Journal of Law and the Biosciences, 1–13
https://doi.org/10.1093/jlb/lsad030
Essay

OXFORD

CRISPR-phage antibacterials to address the antibiotic resistance crisis: scientific, economic, and regulatory considerations

Danielle M. Pacia[†], Beatrice L. Brown[‡], Timo Minssen[**] and Jonathan J. Darrow[‡‡,*]

*Corresponding author. E-mail: jjdarrow@bwh.harvard.edu

KEYWORDS: antibacterials, new genomic technologies, CRISPR, CRISPR-phage, individualized therapies, phage therapies, public health

I. INTRODUCTION

The COVID-19 pandemic has served as a reminder that infectious diseases are among the greatest threats to public health.[1] Although the harms of many once-common infectious diseases have been dramatically reduced through the development of antibiotics

† Danielle M. Pacia, MBE, is a research associate at the Hastings Center.

‡ Beatrice L. Brown, MBE, is a student at Yale Law School. She was formerly a research specialist at the Program On Regulation, Therapeutics, And Law (PORTAL).

** Timo Minssen, Dipl. Jur., LL.M., LL.Lic., LL.D., is a professor of law specializing in legal aspects of bioscience innovation at the University of Copenhagen (UCPH). He is the founding director of UCPH's Center for Advanced Studies in Biomedical Innovation Law.

‡‡ Jonathan J. Darrow, S.J.D., LL.M., J.D., M.B.A., was an assistant professor at Harvard Medical School and PORTAL at the time of article conception and drafting.

1 Timo Minssen et al., *Preparing for Antimicrobial Resistance: Vision and Social Science Mission of the INAMRSS Network*, Bill of Health (Dec. 11, 2020), http://blog.petrieflom.law.harvard.edu/2020/12/11/antimicrobial-resistance-inamrss-network. Some have noted the potential risks of gain-of-function research, including possible connections to future pandemics. For a discussion of these potential risks, see, for example, National Research Council and Institute of Medicine, Potential Risks and Benefits of Gain-of-Function Research: Summary of a Workshop 7–20 (2015).

© The Author(s) 2024. Published by Oxford University Press on behalf of Duke University School of Law, Harvard Law School, Oxford University Press, and Stanford Law School. This is an Open Access article distributed under the terms of the Creative Commons Attribution NonCommercial-NoDerivs licence (https://creativecommons.org/licenses/by-nc-nd/4.0/), which permits non-commercial reproduction and distribution of the work, in any medium, provided the original work is not altered or transformed in any way, and that the work properly cited. For commercial re-use, please contact journals.permissions@oup.com

and vaccines, as well as other public health interventions,[2] the evolution of resistance means that these diseases may eventually reemerge with deadly new force.[3] Already, >2.8 million antibiotic-resistant infections are estimated to occur each year in the USA, and these are responsible for >35,000 deaths.[4] Drug-resistant bacteria kill 1.27 million people annually, more than HIV and malaria combined.[5] Furthermore, deaths are disproportionately concentrated in low- and middle-income countries, especially in children under 5 years old, and some estimates suggest that the death toll may rise to 10 million annually by 2050.[6]

One means to address this precarious situation is the development of new antibacterials. Among the promising potential technologies is bacteriophage ('phage') therapy, which uses viruses (phages) that precisely target and kill bacteria.[7] Although phage therapies have been studied for a century, the development of antibiotics in the 1940s led to decades of dormancy in phage research. Recently, however, the increasing threat of antibiotic resistance and improved understanding of genetics have not only reinvigorated scientific interest but also stimulated massive investments in the development of phage therapies.[8] In particular, the rise of new genomic technologies, including genome editing techniques with the potential to augment phage effectiveness, have contributed to renewed interest. One of the most significant such technologies leverages genetic sequences known as 'clustered regularly interspaced short palindromic repeats' (CRISPR).[9] CRISPR-based technologies utilize a natural defense mechanism of bacteria that, although normally directed against invading virus particles, can be repurposed to attack human pathogens.[10]

However, before CRISPR-phage therapy can be utilized, many interrelated challenges will have to be addressed.[11] These range from regulatory and safety concerns to

2 Ian T. Liu & Jonathan J. Darrow, *Reconsidering Eradication to Address the Global Infectious Disease Burden*, 24 Quinnipiac Health L.J. 279, 282–83 (2020).

3 Brad Spellberg et al., *The Future of Antibiotics and Resistance*, 368 New Eng. J. Med. 299, 300 (2013).

4 *Antibiotic Resistance Threats in the United States*, Ctrs. for Disease Control & Prevention 3, https://stacks.cdc.gov/view/cdc/82532/cdc_82532_DS1.pdf (last visited Sept. 9, 2023).

5 Christopher J.L. Murray et al., *Global Burden of Bacterial Antimicrobial Resistance in 2019: A Systematic Analysis*, 399 Lancet 629, 637 (2022).

6 *Id.* at 631; Jim O'Neill, *Review on Antimicrobial Resistance: Tackling a Crisis for the Health and Wealth of Nations*, Revi. on Antimicrobial Resistance 5 (2014).

7 Sadhana Sagar et al., Antibiotic Resistant Bacteria: A Challenge to Modern Medicine 153–64 (2020).

8 *ACD Pharma Constructing the World's Large-Scale Phage Production Plant*, Bacteriophage. news, https://www.bacteriophage.news/acd-pharma-constructing-the-worlds-large-scale-phage-production-plant (last visited Jan. 8, 2023).

