



# A Scientific Roadmap for Antibiotic Discovery

A sustained and robust pipeline of new antibacterial drugs and therapies is critical to preserve public health

## The Pew Charitable Trusts

**Susan K. Urahn**, *executive vice president*

**Allan Coukell**, *senior director*

**Elizabeth Jungman**, *director*

## The antibiotic resistance project team members

**Kathy Talkington**, *project director*

**Carolyn Shore**, *officer*

**Pooja Kothari**, *associate*

## External reviewers

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# Contents

## 1 Overview

## 7 Scientific priorities for antibiotic discovery

1. Generate and tailor chemical matter for antibacterial discovery **7**
  - Goal: Understand and overcome barriers to drug penetration and efflux avoidance for Gram-negative bacteria **9**
  - Goal: Generate and tailor chemical matter for antibacterial discovery **11**
2. Conduct key proof-of-concept studies for nontraditional therapies **13**
  - Goal: Assess whether single-target antibacterials can be used in combination to overcome resistance **14**
  - Goal: Validate nontraditional therapies **16**
3. Share data, materials, and knowledge across disciplines and between sectors **17**
  - Goal: Share data and information **17**
  - Goal: Share materials **18**
  - Goal: Share knowledge and expertise **19**
4. Models for antibiotic discovery **20**
  - Governance and organizational structure **20**
  - Intellectual property **21**
  - Funding **22**

## 22 Conclusion

## 24 Appendix A: Key deliverables

- Catalytic phase (years 1-2) **24**
- Pilot phase (years 3-4) **25**
- Implementation phase (year 5) **26**

## 27 Appendix B: Alternatives to traditional antibiotic use currently in clinical development

## 29 Appendix C: Organizational structures

## 37 Endnotes

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**Contact:** Heather Cable, officer, communications **Email:** hcable@pewtrusts.org **Phone:** 202-552-2059

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**The Pew Charitable Trusts** is driven by the power of knowledge to solve today's most challenging problems. Pew applies a rigorous, analytical approach to improve public policy, inform the public, and invigorate civic life.

## Overview

In recent decades, the discovery and development of new antibiotics have slowed dramatically as scientific barriers to drug discovery, regulatory challenges, and diminishing returns on investment have led major drug companies to scale back or abandon their antibiotic research. Consequently, antibiotic discovery—which peaked in the 1950s—has dropped precipitously. Of greater concern is the fact that nearly all antibiotics brought to market over the past 30 years have been variations on existing drugs.<sup>1</sup> Every currently available antibiotic is a derivative of a class discovered between the early 1900s and 1984.<sup>2</sup>

At the same time, the emergence of antibiotic-resistant pathogens has accelerated, giving rise to life-threatening infections that will not respond to available antibiotic treatment. Inevitably, the more that antibiotics are used, the more that bacteria develop resistance—rendering the drugs less effective and leading public health authorities worldwide to flag antibiotic resistance as an urgent and growing public health threat.

Reducing the inappropriate and unnecessary use of antibiotics will help slow this process, but it cannot halt it. Existing antibiotics will continue to lose their effectiveness over time, and patients will continue to need new drugs and therapies. Regulatory policies and economic incentives that encourage antibiotic development are vital; however, it is also critical to address fundamental gaps in basic scientific research that hinder new drug discovery.

The Pew Charitable Trusts convened a multidisciplinary group of leading industry and academic experts to identify the key scientific roadblocks to antibiotic discovery and consulted with numerous other public and private sector stakeholders to develop a Scientific Roadmap for Antibiotic Discovery. The roadmap outlines a concrete approach—both a scientific plan and organizational structure to support this research—that would lay a foundation for the sustained and diversified discovery and development of new antibiotics and therapies over the coming decades.

The report's key findings show a need for:

- A targeted approach to tackle the basic scientific barriers impeding antibiotic discovery and development.
- A better understanding of how to overcome the cellular defenses of drug-resistant Gram-negative bacteria, which cause some of the most difficult-to-treat infections.
- Generation of new chemical matter designed for antibiotic discovery.
- Tools and methodologies to evaluate promising alternatives to traditional antibiotic use.
- A framework for sharing information, expertise, and materials across the research community to foster innovative science and spur the discovery of novel antibacterial therapies.

Success will require dedicated teams of multidisciplinary scientists to tackle key questions and share knowledge and skills across sectors.

- A core scientific leadership group would set priorities and direct and manage milestone-driven research.
- New methodologies and guidelines for antibiotic discovery generated by this initiative would provide scientists in industry and academia with a foundation to support the discovery of new drugs over a sustained period of time.

If successfully implemented, this initiative has the potential to revitalize innovation in antibiotic research and accelerate the discovery of new types of antibacterial drugs and therapies.

## The state of the field

Once a model of productivity and innovation, research efforts to discover new antibiotics have stalled. In the post-World War II period following Alexander Fleming's breakthrough discovery of penicillin and the partnership between industry and government to produce this lifesaving drug on an industrial scale, new antibiotics were discovered and developed at a breathtaking pace. Such efforts led to dramatic advances in human health, as antibiotics were used to treat an increasingly wide range of infections while allowing for the evolution of the complex medical care that is now taken for granted, such as hip replacement, intensive care medicine, dialysis, and cancer treatment.

