosing by claiming a method of measuring the concentration of two known metabolites of thiopurine in a patient's blood, and comparing them to specified maximum and minimum threshold values in order to determine the proper dosage.[135]

The statute at issue in *Mayo*, 35 U.S.C. § 101, defines the parameters of patentable subject matter as including the invention or discovery of "any new and useful process, machine, manufacture, or composition of matter, or any new and useful improvement thereof."[136] However, the Court acknowledged a longstanding exception to § 101 that excludes "laws of nature, natural phenomena, and abstract ideas" from inclusion as patent-eligible subject matter.[137] The Court in *Mayo* analyzed whether the patent claims at issue fell under the first exclusion category as a "law of nature." Looking first at the correlation between the concentration of metabolites and the likelihood of over- or underdosage, the Court found the relationship to be unpatentable as a "natural law."[138] The correlation, argued the Court, concerns "the ways in which thiopurine compounds are metabolized by the body—entirely natural processes."[139] The Court then considered whether the patent claims did "significantly more than simply describe these natural relations," or whether the application of the law of nature in the claimed method was sufficiently transformative.[140] The Court found that the claimed application of the law—having a physician "first administer a thiopurine drug and [then] measure the resulting metabolite concentrations" to determine proper dosage—constituted no more than an instruction to use the "well-understood, routine, conventional activit[ies] already engaged in by the scientific

132. Mayo Collaborative Servs. v. Prometheus Labs., Inc., 566 U.S. 66 (2012).
133. *Id.* at 77.
134. *Id.* at 73.
135. *Id.* at 73–74.
136. 35 U.S.C. § 101 (2012).
137. *Mayo*, 566 U.S. at 70 (quoting Diamond v. Diehr, 447 U.S. 175, 185 (1981)).
138. *Id.* at 77.
139. *Id.*
140. *Id.*

community," by which a physician would normally utilize such a law.[141] The Court therefore held that the claimed application lacked a sufficiently inventive step.[142]

The life sciences were dealt another blow the next year by the Supreme Court's unanimous decision in *Association for Molecular Pathology v. Myriad Genetics, Inc.*[143] Prior to that litigation, Myriad identified and patented the sequences of the BRCA1 and BRCA2 genes, in which are found mutations linked to higher risks of breast and ovarian cancers.[144] The challenged patents covered sequences of parts of the genes' isolated DNA and "cDNA"—a synthetic type of DNA that is created in a lab.[145] Unlike naturally occurring DNA, cDNA is manufactured to include only the portions of the targeted genetic sequence that code for proteins, with the naturally interspersed noncoding regions removed.[146] The *Myriad* Court analyzed whether the patent claims fell under the second exclusion category as a "natural phenomena," that is, whether they claimed a product of nature. Beginning its § 101 analysis with the claims covering isolated genetic DNA, the Court explained that the company "did not create anything" new by identifying and isolating the BRCA sequences.[147] The BRCA DNA sequence exists as is in nature, and as such was found to be unpatentable.[148] Unlike genomic DNA, however, cDNA is man-made; the Court explained that cDNA is therefore distinct from DNA because "something new" is created when a laboratory technician produces a DNA product with the noncoding regions removed.[149] As such, cDNA was found to be patent-eligible.

The final case that largely reshaped patentability under § 101 was *Alice Corp. v. CLS Bank International*,[150] which considered the patentability of a computer program under § 101's third judicial exception for "abstract ideas."[151] In *Alice*, the Supreme Court refined and solidified its test for patent subject-matter eligibility under § 101

141. *Id.* at 79–80.
142. *Id.*
143. Association for Molecular Pathology v. Myriad Genetics, Inc., 569 U.S. 576 (2013).
144. *Id.* at 583.
145. *Id.* at 580, 582.
146. *Id.* at 582.
147. *Id.* at 590–91.
148. *Id.*
149. *Id.* at 594–95.
150. Alice Corp. Pty. Ltd. v. CLS Bank Int'l, 134 S. Ct. 2347 (2014).
151. *Id.* at 2354.

into a two-step framework that has become known as the "*Mayo*/*Alice* test." According to January 2018 guidance from the U.S. Patent and Trademark Office ("USPTO") on patentable subject matter, the *Mayo*/*Alice* test first requires determining whether a patent claim is within a judicial exception, that is, whether the claim is "directed to a law of nature, a natural phenomenon (product of nature) or an abstract idea." If so, then a court must determine whether the claim is nevertheless entitled to patent protection because it involves an inventive concept, that is, whether "the claim recite[s] additional elements that amount to significantly more than the judicial exception."[152]

Neither the relevant industries nor the lower courts have received the *Mayo*/*Alice* test favorably. Major concerns are percolating in the life sciences sector over future patent eligibility[153] as the U.S. Court of Appeals for the Federal Circuit struggles to understand the Court's broad, abstruse test.[154] Applications of the test following *Alice* have largely favored ineligibility, with over 90 percent of post-*Alice* Federal Circuit decisions on the issue finding patent ineligibility under *Mayo*, *Myriad*, and *Alice*, as of March 2017.[155] In *Ariosa Diagnostics, Inc. v. Sequenom, Inc.*,[156] the Federal Circuit applied the *Mayo*/*Alice* test to invalidate a patent claiming a method of amplifying and detecting paternally inherited cell-free fetal DNA located in a sample of a

152. U.S. PAT. & TRADEMARK OFF., MPEP § 2106 (9th ed. Rev. 08.2017, Jan. 2018). While it was initially thought that *Alice* might be limited to software patents, the Federal Circuit validated its applicability to the life sciences by invoking the test in subsequent biotechnology cases. Douglas Hallward-Driemeier, *Federal Circuit Applies* Alice *to Biotechnology in Striking Down Myriad Method of Screening Claims, Leaves Door Open for Narrower Method Claims*, ROPES & GRAY: NEWSROOM (Dec. 18, 2014), https://www.ropesgray.com/en/newsroom/alerts/2014/December/Federal-Circuit-Applies-Alice-to-Biotechnology-in-Striking-Down-Myriad-Method-of-Screening-Claims [https://perma.cc/6VMW-P46W].