9 For an overview of various genome editing technologies, see generally Ana Nordberg et al., *Cutting Edges and Weaving Threads in the Gene Editing (Я)evolution: Reconciling Scientific Progress with Legal, Ethical, and Social Concerns*, 5 J.L. & Biosciences 35 (2018).

10 Adrienne C. Greene, *CRISPR-Based Antibacterials: Transforming Bacterial Defense into Offense*, 36 Trends Biotechnology 127, 128 (2018).

11 Charlotte Brives & Jessica Pourraz, *Phage Therapy as a Potential Solution in the Fight Against AMR: Obstacles and Possible Futures*, 6 Palgrave Commc'ns 100, 103 (2020).

intellectual property issues and economic considerations.[12] Although more evidence is needed before the US Food and Drug Administration (FDA) and other regulatory bodies are likely to approve phage therapies as safe and effective, there is increasing confidence that they may soon be more widely used to fight bacterial infections. This article evaluates the potential of CRISPR-enhanced phage therapy (CRISPR-phage therapy) as a means of addressing antibiotic resistance, providing an evaluation of the scientific and economic challenges to its development and regulatory implications.

II. SCIENTIFIC CHALLENGES

Phage therapy and new genomic technologies, including CRISPR technology, face challenges to their development. These obstacles include the development of bacterial resistance toward the phage and compatibility challenges between the different phage components (ie delivery vectors and CRISPR).

II.A. The Science of Phage Therapy

Phage therapy has been studied since the 1920s for its ability to treat human bacterial infections.[13] Amid the deprivations of World War II, Polish physicians used phage therapy when antibiotics were not available.[14] Although the technology was not secret, published studies on phage as an effective antibacterial appeared predominantly in Eastern European and Russian language journals, which limited their reach in Western Europe and the USA.[15] After the invention and widespread use of antibiotics, interest in commercializing phage therapy in the USA waned,[16] only to rise in popularity decades later as antibiotic resistance emerged as an ever greater threat to public health.[17]

For around a century, human phage therapy trials have taken place in Eastern Europe. Most notably, the nonprofit Eliava Institute of Bacteriophages in Tblisi, Georgia, and the Institute of Immunology and Experimental Therapy in Wroclaw, Poland, have been pivotal in creating an evidence base for phage therapy.[18] In a successful trial in 1938, 219 patients with bacterial dysentery were treated with a 'cocktail' consisting of multiple phage types, and 74 per cent showed improvement or were completely relieved of symptoms.[19] In 1974, during a typhoid epidemic, 18,577 children were enrolled in

12 Timo Minssen, *The Revival of Phage Therapy to Fight Antimicrobial Resistance – Part I: What Are the Legal Implications?*, Bill of Health (Aug. 4, 2014), https://blog.petrieflom.law.harvard.edu/2014/08/04/the-revival-of-phage-therapy-to-fight-antimicrobial-resistance-part-i-what-are-the-legal-implications; Kelly Todd, *The Promising Viral Threat to Bacterial Resistance: The Uncertain Patentability of Phage Therapeutics and the Necessity of Alternative Incentives*, 68 Duke L.J. 767, 769–70 (2019).

13 Xavier Wittebole et al., *A Historical Overview of Bacteriophage Therapy as an Alternative to Antibiotics for the Treatment of Bacterial Pathogens*, 5 Virulence 226, 226–27 (2014).

14 Maciej Żaczek et al., *Phage Therapy in Poland – A Centennial Journey to the First Ethically Approved Treatment Facility in Europe*, 11 Frontiers Microbiology 1, 2 (2020).

15 *Id.* at 1.

16 *Id.* at 1–2.

17 Tom Parfitt, *Georgia: An Unlikely Stronghold for Bacteriophage Therapy*, 365 Lancet 2166, 2167 (2005).

18 Derek M. Lin et al., *Phage Therapy: An Alternative to Antibiotics in the Age of Multi-Drug Resistance*, 8 World J. Gastrointestinal Pharmacology & Therapeutics 162, 165 (2017).

19 *Id.*

Trials aimed at drug resistant, chronic, and/or recurring bacterial infection	17
Trials aimed at reducing or preventing colonization of bacterial species known to be antibiotic resistant	23
Trials that do not mention bacterial species known to be antibiotic resistant	18
Total	58

Figure 1. Clinical Trials of Phage Interventions.

a prophylactic intervention trial at the Eliava Institute using typhoid phage, resulting in a 5-fold decrease in typhoid incidence compared to placebo.[20]

Despite the use of phage therapy in humans in Eastern Europe, no phage therapy—aside from agricultural use—has yet been approved by the FDA, though many are in development.[21] Clinicaltrials.gov lists 58 clinical trials of various phage interventions as of September 2, 2023. Of these, 17 studies state that they are aimed at treating drug-resistant, chronic, or recurring bacterial infections, and several others are aimed at treating and/or preventing infections caused by bacterial species known to be antibiotic resistant (Figure 1).[22]