153. Robert L. Stoll, *New Patent Subject-Matter Eligibility Test Hurts US Competitiveness*, THE HILL (Jan. 27, 2016), http://thehill.com/blogs/pundits-blog/technology/267139-new-patent-subject-matter-eligibility-test-hurts-us [https://perma.cc/EQG3-WT92].

154. *See* Steven M. Amundson, *The Supreme Court's Decision in* Alice Corp. v. CLS Bank *Has Taken a Heavy Toll on Patents for Computer-Related Inventions*, LEXOLOGY (Feb. 16, 2016), https://www.lexology.com/library/detail.aspx?g=300e6862-012d-49dd-bed4-ba8ae4477397 [https://perma.cc/TL5W-BMQT] ("Absent clear guidance from the Supreme Court, lower courts have at times had difficulty determining what constitutes an abstract idea and what amounts to an inventive concept.").

155. David Kappos, Dir., U.S. Pat. & Trademark Off. 2009–2013, Address at the Federal Circuit Bar Association & the Center for Innovation Policy at Duke Law Symposium: Are Patents Under Attack? 9 (Apr. 6, 2018) (PowerPoint slides on file with *Duke Law Journal*).

156. Ariosa Diagnostics, Inc. v. Sequenom, Inc., 788 F.3d 1371 (Fed. Cir. 2015).

pregnant woman's circulating blood.[157] Though the court agreed that the discovery "revolutionized prenatal care" by establishing a noninvasive means of detecting genetic conditions of a fetus,[158] the court found the method was not an inventive application of a law of nature under the *Mayo*/*Alice* test because the methods of fractioning blood and amplifying and detecting nucleic acid are "routine, conventional techniques."[159] The Federal Circuit used similar reasoning in 2016 to invalidate the patent at issue in *Genetic Technologies Ltd. v. Merial L.L.C.*,[160] which claimed a method of detecting a coding region of an individual's DNA by amplifying and analyzing linked noncoding regions.[161]

The courts have invalidated a number of other diagnostic and method of treatment patents in the wake of *Mayo*, *Myriad*, and *Alice*. Examples include patents claiming a method of treating patients with inhaled nitric oxide in a way that decreases the risk of pulmonary edema,[162] patents claiming a method for determining whether a particular type of drug is likely to be effective based on the presence or absence of certain genetic mutations,[163] and patents covering a method of diagnosing cardiovascular risk by detecting and analyzing the levels of a specific enzyme in a biological sample.[164]

Composition of matter claims have also fared poorly under the *Mayo*/*Alice* test. In *Natural Alternatives International, Inc. v. Creative Compounds, L.L.C.*,[165] the U.S. District Court for the Southern District of California considered patents claiming a dietary supplement comprised of the amino acid beta-alanine.[166] The court found that the claims were actually directed to beta-alanine itself, a naturally occurring phenomenon.[167] As such, even isolated in the form of a

157. *Id.* at 1373–74.

158. *Id.* at 1379 (quoting Brief of Appellant at 25, Ariosa Diagnostics, Inc. v. Sequenom, Inc., 788 F.3d 1371 (Fed. Cir. 2015) (Nos. 2014-1139, 2014-1144)).

159. *Id.* at 1377 (citing 35 U.S.C.A. § 101 (2012)).

160. Genetic Techs. Ltd. v. Merial L.L.C., 818 F.3d 1369 (Fed. Cir. 2016).

161. *Id.* at 1372.

162. Mallinckrodt Hosp. Prods. IP Ltd. v. Praxair Distribution, Inc., No. 15-170-GMS, 2017 WL 3867649, at *2 (D. Del. Sept. 5, 2017).

163. Esoterix Genetic Labs. LLC v. Qiagen Inc., 133 F. Supp. 3d 349, 351–52 (D. Mass. 2015).

164. Cleveland Clinic Found. v. True Health Diagnostics LLC, 859 F.3d 1352, 1355 (Fed. Cir. 2017).

165. Nat. Alternatives Int'l, Inc. v. Creative Compounds, LLC, Nos. 16-cv-02146-H-AGS, 16-cv-02343-H-AGS, 2017 WL 3877808 (S.D. Cal. Sept. 5, 2017).

166. *Id.* at *5.

167. *Id.*

supplement, the claims were directed at a patent-ineligible product of nature.[168] Because placing a natural substance into a dietary supplement and administering it to an individual to achieve a therapeutic effect is a conventional activity, the claims also failed under step two, the inventive concept prong, of the *Mayo*/*Alice* test.[169]

Life sciences companies are not completely without hope, however. A few months after *Merial*, the Federal Circuit upheld a patent in *Rapid Litigation Management Ltd. v. CellzDirect, Inc.*[170] that claimed a method of producing liver cells that remain viable following multiple cryopreservations using density gradient fractionation.[171] The court's decision was based on its finding that the claim was directed not at the natural law defining liver cells' ability to survive multiple freeze-thaw cycles, but rather at a "new and useful laboratory technique for preserving [liver cells]."[172] The court went on to explain that the claim would succeed under the *Mayo*/*Alice* test's second step regardless because while the "individual steps of freezing and thawing were well known," the process of repeating those steps to preserve liver cells for multiple cycles was, as a whole, "far from routine and conventional."[173]

CellzDirect clarifies that claims that touch upon a natural law are not necessarily ineligible for patents, and that the judicial exceptions are limited to "claims that 'amount to nothing more than observing or identifying the ineligible concept itself.'"[174] For example, in *Xlear, Inc. v. STS Health, L.L.C.*,[175] the U.S. District Court for the District of Utah found that a patent claiming a method of cleaning the nasopharynx of individuals by nasally administering a solution containing xylitol *is* patent-eligible subject matter.[176] Though xylitol is a product of nature,

168. *Id.*

169. *Id.* at *6. Other post-*Mayo*/*Myriad* composition patents have been invalidated, including patents that cover single-stranded DNA primers, *In re* BRCA– & BRCA2–Based Hereditary Cancer Test Patent Litig., 774 F.3d 755, 761 (Fed. Cir. 2014), and cloned animals, *In re* Roslin Inst. (Edinburgh), 750 F.3d 1333, 1337 (Fed. Cir. 2014).

170. Rapid Litig. Mgmt. Ltd. v. CellzDirect, Inc., 827 F.3d 1042 (Fed. Cir. 2016).

171. *Id.* at 1046.

172. *Id.* at 1048.

173. *Id.* at 1051.

174. Bruce M. Wexler, Evan D. Diamond, Edwin Mok & Alexander Plushanski, *Federal Circuit Upholds Patent Eligibility of a Method of Preserving Liver Cells, Giving Guidance on Applying Section 101's Exclusion of Natural Laws*, PAUL HASTINGS: INSIGHTS (July 7, 2016) (quoting *CellzDirect*, 827 F.3d at 1048), https://www.paulhastings.com/publications-items/details/?id=b3eee969-2334-6428-811c-ff00004cbded [https://perma.cc/3QB9-JUA3].

175. Xlear, Inc. v. STS Health, LLC, No. 2:14-cv-00806-DN, 2015 U.S. Dist. LEXIS 167707 (D. Utah Dec. 15, 2015).

176. *Id.* at *15.

the court held that a claim directed to "a new or novel application of xylitol" was patentable as an inventive process or method.[177]

Another Federal Circuit case, *Vanda Pharmaceuticals, Inc. v. West-Ward Pharmaceuticals International Ltd.*,[178] considered claims covering a method of treating schizophrenia with iloperidone by testing for whether a patient has a poor metabolizer genotype and then administering either a lower or higher dosage based on the results.[179] The court determined that the claims were not directed to the natural law governing the relationship between iloperidone, metabolism, and the specified health outcome, but to an application of that natural law.[180] According to the court, "the claims here are directed to a specific method of treatment for specific patients using a specific compound at specific doses to achieve a specific outcome."[181] The patent was therefore found valid.[182] A few other cases have upheld patents that are directed to natural laws or products under the second step of the *Mayo*/*Alice* test. One example is a patent that claims a method of approximating core body temperature based on readings from a lateral scan of the forehead and ambient temperature.[183] Another example is a claim that recites a method of monitoring drug metabolite levels that involves quantifying the levels in a urine sample in a way that accounts for the patient's degree of hydration.[184]

Those who find recent 35 U.S.C. § 101 jurisprudence murky and unclear with regards to the life sciences are in good company. Many critics argue that the *Mayo*/*Alice* test and its subsequent applications have "undermined certainty and protection for worthy inventions" in a number of ways.[185] This uncertainty is exemplified by "conflicting Federal Circuit subject matter eligibility decisions regarding patents covering very similar technologies, and patents found to be ineligible in the US, but eligible in other countries."[186]

177. *Id.* at *12–15.

178. Vanda Pharms., Inc. v. West-Ward Pharms. Int'l Ltd., 887 F.3d 1117 (Fed. Cir. 2018).

179. *Id.* at 1121.

180. *Id.* at 1136.

181. *Id.*

182. *Id.*

183. Exergen Corp. v. Kaz USA, Inc., 725 F. App'x 959, 961 (Fed. Cir. 2018).

184. Ameritox, Ltd. v. Millennium Health, LLC, 88 F. Supp. 3d 885, 890 (W.D. Wis. 2015).

185. Manny Schecter, *Patent Subject Matter Eligibility 101*, IPWATCHDOG (May 8, 2018), https://www.ipwatchdog.com/2018/05/08/patent-subject-matter-eligibility-101/id=96928/ [https://perma.cc/YRJ5-BXMB].

186. *Id.*

C. The Dubious Patentability of Phage Therapies Under the Mayo/Alice *Test*

Although antibacterial resistance is becoming a more pressing concern and interest in phage-based therapeutics continues to grow, recent jurisprudence concerning patentable subject matter has cast a long shadow over the field. Phage-based therapeutic products would likely be patented under § 101 as a "composition of matter" or a "new and useful process" for treating an infection.[187] Should the product be patented as a composition of matter, phages isolated from nature would undoubtedly be patent-ineligible under *Myriad*.[188] Like the isolated DNA sequences in *Myriad*, naturally occurring phages would likely be considered a product of nature.[189] One could argue that the isolation, purification, and sterilization of phages that is necessary to get the viruses into an administrable form would produce iterations of phages unlike any that exist naturally. However, a similar argument was rejected in *Myriad*; though the isolation of a sequence of DNA creates a nonnaturally occurring compound, the sequence itself was the subject matter of the claim.[190] Should a phage therapy manufacturer attempt to patent its product by claiming a naturally occurring phage as a composition of matter, the manner in which the phage is claimed—that is, as a purified therapeutic—would therefore likely be insufficient to save the patent under *Myriad*.

Though naturally occurring phages are very unlikely to be patentable as compositions of matter, a stronger argument may be made for the patentability of modified phages.[191] Current advances in synthetic biology have made it possible for researchers to alter the phenotypic expression of phages.[192] Using CRISPR/Cas-9 or other methods, the viral DNA of a phage can be altered to achieve a number of ends, such as changing the range of hosts the phage can infect.[193] Phage display technology, which allows for the synthetic expression of different proteins on the surfaces of phages, is another technique of

187. 35 U.S.C. § 101 (2012).