Phages are viruses that infect and kill bacteria.[23] Phage therapy aims to leverage these natural enemies of bacteria by identifying phage that can precisely target those bacterial species that cause treatment-resistant human disease.[24] The three-dimensional structure of phages includes an icosahedral head (a dice-like geometric shape with 20 faces), which contains the genetic material of the virus, and a long tail with fiber-like legs.[25] Phages must have a host within which to reproduce in order to survive. Their tail fibers attach to receptors on the host bacteria, and then the phage inserts its genetic material into the bacterium. Once the bacterial cell has become infected, it produces millions of copies of the phage's genetic material, eventually causing the cell to burst and allowing those new phage copies to infect and kill nearby host cells. Because different host bacteria have different receptors, a phage can bind only to those bacteria for which the proteins that make up the phage tail fibers (as determined by their genetic sequence) match the proteins on the surface of the host cell receptor, making each phage highly selective for particular host organisms.[26]

20 Mzia Kutateladze & Revaz Adamia, *Phage Therapy Experience at the Eliava Institute*, 38 Médecine et Maladies Infectieuses 426, 427–28 (2008).

21 *See* Maryanne Kuek et al., *Application of Bacteriophages in Food Production and Their Potential as Biocontrol Agents in the Organic Farming Industry*, 165 Biological Control 104817, 104817 (2022).

22 ClinicalTrials. gov, https://clinicaltrials.gov (last visited Jan. 9, 2023).

23 Wittebole et al., *supra* note 13, at 228.

24 Diana P. Pires et al., *Genetically Engineered Phages: A Review of Advances over the Last Decade*, 80 Microbiology & Molecular Biology Revs. 523, 524–33 (2016).

25 Jessica Nicastro et al., *Bacteriophage Lambda Display Systems: Developments and Applications*, 98 Applied Microbiology & Biotechnology 2853, 2855 (2014).

26 Alexander Sulakvelidze et al., *Bacteriophage Therapy*, 45 Antimicrobial Agents & Chemotherapy 649, 650–56 (2001).

The selectivity of a phage can allow it to precisely target a pathogen of interest while leaving the remainder of the human microbiome relatively undisturbed.[27] Phage therapy therefore has the potential to treat the patient while minimizing the untoward side effects sometimes caused by the use of antibiotics.[28] This selectivity and narrow host range also reduce the risk for bacterial resistance since only the bacteria causing a particular infection are targeted, unlike the traditional antibiotics that target a wide-spectrum of bacteria.[29]

Phage therefore hold the potential to improve patient survival rates, decrease adverse effects, and offer new treatment possibilities against resistant bacteria. Already, phage therapy has emerged in the USA as an option of last resort, albeit in very limited circumstances. In 2015, infectious disease epidemiologist Steffanie Strathdee leveraged an international network of researchers to give an experimental phage therapy to her husband after other treatments had failed to cure him of a deadly antibiotic-resistant bacterial infection.[30] After obtaining permission from the FDA under an expanded access protocol, he was treated with phage and recovered.

II.B. The Science of CRISPR

To counteract the threat of viruses, bacteria have developed protection mechanisms known collectively as the CRISPR-Cas system, which acts as a bacterial immune system against invading viruses.[31] Through this system, bacteria are able to systematically transcribe the DNA or RNA of invading viruses, store this genetic material using CRISPR arrays, and later use the stored nucleic acid sequences to identify similar invading viruses and destroy them. When a virus with similar DNA to a previous invader is encountered, the CRISPR array produces an RNA segment that acts as a guide for the 'Cas' protein, which enables the Cas protein to recognize a similar DNA complex that matches the RNA segment. The Cas protein then cleaves the invading nucleic acid, causing viral death as the necessary genes for survival have been shredded or cleaved.[32]

Because the CRISPR system evolved to have the ability to capture and store nucleic acid sequences, researchers can exploit this capability by exposing the Cas protein to a lab-created RNA sequence that allows the CRISPR sequence to identify a desired genetic target.[33] The Cas enzyme, guided by the manufactured RNA sequence, then homes in on the corresponding DNA sequence and shreds it, disabling specific genes.

---

27 Sharita Divya Ganeshan & Zeinab Hosseinidoust, *Phage Therapy with a Focus on Microbiota*, 8 Antibiotics 1, 6 (2019).

28 Catherine Loc-Carrillo & Stephen T. Abedon, *Pros and Cons of Phage Therapy*, 1 Bacteriophage 111, 112 (2011).

29 *Id.*

30 Zoë Corbyn, *Steffanie Strathdee: 'Phages Have Evolved to Become Perfect Predators of Bacteria,'* Guardian (June 15, 2019), https://www.theguardian.com/science/2019/jun/15/steffanie-strathdee-phage-therapy-interview-perfect-predator.

31 Chase L. Beisel et al., *A CRISPR Design for Next-Generation Antimicrobials*, 15 Genome Biology 516, 516 (2014).

32 David Bikard & Rodolphe Barrangou, *Using CRISPR-Cas Systems as Antimicrobials*, 37 Current Op. Microbiology 155, 156-57 (2017); Muhammad Abu Bakr Shabbir et al., *Survival and Evolution of CRISPR-Cas System in Prokaryotes and its Applications*, 7 Frontiers Immunology 375, 376–78 (2016).

33 Robert Heler et al., *Adapting to New Threats: The Generation of Memory by CRISPR-Cas Immune Systems: Acquisition of New Spacers by CRISPR-Cas Immune Systems*, 93 Molecular Microbiology 1, 2 (2014).