188. Reardon, *supra* note 89.

189. *Id.*

190. Ass'n for Molecular Pathology v. Myriad Genetics, Inc., 569 U.S. 576, 580 (2013).

191. Reardon, *supra* note 89.

192. Antonia P. Sagona, Aurelija M. Grigonyte, Paul R. MacDonald & Alfonso Jaramillo, *Genetically Modified Bacteriophages*, 8 INTEGRATED BIOLOGY 465, 465 (2016).

193. *Id.* at 465–67.

synthetically modifying phages.[194] Finally, phage genomes can be modified through directed evolution.[195] Patents covering phage therapeutics that claim a modified phage as a composition of matter would more closely resemble the synthetic cDNA patents found valid in *Myriad*. Regardless, uncertainty in the validity of such patents remains. A January 2018 article authored by a life sciences patent expert argues that the wide availability and applicability of CRISPR to virtually all situations may threaten the patentability of CRISPR-derived products in the future.[196] Increasing reliance and knowledge that genetic engineering techniques can be used to achieve diverse results could cause the resulting patents to fail to be nonobvious as is required under other provisions of the patent statute.[197] Phages developed through directed evolution may also be of dubious patentability as compositions of matter. Because directed evolution uses serial passaging—continuous culturing within a bioreactor—to guide or amplify a phage's natural ability to evolve, the actual modification of the phage is due to naturally occurring evolutionary processes.[198] Evolution is undoubtedly a natural law, and as one court explained, claims covering a product of nature whose only inventiveness come from an application of a law of nature are not sufficiently inventive under *Mayo*/*Alice*.[199]

Method or process patents covering phage therapeutics—as opposed to composition of matter patents—may fare slightly better under *Mayo*/*Alice*. Even if phage products themselves are products of nature, methods of producing modified phages may be patent eligible if they claim more than an application of a law or product of nature using "well-understood, routine, conventional activit[ies] already

194. *Id.* at 468.

195. *Id.* at 467–68.

196. *See* Jacob S. Sherkow, *The CRISPR Patent Landscape: Past, Present, and Future*, 1 CRISPR J. 5, 7–8 (2018) (noting that the "reasonable expectation of success in using CRISPR as a genome-editing tool for any system or cell type" and the obviousness of "using CRISPR to accomplish these goals" discourage "the patenting of follow-on inventions").

197. 35 U.S.C. § 103 (2012); *see* Sherkow, *supra* note 196, at 7 ("Now that the power of CRISPR as a genome-editing technology has been elucidated, is any future application of it nonobvious?").

198. *See* Sagona et al., *supra* note 192, at 467–68 (explaining the process by which phages can be directed to evolve through "serial passaging" in a bioreactor).

199. *See* Nat. Alternatives Int'l, Inc. v. Creative Compounds, LLC, No. 16-cv-02343-H-AGS, 2017 WL 3877808, at *6 (S.D. Cal. Sept. 5, 2017) ("[E]mploying a dietary supplement to administer beta-alanine—a natural phenomenon—to achieve a high level of carnosine synthesis in a human—applying a natural law—is insufficient to render the claims at issue patent eligible . . . .").

engaged in by the scientific community."[200] However, the use of genetic engineering, phage display, and directed evolution methodologies are already common practices for modifying phages, making such method claims dubious under both § 101 and § 103.[201]

Arguably the best option for procuring valid phage therapy patents would be to mimic the construction of patents seen in *Xlear* as a novel method of treatment. Like phages, xylitol is a natural product.[202] However, the *Xlear* patents were valid only insofar as they claimed the process by which that natural product would be used in the treatment of a condition for which it had never been used.[203] Though general knowledge of the ability to treat bacterial infections with phages has existed for decades, an argument could be made that developing a treatment method that uses a new strain or combination of phages that has never been used to treat a certain bacterial infection is an inventive application of a natural product. However, the authority and persuasive power of *Xlear* and its reasoning will remain limited unless affirmed by higher courts.

D. Current Patenting Efforts and Litigation in the Phage Therapy Field

While the patentability of phage therapeutics remains uncertain, phage therapy developers continue to apply for patents in the hopes of acquiring enforceable protection. Intralytix reports protecting its investment through the use of "a multi-prong [patenting] approach, which provides broad and strong protection ranging from protecting specific bacteriophages . . . to [protecting] methods and applications of those bacteriophages in various settings."[204] Intralytix's "throw everything at the wall to see what sticks" patenting strategy sheds light on the inner workings of the industry as a whole. Many of the patents relating to phage therapeutics that have been filed, of which there are relatively few, employ vastly different strategies for protection. These strategies include claiming methods of treatment in which phages are

200. *See* Mayo Collaborative Servs. v. Prometheus Labs., Inc., 566 U.S. 66, 79–80 (2012).

201. *See* Sagona et al., *supra* note 192, at 466–68 (discussing the use of genetic engineering, phage display, and directed evolution methodologies on phages).

202. Xlear, Inc. v. STS Health, L.L.C., No. 2:14-cv-00806-DN, 2015 U.S. Dist. LEXIS 167707, at *12 (D. Utah Dec. 15, 2015).

203. *Id.* at *12–15.

204. *Patents*, INTRALYTIX, http://www.intralytix.com/index.php?page=patents [https://perma.cc/6NK2-9L8Q].

administered,[205] patenting phage enzymes as opposed to full phages,[206] claiming the use of phages in animals,[207] and patenting strains of phages directly.[208] While the diversity of these strategies may be a product of necessity, it is likely that such wide variety, at least to some degree, reflects an uncertainty among those invested in phage product R&D as to how best to achieve strong patent protection. Alternatively, these diverse strategies may reflect that phage patents still hold some value as signaling mechanisms for investors, regardless of the actual enforceability of the patents. This shotgun approach to patent claims may also reflect expectations in the field that the law under *Mayo*, *Myriad*, and *Alice* will soon be changed, albeit in an unknown direction.

Very few suits regarding the validity of patents pertaining to phages have been brought in recent years. Furthermore, most of these suits involve patents that only tangentially touch on phages,[209] and they analyze validity based on challenges outside of § 101.[210] Because no case has been brought yet that directly addresses the validity of phage therapy as patentable subject matter, the uncertainty surrounding phage therapeutics remains. As more players enter the field, the likelihood of an impending clash between competitors' patents is ever increasing.

IV. INCENTIVIZING INVESTMENT IN PHAGE THERAPIES THROUGH NONPATENT MEANS

Patent protection has generally been "considered the gold standard for invention protection," due in large part to the strength,

205. *See* U.S. Patent No. 9,850,467 (claiming "[a] method for improving the state of health of patients infected with adenovirus HadV-5, comprising providing [and administering to the patient] a T4 phage preparation comprising an effective amounts of T4 phage to inhibit the proliferation of adenovirus HadV-5 by 50%").

206. *See* U.S. Patent No. 9,034,322 (claiming compositions "comprising an effective amount of [certain] isolated lysin polypeptide[s]").

207. *See* U.S. Patent No. 9,433,653 (claiming "[a] method of treating or reducing mortality due to E. coli diarrhoea in a non-human animal subject" that involves the use of "a composition comprising as the active ingredient an effective concentration of the isolated bacteriophage EK88P-1").

208. *See* U.S. Patent No. 8,440,446 (claiming "[a]n isolated bacteriophage strain specific against bacteria belonging to the genus Enterococcus").

209. *See, e.g.*, Regeneron Pharms., Inc. v. Merus B.V., 144 F. Supp. 3d 530, 574–75 (S.D.N.Y. 2015) (considering a phage-derived recombination system).

210. *See, e.g.*, *In re* Droge, 695 F.3d 1334, 1335–36 (Fed. Cir. 2012) (determining whether a claim tangentially related to phages was invalid under 35 U.S.C. § 103).

ease, and breadth with which patents can be enforced.[211] A therapeutic with limited patent protection is thus unlikely to be a financially attractive investment for manufacturers under normal market conditions.[212] However, phage therapy is not the first important field to suffer from being underincentivized or underprotected by the existing patent framework.[213] Finding workable alternatives or supplements to patent protection has proven successful in other fields and has strong potential in the field of phage therapeutics.

Trade secrecy—one of the most common nonpatent protections used in the biopharmaceutical industry—is already being employed by phage therapy developers. While trade secrecy is an easy way to achieve some protection for phage therapies, this protection is limited. A strong case can be made for establishing a period of regulatory exclusivity for phage therapies to supplement trade secrecy, though such periods are generally granted only for a short time. Although they do not address the threats posed by competitors, government-sponsored research funding and collaborations, as well as alternative payment models for phage therapies could provide additional incentives in the field by addressing cash flow issues at different points in the product's life cycle.

A. Trade Secrecy

Chief among nonpatent protections in the pharmaceutical field is trade secrecy. A trade secret is confidential information that gives a business a competitive edge.[214] These rights are judicially enforceable when the secret is not generally known to the public, and derives some economic benefit from being unknown, and is kept secret through

211. John Artz, Brandon Debus & Franklin Smith, *To Disclose or Not to Disclose: Trade Secrets vs. Patents*, LAW360 (Sept. 25, 2017), https://www.law360.com/articles/964200/to-disclose-or-not-to-disclose-trade-secrets-vs-patents [https://perma.cc/37GW-BSXH].

212. Alexandra Henein, *What Are the Limitations on the Wider Therapeutic Use of Phage?*, 3 BACTERIOPHAGE, Apr.–June 2013, 4–5 (2013).

213. For example, discoveries in the field of basic research are generally patent ineligible as laws or products of nature; these discoveries are nevertheless highly important building blocks for future innovation. Instead of relying on private patent rights, basic research is incentivized by an alternative model, whereby public funding is awarded to universities that conduct such research. *See* Désirée Schauz, *What is Basic Research? Insights from Historical Semantics*, 52 MINERVA 273, 318–19 (2014) (detailing the development of "basic research" as a concept so federal funding could be secured for research that does not produce immediate commercial benefit).

214. Tara Nealey, Ronald M. Daignault & Yu Cai, *Trade Secrets in Life Science and Pharmaceutical Companies*, COLD SPRING HARBOR PERSP. MED., Nov. 2014, 3.

reasonable efforts.[215] Trade secrecy offers protection for information that may not be eligible for patent protection.[216] It also has additional competitive benefits; unlike patents, trade secrets do not require disclosure to competitors, and they can be held indefinitely.[217] As such, using trade secrecy to protect investments has become the norm in a number of life sciences fields where patent protection is insufficient.[218]

Two fields in which trade secrecy has played an important role in incentivizing competition and innovation are biologics and genetic testing. In the biologics space, the complexity and sensitivity of the product requires the development of highly sophisticated manufacturing processes.[219] However, it can be difficult to protect that investment through manufacturing process patents, as they can be difficult to enforce and offer only temporary protection.[220] Trade secrecy has therefore been adopted by many biologics producers to protect intellectual property relating to manufacturing processes.[221] Because trade secrecy extends indefinitely and the details of those processes are not forced into the public domain, fewer biosimilar competitors find it financially viable to reverse engineer the complex processes with enough precision to produce acceptable biosimilars.[222] This indefinite pseudomonopoly makes trade secrecy extremely valuable to biologics manufacturers.[223]

Trade secrecy could have a number of applications for phage therapy manufacturers. As is the case with biologics, keeping production processes as trade secrets could provide a competitive edge by making it harder for others to reverse engineer similar phage products.[224] Innovative methods of purifying, preparing, amplifying, or

215. *Id.*

216. W. Nicholson Price II, *Making Do in Making Drugs: Innovation Policy and Pharmaceutical Manufacturing*, 55 B.C. L. REV. 491, 533 (2014).