II.C. CRISPR-Augmented Phage Therapy

Scientists are now seeking to create phages that are augmented with CRISPR to enhance their effectiveness as antimicrobial agents. In the laboratory, researchers can create novel guide RNA sequences that allow the Cas enzyme to target a desired bacterial (rather than viral) DNA sequence. Once the CRIPSR-Cas system is designed, it can be inserted into the phage's genome to encode the CRISPR-Cas system. When the phage propagate, each phage will contain the CRISPR-Cas system sequence along with its usual genetic material that is then injected into the targeted bacteria (causing it to burst and further propagate the phage). Scientists can thus repurpose the CRISPR system and use a bacterium's own defense mechanism against itself.[34]

Both Cas9 and Cas3 (two different kinds of enzymes that accompany the CRISPR mechanism) are being studied for antibacterial development. One such CRISPR-phage antibacterial is being developed by Janssen Pharmaceuticals, a part of Johnson & Johnson.[35] In 2020, the product entered Phase 1 clinical trials for use against *Escherichia coli*, the furthest along in development for a drug of its kind.[36] As of September 2022, the Phase 1 trial is complete and results have been posted.[37] The experimental therapy is currently being tested against urinary tract infections,[38] with plans to later test for efficacy against infections at other sites in the body, such as the lungs and abdomen.[39] In laboratory studies, phage genetically engineered to contain CRISPR-Cas have been more effective than naturally occurring ('wild-type') phage in eliminating *Clostridioides difficile*—a bacterial species prone to antibiotic resistance.[40]

Bacterial resistance to phage occurs quickly.[41] The addition of CRISPR-Cas3 to phage enhances the bactericidal effect because it produces faster elimination by several orders of magnitude,[42] reducing the potential for resistance. CRISPR-phage kill host bacteria more quickly because, while phage replicate within the bacterial cell, the essential genes of the cell are being shredded by the CRISPR-Cas system, potentially

---

34 Bikard & Barrangou, *supra* note 32, at 159.

35 Mark Terry, *Locus and Janssen Ink Potential $818 Million Deal to Develop CRISPR-Based Antibacterials*, BioSpace, https://www.biospace.com/article/locus-and-janssen-ink-potential-818-million-deal-to-develop-crispr-based-antibacterials (last visited Sept. 9, 2023).

36 ClinicalTrials.gov, *supra* note 22; *Locus Biosciences Initiates World's First Controlled Clinical Trial for a CRISPR Enhanced Bacteriophage Therapy*, Locus Biosciences (Jan. 8, 2020), https://www.locus-bio.com/locus-biosciences-initiates-worlds-first-controlled-clinical-trial; *Safety, Tolerability, and PK of LBP-EC01 in Patients with Lower Urinary Tract Colonization Caused by E. Coli*, ClinicalTrials. gov, https://clinicaltrials.gov/ct2/show/NCT04191148 (last visited Jan. 8, 2023).

37 ClinicalTrials.gov, *supra* note 22.

38 *Locus Biosciences Initiates World's First Controlled Clinical Trial for a CRISPR Enhanced Bacteriophage Therapy*, *supra* note 36.

39 Locus Biosciences, *Locus Biosciences Signs Contract with CARB-X to Advance $14 Million Precision Medicine Program to Develop CrPhage Product Targeting Klebsiella Pneumoniae Infections*, PR Newswire (Nov. 10, 2020), https://www.prnewswire.com/news-releases/locus-biosciences-signs-contract-with-carb-x-to-advance-14-million-precision-medicine-program-to-develop-crphage-product-targeting-klebsiella-pneumoniae-infections-301167967.html.

40 Kurt Selle et al., *In Vivo Targeting of Clostridioides difficile Using Phage-Delivered CRISPR-Cas3 Antimicrobials*, 11 mBio 1, 3-4 (2020); Yilmaz Emry Gencay et al., *Engineered Phage with Antibacterial CRISPR-Cas Selectively Reduce E. Coli Burden in Mice*, 2023 Nature Biotechnology, at 1, 2–4.

41 Anni-Maria Örmälä & Matti Jalasvuori, *Phage Therapy: Should Bacterial Resistance to Phages Be a Concern, Even in the Long Run?*, 3 Bacteriophage 1, 1–2 (2013).

42 Selle et al., *supra* note 40, at 4.

leading to cell death even before phage-mediated biochemical processes cause cell lysis.[43]

II.D. Scientific Challenges to CRISPR-Phage Therapy

The ability of phages to precisely target particular pathogens is one of the most important benefits of phage therapy over traditional broad-spectrum antibiotics. However, the extreme precision creates a challenge in identifying which phage to use. Among the largest hurdles is determining whether laboratory evidence that a given phage successfully targets a particular bacterial strain will translate to the clinical context. Laboratory measures of virulence can vary based on several factors, such as the viral dose used. The phage's genome must also be sequenced, and the phage should not contain certain genes, such as those that code for integrase (an enzyme that could inadvertently integrate phage DNA into the bacterial genome, allowing the phage DNA to replicate passively as its host cell continues to divide, delaying lysis of the host and potentially strengthening host resistance to the immune system or other phage)[44] or any antibiotic resistant genes (because phages can be reservoirs of antimicrobial resistance genes, wherein they can transfer these genes to the host bacteria and thereby induce the bacteria to become resistant).[45] Although the sequencing of the phage itself may not be difficult, finding phage genomes without these characteristics can be.

Phage can also mutate during treatment, potentially requiring further diagnosis and the time-consuming creation or identification of another appropriate phage. The use of phage cocktails, wherein multiple phage species are used, can help to mitigate these problems, but can enlarge the impact on the microbiome.[46] Phage are also immunogenic, meaning that the human body may learn to neutralize their effect over time.[47]

Finally, research suggests that CRISPR-Cas editing may result in gross structural defects of the host nucleus, such as the formation of micronuclei (damaged chromosome fragments or whole chromosomes that are erroneously left outside the nucleus during cell division), which initiate a mutational process called chromothripsis and could potentially cause malignancy.[48] Neither the level of risk to patients based on these genetic changes nor the more general risk to third parties or future generations from possible unanticipated effects on the microbial environment is well characterized. Nevertheless, as technological advances increase the safety and precision of CRISPR

43 *Id.* at 3.

44 Casandra Philipson et al., *Characterizing Phage Genomes for Therapeutic Applications*, 10 Viruses 1, 2–7 (2018).

45 Marta Colomer-Lluch et al., *Antibiotic Resistance Genes in the Bacteriophage DNA Fraction of Environmental Samples*, 6 PLOS One 1, 7-8 (2011); Elizabeth Pursey et al., *CRISPR-Cas Antimicrobials: Challenges and Future Prospects*, 14 PLOS Pathology 1, 3–4 (2018).

46 Lin et al., *supra* note 18, at 168–69.

47 Kevin Champagne-Jorgensen et al., *Immunogenicity of Bacteriophages*, 31 Trends Microbiology 1058, 1064 (2023).

48 Mitchell L. Leibowitz et al., *Chromothripsis as an On-Target Consequence of CRISPR-Cas9 Genome Editing*, 53 Nature Genetics 895, 896–97 (2021).

techniques, the regulatory system will soon have to adapt to protect the public from the potential risks while also supporting new opportunities.[49]

III. SELECTED ECONOMIC CHALLENGES TO CRISPR-PHAGE THERAPIES

The science of CRISPR-phage therapy raises important economic and regulatory challenges. Even if CRISPR-phage therapy is safe and effective, these economic and regulatory challenges will need to be overcome to incentivize the research needed to obtain FDA approval and bring these new therapeutics to market.

III.A. Scientific Uncertainties, Market Failures, and Investment Risks

Despite their sophistication and therapeutic potential, CRISPR-phage therapies will face many of the same financial challenges as traditional antibacterials.[50] As with pharmaceuticals generally, new CRISPR-phage therapies could experience high failure rates during development, lowering expected returns on investment.[51] Compared to chronically administered drugs, courses of treatment for antibacterials tend to be short, depressing sales volume. Many older antibacterials are inexpensive and continue to be effective for the large majority of patients, so costly new products are reserved for when other options have been exhausted (a desirable practice known as "stewardship"), reducing volume and therefore profit. The high specificity of CRISPR-phage therapies means that they are likely to generate only modest revenues since each phage would be expected to treat only a very small number of patients suffering from a particular treatment-resistant pathogen. Unlike traditional antibiotics which can be stored in a pharmacy, the phage selection process may require bespoke manufacturing [52] that is both costly and time consuming, potentially reducing the circumstances in which phage treatments are used. These factors combine to reduce expected profits, diminishing the interest of pharmaceutical companies.[53]

Advances in biotechnology are helping to reduce the costs of phage therapy development. Genetic sequencing has become more affordable, which aids the speed and accuracy of identifying an appropriate phage for a specific bacterial strain.[54] Furthermore, using cell-free reactions—platforms where biochemical reactions occur independently of living cells—to produce bacteriophage can help ensure safety and reduce production costs.[55]

---

49 For an overview of ways of using CRISPR-Cas, see generally Jianli Tao, Daniel E. Bauer & Roberto Chiarle, *Assessing and Advancing the Safety of CRISPR-Cas Tools: From DNA to RNA Editing*, 14 Nature Commc'ns 1 (2023).

50 For an overview of financial challenges associated with traditional antibiotic development, see generally Christine Årdal et al., *Antibiotic Development — Economic, Regulatory and Societal Challenges*, 18 Nature Revs. Microbiology 267 (2020); A.D. So et al., *Towards New Business Models for R&D for Novel Antibiotics*, 14 Drug Resistance Updates 88, 89–90 (2011).

51 Duxin Sun et al., *Why 90% of Clinical Drug Development Fails and How to Improve It?*, 12 Acta Pharmaceutica Sinica B 3049, 3050 (2022).

52 Helen J. Stacey et al., *The Safety and Efficacy of Phage Therapy: A Systematic Review of Clinical and Safety Trials*, 11 Antibiotics 1, 1–3 (2022).

53 For an explanation of how market dynamics may disincentivize pharmaceutical company investment in antibacterial products, see generally Jonathan J. Darrow et al., *When Markets Fail: Patents and Infectious Disease Products*, 73 Food & Drug L.J. 361 (2018).

54 E. Magdu Barbu et al., *Phage Therapy in the Era of Synthetic Biology*, 8 Cold Spring Harbor Persps. Biology 1, 6–7 (2016).