217. *Id.*

218. Eric Lawrence Levi, *Using Data Exclusivity Grants to Incentivize Cumulative Innovation of Biologics' Manufacturing Processes*, 66 AM. U. L. REV. 911, 947 (2017).

219. *Id.* at 923.

220. Price, *supra* note 216, at 533.

221. W. Nicholson Price II & Arti K. Rai, *Manufacturing Barriers to Biologics Competition and Innovation*, 101 IOWA L. REV. 1023, 1046 (2016).

222. *Id.*

223. *Id.* at 1046–48.

224. Sofie Rombouts, Management of the Bacterial Pathogens *Xanthomonas Campestris PV. Campestris* and *Pseudomonas Syringae PV. Porri* in Cabbage and Leek Production Using Novel Bacteriophages, at *149 (Feb. 16, 2017) (unpublished Ph.D. dissertation, The Katholieke Universiteit Leuven).

storing phages would be protectable as trade secrets. AmpliPhi Biosciences has already incorporated trade secrecy into its business model, reporting in its 2018 SEC Annual Report that to "protect [its] proprietary know-how, which is not patentable, and for inventions for which patents may be difficult to enforce, [it] currently and will in the future rely on trade secret protection . . . to protect [its] interests."[225] The significant genetic variability of phages may also lead to the building of large phage libraries that can be used to create personalized treatments. Such libraries could possibly be maintained as trade secrets. However, this trade secrecy would not be boundless. Knowledge of the strains of phages themselves, of the composition of a cocktail of phages, and of their efficacy against a certain bacterium would likely no longer be considered a trade secret once the product is administered to members of the public. Therefore, while trade secrecy does provide some value for phage therapy manufacturers, its protection is likely limited to certain internal processes that would be difficult to replicate.[226]

Overreliance on trade secrecy may also have its drawbacks. As with biologics and biosimilars, maintaining extensive trade secrecy over phage product manufacturing processes may ratchet up the costs of follow-on innovation.[227] Hiding the discovery of new strains of phages in private silos may also inhibit the efficiency of basic and applied research[228] by shielding the "building blocks of human ingenuity" from potential future phage researchers and inventors.[229] Furthermore, phages have possible applications outside of human health in industries ranging from food safety to environmental

https://lirias.kuleuven.be/bitstream/123456789/562531/1/Dissertation+Sofie+Rombouts_final.pdf [https://perma.cc/XSW4-US9A].

225. AmpliPhi Biosciences Corp., Annual Report (Form 10-K) (Mar. 14, 2018).

226. *See generally* Jacob S. Sherkow, *Protecting Products Versus Platforms*, NATURE BIOTECHNOLOGY: BIOENTREPRENEUR (May 6, 2016), https://www.nature.com/bioent/2016/160401/pdf/bioe.2016.4.pdf [https://perma.cc/9CET-VUCG] (identifying specific biotechnology fields that may benefit from trade secrecy because those fields internally use some method or know-how that would be nearly impossible for an outsider to replicate by reverse engineering the end product).

227. *See* Price & Rai, *supra* note 221, at 1028 (describing the high costs of bringing new biologics to market due to trade secrecy in their manufacturing processes).

228. "Basic" research refers to research undertaken primarily for the sake of producing new knowledge, while "applied" research is geared toward more practical outcomes. Peter James Bentley, Magnus Gulbrandsen & Svein Kyvik, *The Relationship Between Basic and Applied Research in Universities*, 70 HIGHER ED. 689, 689–90 (2015).

229. Alice Corp. v. CLS Bank Int'l, 134 S. Ct. 2347, 2354 (2014).

sanitation to animal health.[230] Keeping new strains or related information secret could have the unfortunate off-target effect of creating deadweight loss in non-health industries by hiding from potential noncompetitor inventors the key building blocks for innovation in their fields.

At bottom, while trade secrecy holds some value for phage therapy developers, it is lacking in a number of ways. In the absence of patent protection, additional solutions are likely needed to supplement trade secrecy in the phage therapeutic field.

B. Regulatory Exclusivities

Another alternative for incentivizing innovation in phage therapeutics is regulatory exclusivity. A number of different regulatory exclusivities are currently awarded by the FDA to incentivize investment by pharmaceutical companies.[231] One of the broadest categories of exclusivity offered by the FDA is for new chemical entities, which are drugs that contain no active moiety—a molecule or ion that is responsible for the pharmacological effect of the drug—that has previously been approved by the FDA.[232] Exclusivity granted for a new chemical entity rewards manufacturers with a five-year period of data exclusivity, during which time no competitor can be approved to market a product that relies on the originator's safety and efficacy data.[233] Relying on an innovator drug's safety and efficacy data allows follow-on manufacturers to avoid the significant expenses associated with full clinical trials so they can bring a cheaper version of the drug to market through a generic approval pathway established by Congress.[234] When this cheaper route to regulatory approval is not available, generic manufacturers are unlikely to enter the market and innovator drugs can maintain their market share. This kind of data exclusivity, however, may provide little incentive for investing in phage therapeutics, as no similar generic approval pathway currently exists for phage products.

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230. *Platform Technologies & Market Applicability*, INTRALYTIX, http://www.intralytix.com/index.php?page=tech [https://perma.cc/P262-J7FL].

231. *Patents and Exclusivity*, FDA/CDER SBIA CHRON., 2–3 (May 19, 2015), https://www.fda.gov/downloads/drugs/developmentapprovalprocess/smallbusinessassistance/ucm447307.pdf [https://perma.cc/N78W-XADA].

232. *Id.* at 2.