55 *Id.*

It has been proposed that organizations such as the National Institutes of Health invest in the creation of phage libraries, repositories where multiple species of phage are cataloged and stored.[56] Such repositories can be used by laboratories, hospitals, and universities to research phage therapies.[57] Private firms may be hesitant to invest money in developing phage therapies because of the market risks and small expected financial rewards involved. The government should therefore help fund early-stage phage therapy research, creating an evidence base that would de-risk later-stage development and give investors some assurance when investing in phage therapy projects.[58]

III.B. Challenges in Intellectual Property Law

In addition to the typical barriers to antibiotic development, phage therapy potentially faces a less common hurdle[59] in that products of nature, including naturally occurring organisms such as phage, may not be patentable even if they have been isolated from their natural environment.[60] Without patents, it is more difficult for manufacturers to temporarily exclude competitors and recoup their investment costs. However, as with antibacterials derived from natural products, phage that are changed in some way to yield 'markedly different characteristics', such as through genetic modification, may be patentable so long as the resulting product meets the usual requirements for patentability, including novelty, usefulness, and non-obviousness.[61] This means that phage enhanced with the CRISPR-Cas3 system are more likely to stand on stronger legal footing than wild-type phage, though even then patentability may be negated if the particular modification was obvious over what was previously known. Locus Biosciences, through its relationship with North Carolina State University, is the exclusive global licensee of a CRISPR-Cas3 patent estate that is claimed to cover all therapies that use Type 1 CRISPR-Cas in modified phage.[62]

Not only can modified phage potentially be patented, but so too can related advances, such as new formulations, cocktails, methods of treatment, processes of manufacturing, or methods of storage or transportation. A number of phage patents have already been issued.[63] For example, Intralytix, a corporation that specializes in phage therapy, has successfully patented several kinds of bacteriophages targeted against shigellosis,[64] as well as methods of using these bacteriophages to maintain healthy gut microflora by reducing either *Shigella* contamination of food products (deli meat, smoked salmon, pre-cooked chicken, lettuce, melon, and yogurt) or *Shigella* colonization in the gut.[65]

---

56 Jonathan Anomaly, *The Future of Phage: Ethical Challenges of Using Phage Therapy to Treat Bacterial Infections*, 13 Pub. Health Ethics 82, 84 (2020).

57 *Id.*

58 *Id.*

59 Todd, *supra* note 12, at 783.

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

61 *Id.* at 576; Todd, *supra* note 12, at 793; Mateo Aboy et al., *After* Myriad*, What Makes a Gene Patent Claim 'Markedly Different' from Nature?*, 35 Nature Biotechnology 820, 820–21 (2017).

62 *Locus Biosciences Acquires EpiBiome, Speeding Race for New Antibiotic Technology*, N.C. Biotechnology Ctr. (July 18, 2018), https://www.ncbiotech.org/news/locus-biosciences-acquires-epibiome-speeding-race-new-antibiotic-technology; U.S. Patent No. 11,680,259 (issued June 3, 2023).

63 Alan Fauconnier, *Phage Therapy Regulation: From Night to Dawn*, 11 Viruses 1, 2 (2019).

64 U.S. Patent No. 10,711,252 (issued July 14, 2020).

65 *Id.*

The outcome of a patentability challenge is often difficult to predict.[66] To better protect all aspects of their inventions, manufacturers are likely to seek multiple patents covering different aspects of a given phage technology, as has occurred for some biologics and other drugs.[67] Phage and CRISPR-based therapies can also benefit from intellectual property-like regulatory exclusivity schemes, including 7-year exclusivity under the Orphan Drug Act for rare disease treatments, 12-year new biologic exclusivity,[68] and 6-month add-on exclusivity when drugs are tested on pediatric populations at the request of the FDA.[69] (Biologics are not eligible for the 5-year add-on exclusivity applicable to 'qualified infectious disease products' under the 2012 Generating Antibiotic Incentives Now Act.)[70]

IV. IMPLICATIONS OF REGULATORY STRUCTURES AND CRISPR-PHAGE DEVELOPMENT

Until the first phage therapy is approved, the primary means for patients to access phage therapy in the USA outside of clinical trials (where randomization to placebo or a comparator treatment might also occur) is through the FDA's expanded access program, which provides access to experimental therapies for seriously ill patients who have exhausted alternative treatment options.[71] For example, in 2019, a patient who had acquired an antibiotic-resistant *Acinetobacter baumanii* infection while vacationing in Egypt was given phage therapy under the FDA's expanded access program after 15 antibiotics had been tried and failed, and he survived.[72] However, because drugs available under expanded access have not been established as safe and effective by the FDA, clinicians may not be aware of the expanded access program, and manufacturers may be unwilling or unable to provide expanded access, given the administrative burdens and limited cost-recovery permitted by law.[73]

Because no phage therapy has yet been approved by the FDA, there is uncertainty surrounding how the FDA will regulate these potential medicines.[74] In general, phage therapies are biologics that are regulated in a manner similar to traditional antibiotics or other drugs.[75] Each phage and new fixed combination of phage ('phage cocktail')

66 Todd, *supra* note 12, at 796.

67 *Id.* at 795–96.

68 *Id.* at 801–02.

69 Michael Sinha et al., *Addressing Exclusivity Issues During the COVID-19 Pandemic and Beyond*, *in* COVID-19 AND THE LAW: DISRUPTION, IMPACT, AND LEGACY 237, 240–41 (I. Glenn Cohen, Abbe R. Gluck, Katherine L. Kraschel & Carmel Shachar, eds. 2023).

70 Jonathan J. Darrow & Aaron S. Kesselheim, *Incentivizing Antibiotic Development: Why Isn't the Generating Antibiotic Incentives Now (GAIN) Act Working?*, 7 OPEN F. INFECTIOUS DISEASES 1, 2 (2020).

71 Jonathan J. Darrow et al., *Practical, Legal, and Ethical Issues in Expanded Access to Investigational Drugs*, 372 NEW ENG. J. MED. 279, 280 (2015).

72 Natasha Lipman, *'My Husband Squeezed My Hand to Say He Wanted to Live, Then I Found a Way to Save Him,'* BBC NEWS (Nov. 4, 2019), https://www.bbc.com/news/stories-50221375; Nicola Twilley, *When a Virus Is the Cure*, NEW YORKER (Dec. 14, 2020), https://www.newyorker.com/magazine/2020/12/21/when-a-virus-is-the-cure.

73 21 C.F.R. § 312.8 (2023).

74 Katie Kingwell, *Bacteriophage Therapies Re-Enter Clinical Trials*, 14 NATURE REVS. DRUG DISCOVERY 515, 516 (2015).

75 Fauconnier, *supra* note 63, at 4-8; Samuel Kilcher & Martin J. Loessner, *Engineering Bacteriophages as Versatile Biologics*, 27 TRENDS MICROBIOLOGY 355, 364 (2019).

must undergo clinical trials even if the individual components have been previously approved.

Although the FDA has purview over phage therapies, the hyper-individualized nature of these interventions may require new regulatory approaches, especially for the post-market surveillance of cocktails mixed at the bedside. For example, while clinical trials have typically focused on measuring the efficacy of a defined intervention, the FDA could find ways to assess not the therapy itself, but the process of developing the therapy, including how the phage is sourced and screened as well as how each cocktail is created. Although the term 'non-traditional' may have limited relevance for regulatory structures that continuously review novel treatments, the individualized nature of new antibacterial agents presents a relevant difference for regulators to consider.[76]

Other aspects of phage testing and approval are likely to present less common considerations. Phage libraries may be so large that not all phages contained in them are well characterized. In such cases, the use of established manufacturing processes and careful controls over manufacturing quality could help to ensure safety and effectiveness.[77] To minimize the burdens associated with fixed-dose combinations, the FDA could approve an individual phage with the awareness that physicians may mix cocktails at the bedside as part of the practice of medicine. Bedside mixing can be aided by solutions such as Adaptive Phage Therapeutics' PhageBank, which consists of a library of phage that are matched in vitro to the pathogen that has infected an individual patient. The FDA has approved the company's Investigational New Drug (IND) application, and a Phase 1/2 trial began in 2020.[78]

FDA guidance surrounding phage therapy has yet to be released. However, guidance addressing other novel individualized therapies may provide useful insight. In 2021, the FDA issued a series of guidance documents for Individualized Antisense Oligonucleotide Drug Products, which are therapies created from a short string of chemically modified DNA or RNA which can be tailored to a patient's specific variant of a genetic disease.[79] These individualized therapies can be custom-made for patients with extremely rare conditions.[80] For example, Milasen was an individualized antisense oligonucleotide drug created for Mila Makovec, an 8-year-old girl who inherited a rare genetic mutation. After submitting an expanded access IND, access was granted and the drug was administered.[81]

---

76 John H. Rex et al., *Designing Development Programs for Non-Traditional Antibacterial Agents*, 10 Nature Commc'ns 1, 3–5 (2019).

77 U.S. Food & Drug Admin., Guidance for Industry: Q8, Q9, & Q10 Questions and Answers, Appendix Q&As from Training Sessions 9 (July 2012), https://www.fda.gov/media/83904/download.

78 Sean Leous, *FDA Clears First Clinical Study for a Polymicrobial Phage Library-Based Treatment for Antibiotic-Resistant Infections*, Bus. Wire (Mar. 12, 2020), https://www.businesswire.com/news/home/20200312005192/en/FDA-Clears-First-Clinical-Study-for-a-Polymicrobial-Phage-Library-Based-Treatment-for-Antibiotic-Resistant-Infections.

79 U.S. Food & Drug Admin., IND Submissions for Individualized Antisense Oligonucleotide Drug Products: Administrative and Procedural Recommendations, Guidance for Sponsor-Investigators 2-3 (Jan. 2021), https://www.fda.gov/media/144872/download.

80 Anaïs M. Quemener et al., *The Powerful World of Antisense Oligonucleotides: From Bench to Bedside*, 11 WIREs RNA 1, 10–12 (2020).

81 Gina Kolata, *Scientists Designed a Drug for Just One Patient. Her Name Is Mila*, N.Y. Times (Oct. 9, 2019), https://www.nytimes.com/2019/10/09/health/mila-makovec-drug.html.