233. *Id.*

234. Erika Lietzan, *The Myths of Data Exclusivity*, 20 LEWIS & CLARK L. REV. 91, 93 (2016).

A more sweeping type of exclusivity is granted by the FDA for orphan drugs, which treat diseases affecting less than 200,000 people in the United States or which have no hope of recovering R&D costs.[235] Orphan drug exclusivity provides seven years of market exclusivity, during which time no other application for the same drug for the same disease can be approved.[236] Market exclusivity is therefore broader than data exclusivity in that it prevents a product from reaching the market even if it is fully supported by original data.[237] This has led some to describe the market exclusivity granted by the Orphan Drug Act[238] as "similar to a patent on a particular use of a drug, [that is] enforced by FDA."[239] Since orphan drug exclusivity was established, there has been a marked increase in drug approvals for orphan diseases, and there has been more interest by manufacturers in the development of orphan drugs.[240]

Scholars have suggested that adopting a reward similar to orphan drug exclusivity would be an appropriate incentive for phage therapy innovation.[241] Similar to orphan drugs, phage therapy products would be unlikely to recoup their costs due to low sales volume. Phage therapies are only taken for a short time period, and they are highly targeted; this means that phage therapies have a small customer base that would only purchase the drugs in small quantities.[242] The principle of effective antibiotic stewardship, whereby newer and stronger drugs are prescribed less to fend off antibiotic resistance, would also impair

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235. *Patents and Exclusivity*, *supra* note 231, at 2.

236. *Id.*

237. *See* Lietzan, *supra* note 234, at 103 (providing proper definitions for market and data exclusivity).

238. Orphan Drug Act, Pub. L. No. 97-414, 96 Stat. 2049 (1983) (codified as amended in scattered sections of 21, 26, 35, 42 U.S.C. (2018)).

239. Rebecca S. Eisenberg, *Patents and Regulatory Exclusivity*, *in* THE OXFORD HANDBOOK OF THE ECONOMICS OF THE BIOPHARMACEUTICAL INDUSTRY 167, 184 (Patricia M. Danzon & Sean Nicholson eds., 2012).

240. Clemens Stockklausner, Anette Lampert, Georg F. Hoffmann & Markus Ries, *Novel Treatments for Rare Cancers: The U.S. Orphan Drug Act is Delivering – A Cross-Sectional Analysis*, 21 ONCOLOGIST 487, 489 (2016). However, it is worth noting that some scholars have recently questioned whether this increased investment is due mainly to the market exclusivity period established by the Orphan Drug Act, or whether other parts of the Act, such as the tax credit it offers for clinical testing costs, may play a bigger role. Ameet Sarpatwari, Reed F. Beall, Abdurrahman Abdurrob, Mengdong He & Aaron S. Kesselheim, *Evaluating the Impact of the Orphan Drug Act's Seven-Year Market Exclusivity Period*, 37 HEALTH AFFAIRS 732, 736 (2018).

241. ADVANCES IN VIRUS RESEARCH: BACTERIOPHAGES, PART B 79 (Malgorzata Lobocka & Waclaw T. Szybalski eds., 1st ed. 2012).

242. Henein, *supra* note 212, at 3.

phage therapy sales.[243] Market exclusivity would help phage therapy manufacturers recoup their costs by allowing them to extract value from their products over a nonpatent monopoly period. Because of the dubious patentability of phage therapeutics, appropriately tailored market exclusivity could serve well as a stand in for patents for protecting phage therapy investment.

Congress recognized the value of regulatory exclusivities for antibacterial innovation in the 2012 Generating Antibiotic Incentives Now ("GAIN") Act.[244] The GAIN Act makes certain qualified infectious disease products ("QIDPs") eligible for fast track and priority review by the FDA.[245] It also extends previously established exclusivities, including new chemical entity exclusivity and orphan drug exclusivity, by five years for QIDPs.[246] While the GAIN Act is encouraging, it is still a flawed fit for phage therapies since the exclusivities extended by the Act are not well tailored to the needs of the industry. Establishing a unique QIDP market exclusivity period would more clearly and comprehensively protect phage therapy investments and serve as a strong complement to trade secrecy. However, because market exclusivities generally protect products for a shorter period than patent protection,[247] additional incentives may still be necessary.

C. Governmental Incentives

As the GAIN Act demonstrates, governmental efforts have the potential to play a pivotal role in incentivizing the development of phage therapeutics. Indeed, increasing awareness of the promise of phage therapies within the government and nonprofit sectors has already prompted a number of such efforts.[248]

Outside of the FDA, two main players in the field are NIAID and the Biomedical Advanced Research and Development Authority ("BARDA"). NIAID's efforts were initiated by President Obama's National Action Plan for Combating Antibiotic-Resistant Bacteria,

243. *Id.*

244. GAIN Act, Pub. L. No. 112-144, §§ 801–806, 126 Stat. 993, 1077–82 (2012).

245. *Id.* §§ 802–803.

246. *Id.* § 801.

247. Patents generally provide protection for an average of 12 years after the product comes to market, while concurrently running regulatory exclusivities usually expire five to seven years after the product comes to market. *See Patents and Exclusivity*, *supra* note 231, at 2 (noting the expiration periods for various categories of regulatory exclusivities).