In one of the antisense oligonucleotide guidance documents, the FDA stressed that early interaction with the agency is necessary and that sponsors should request a pre-IND meeting when a potential participant is identified so that the application process can be as streamlined as possible.[82] In the case of Milasen, the patient suffered from Batten's disease, which often starts in childhood and leads to death by the late teens or early twenties (Ms Makovec died at age 10, about 2 years after receiving her custom-made treatment). Patients with deadly infections may not have nearly as much time for experimental drug development to occur, so processes for rapidly tailoring phage therapy may be needed.[83]

In the future, the FDA can provide further guidance on how it would facilitate the rapid development of hyper-individualized therapies. In the FDA's document on Prescription Drug User Fee Act VII reauthorization goals and procedures, the agency discussed ways to enhance the Center for Biologics Evaluation and Research's capacity to support the development, review, and approval of cell and gene therapy products, such as strengthening staff capacity and capability. Some of these commitments may also aid in the development and approval of CRISPR-phage therapies, given the similarities between CRISPR-phage and specific kinds of cell and gene therapies that are also highly individualized. For example, FDA notes that it will issue draft guidance on evaluating efficacy in small patient populations using a variety of novel trial designs and statistical methods, which could help manufacturers of CRISPR-phage therapies.[84] Experience in regulating CAR-T therapies, which are individualized to each patient on a short timeline, may also provide insight.[85] FDA committed to seeking public input on the challenges faced by cell and gene therapy manufacturers,[86] in part to facilitate the development and approval of individualized therapies or therapies for small populations. Manufacturers of CRISPR-phage therapies will likely face similar challenges, and FDA can also engage in similar discussions with the CRISPR-phage manufacturers to understand any challenges that may be specific to these therapies.

Although there are multiple expedited pathways to speed the approval of drugs directed to unmet needs and serious conditions, Congress should consider whether an additional pathway for individualized therapies is needed. Whether or not a new pathway is needed, it will be helpful to provide clear guidance on what evidence will be required for the approval of individualized therapies such as those based on CRISPR-phage technology. Challenges such as difficulty with clinical trial enrollment may not be solved by current FDA programs since the condition being treated may be hyper-individualized, with perhaps only a few recipients for a given therapy. The FDA has traditionally required manufacturers to provide evidence of safety and efficacy from two well-controlled trials, but providing this level of evidence may not be feasible or realistic for individualized therapies. Regulators could therefore

82 IND Submissions for Individualized Antisense Oligonucleotide Drug Products, *supra* note 79, at 2–3.

83 Nancy Fliesler, *Shooting for the Moon: From Diagnosis to Custom Drug, in One Year*, Bos. Child's Hosp. (Oct. 10, 2019), https://answers.childrenshospital.org/milasen-batten-disease.

84 *PDUFA Reauthorization Performance Goals and Procedures Fiscal Years 2023 Through 2027*, U.S. Food & Drug Admin. 54–55 (Apr. 24, 2023), https://www.fda.gov/media/151712/download.

85 U.S. Food & Drug Admin., Considerations for the Development of Chimeric Antigen Receptor (CAR) T Cell Products: Draft Guidance for Industry 1–5 (Mar. 2022).

86 *PDUFA Reauthorization Performance Goals and Procedures Fiscal Years 2023 Through 2027*, *supra* note 84, at 16.

consider what elements from other currently available expedited pathways could help facilitate the development and review of CRISPR-phage drugs while setting a level of evidence generation that is appropriate, given the known limitations associated with individualized therapies.

For cases of extreme urgency with no remaining alternatives, expedited pathways can be complemented by existing expanded access programs. Similar programs are also available in European countries, such as France, in the form of phage therapy-specific Temporary Use Authorization (TUA).[87] TUAs normally apply to products under evaluation or that are about to obtain a marketing authorization.[88] Although phage therapies generally do not yet meet these requirements, the responsible French national authority (ANSM) has regularly supported the use of phage in pre-clinical development for patient treatment, thus demonstrating its commitment to promoting this therapy.[89] Future research should compare the experiences with these European and US approaches in more detail to gain the best possible insights for improving such pathways.

In the meantime, increased clarity on how IND applications should be filed for each phage combination (and whether applications are even necessary for every combination created) can help phage therapies to advance as drugs that can be created, tested, and utilized. This enhanced clarity will assist manufacturers in risk-assessment, planning, and budgeting and will serve to inform the public of the standards underlying products that are later approved. Without such guidance, developing and manufacturing novel phage therapies may continue to be hampered.

V. CONCLUSIONS

As CRISPR-phage antibacterials advance through development to market authorization, it is important to explore their benefits and limitations. And, since antimicrobial resistance continues to worsen worldwide, it has become increasingly imperative that regulators ensure a clear pathway for the creation of effective, non-traditional antimicrobial products such as those based on CRISPR-phage technology. Government support, streamlined regulatory pathways, existing incentive schemes, and perhaps the creation of additional incentive structures will help to encourage new, non-traditional antibiotics. In the future, further research can focus on the potential public health effects of phage therapy, including implications regarding intergenerational anti-microbial stewardship and perturbing the broader ecological environment.

FUNDING

Timo Minssen's and Jonathan J. Darrow's research for this paper was supported by a Novo Nordisk Foundation Grant for a scientifically independent International Collaborative Bioscience Innovation & Law Programme (Inter-CeBIL programme - grant no. NNF23SA0087056). Jonathan J. Darrow also received funding from Arnold Ventures.

87 Fauconnier, *supra* note 63, at 356.

88 Brives & Pourraz, *supra* note 11, at 105.

89 *Id.*