248. Reardon, *supra* note 89.

which directed governmental agencies to support research into the use of "phage and phage-derived lysins to kill specific bacteria," as well as other nontraditional antibiotics.[249] As part of this initiative, NIAID awarded over $5 million in funding for 24 research projects, seven of which involved phages.[250] This funding has already proved fruitful; for example, one NIAID-funded study used phage lysins to develop a small molecule capable of inhibiting the growth and lethality of *Staphylococcus aureus* and *Bacillus anthracis*.[251] While NIAID's efforts are mostly focused in the field of basic research, BARDA supports the advanced development of medical products aimed at addressing public health threats, including "pandemic influenza, and emerging infectious diseases."[252] As part of this mission, BARDA helped launch and fund the Combating Antibiotic Resistant Bacteria Biopharmaceutical Accelerator, a public-private partnership that provides funding and support for private biotechnology companies engaged in developing products that treat antibiotic-resistant bacteria.[253]

Grant funding is not the only relevant incentive being considered by the government. In March 2017, the Reinvigorating Antibiotic and Diagnostic Innovation Act was introduced into Congress.[254] Similar to the Orphan Drug Act, this legislation, which appears to have since died in committee, would have provided manufacturers up to a 50 percent tax credit for the expenses associated with clinical testing for a QIDP.[255] Another bill, the Promise for Antibiotics and Therapeutics for Health Act, sought to establish a new approval pathway for antibacterial drugs aimed at treating serious infections or diseases in limited populations.[256] However, that bill died in Congress.[257] Another piece of legislation, which met a similar fate, attempted to extend Medicare

249. EXEC. OFF. OF THE PRESIDENT, NATIONAL ACTION PLAN FOR COMBATING ANTIBIOTIC-RESISTANT BACTERIA 44 (2015).

250. New NIH Awards, *supra* note 89.

251. *Research Program Accomplishments*, NAT'L INST. OF ALLERGY & INFECTIOUS DISEASES, https://www.niaid.nih.gov/research/antibacterial-research-program-accomplishments [https://perma.cc/SHS4-RRRX].

252. U.S. DEP'T HEALTH & HUM. SERVS., BARDA STRATEGIC PLAN 2011-2016, at 5 (2011).

253. *CARB-X Injects Up to $48 Million to Accelerate First Powered by CARB-X Portfolio*, B.U. L. NEWS (Mar. 30, 2017), http://www.bu.edu/law/2017/03/30/powered-by-carbx/ [https://perma.cc/4SRW-DH5F].

254. H.R. 1840, 115th Cong. (2017).

255. *Id.* § 45S(a).

256. S. 185, 114th Cong. (2015).

257. *S. 185 (114th): PATH Act*, CONGRESS.GOV, https://www.congress.gov/bill/114th-congress/senate-bill/185 [https://perma.cc/E3NN-TEVS].

coverage for new antibiotic therapies to insulate prescribing decisions from cost concerns.[258]

D. Alternative Payment Models

Finally, alternative payment models have recently been theorized as a novel answer to the issue of underincentivized, low-sales-volume drugs. Delinkage models suggest establishing a predetermined financial reward for any developer who brings a new product to market, thus "delinking" the connection between usage and revenue. One such model would be to reward developers with tradable vouchers that extend patent or regulatory exclusivity, which are highly valuable and can be sold to blockbuster drug manufacturers for hundreds of millions of dollars. Delinkage was incorporated into the Improving Access to Affordable Prescription Drugs Act, which was introduced in Congress in March 2017, although it appears to have since been unfortunately abandoned.[259] This legislation would have offered monetary prizes from a $2 billion fund for antimicrobial developers who developed a high-priority drug.[260]

Other alternative payment models could have the dual benefits in the field of antimicrobials of encouraging appropriate antibiotic use and appropriately compensating manufacturers.[261] Population-based payment models compensate developers based on the value of the drug to society, linking revenue not to sales volume, but to indicators of value such as the availability of the drug when needed, appropriate use of the drug by physicians, and the continued effectiveness of the drug.[262] Because population-based payment theories are rooted in the principle of effective stewardship, under such a model "having a drug for a low prevalence infection would be highly valuable."[263] The applicability of such payment models to phage therapeutics is quite clear. Because of the narrow host range of any one phage-based product, they will likely never replace traditional, widely used, broad-

258. *H.R. 512 - DISARM Act of 2015*, CONGRESS.GOV, https://www.congress.gov/bill/114th-congress/house-bill/512 [https://perma.cc/FY2B-9R2C].

259. S. 771, 115th Cong. (2017).

260. *Id.* § 301.

261. *See* GREGORY W. DANIEL ET AL., DUKE-MARGOLIS CTR. FOR HEALTH POL'Y, VALUE-BASED STRATEGIES FOR ENCOURAGING NEW DEVELOPMENT OF ANTIMICROBIAL DRUGS 12–13 (2017) (describing several potential models for encouraging antimicrobial development).

262. *Id.* at 13.

263. *Id.*

spectrum antibiotics.[264] However, their targeted nature and adaptability make them an extremely powerful last line of defense against particularly aggressive pathogens.[265] As such, phage therapies are a prime example of a drug that provides very high value to a small population.

CONCLUSION

Innovation in the pharmaceutical industry currently relies heavily on patent protection to incentivize investment by providing strong monopoly pricing power for new drugs. However, recent § 101 jurisprudence will likely make patenting phage products difficult, if not entirely impossible. Without strong patent protection, alternative incentives are likely needed to encourage the level of innovation that is necessary to address the antibiotic resistance crisis. Trade secrecy and process patents will likely remain somewhat valuable for protecting phage product manufacturing processes. However, establishing an FDA-mandated market exclusivity for phage therapies, similar to orphan drug exclusivity, would likely be more effective in creating patent-like monopoly power. Because regulatory exclusivities generally last for a shorter time than the effective life of a patent, additional incentives—such as financial subsidies for R&D through the government or nonprofits, or the decoupling of revenue from sales volume—will likely be needed for robust innovation in the phage therapeutics market. With the specter of a catastrophic antibiotic-resistant bacterial epidemic likely looming in the near future,[266] it is imperative that innovative phage therapies and other nontraditional antimicrobials are properly incentivized before it is too late.

264. Reardon, *supra* note 89.

265. *Id.*

266. *See* Jonathan Quick, *Are We Prepared for the Looming Epidemic Threat?*, THE GUARDIAN (Mar. 18, 2018), https://www.theguardian.com/commentisfree/2018/mar/18/end-epidemics-aids-ebola-sars-sunday-essay [https://perma.cc/JHL3-HHKW] (describing the risk of a new virus causing an epidemic).