Drug discovery, the process of finding or designing molecules that could someday lead to new therapies, underpins drug development, the process of rigorously testing a therapeutic candidate for safety and efficacy in order to bring a new medication to market.

The "golden age" of antibiotic discovery peaked in the 1950s, bringing forth lifesaving drug classes, such as erythromycin, vancomycin, and metronidazole. During this period, the pharmaceutical industry was the engine of innovation as nearly every major company maintained an active research and development (R&D) program in antibiotic research.<sup>3</sup> Yet, after the initial rush of new compounds—many isolated from actinomycetes, bacteria that are mainly found in soil—new starting points for antibacterial drugs became harder to find, and the scientific hurdles more apparent.

New discoveries dropped precipitously from the 1980s onward. As a result, the development of antibiotics has declined, with new Food and Drug Administration (FDA) approvals for these drugs falling from 29 during the 1980s to nine in the first decade of the 2000s.<sup>4</sup> All antibiotics approved for use in patients today are derived from a limited number of types, or classes, of antibiotics that were discovered by the mid-1980s (Figure 1).<sup>5</sup> This is even more concerning than the decline of drug approvals because resistance to one antibiotic often leads to resistance to multiple antibiotics within the same class. While drugs can be categorized or classified in a variety of ways, for the purposes of this document, antibiotic classes are based on similarities in chemical structure.

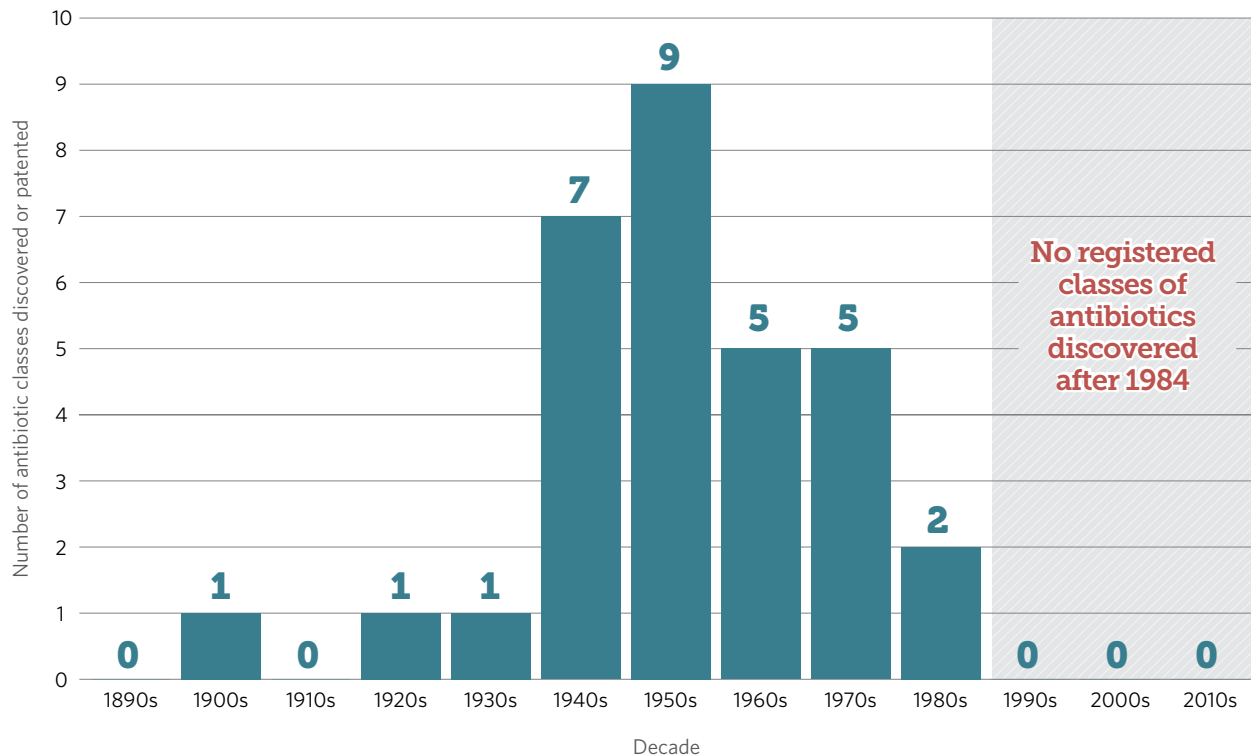
Faced with poor discovery prospects and diminishing returns on investment, major drug companies have cut back or pulled out of antibiotic research altogether. This has left much of the remaining discovery work to small, "pre-revenue" companies with no products on the market and limited budgets and R&D capacity. Most industry antibiotic development programs are primarily focused on modifying existing classes of drugs discovered decades ago to circumvent bacterial resistance and better target difficult-to-treat infections. Though essential, such incremental advances are not likely to meet the looming public health challenge of antibiotic resistance in the long term.

As successful antibiotic discovery has plummeted, widespread resistance to existing drugs has proliferated, placing humanity on the precipice of what the World Health Organization has called a "post-antibiotic era," in which common infections and minor injuries may once again be lethal.<sup>6</sup> Resistance is spreading globally, affecting both wealthy and developing nations. In the United States, the Centers for Disease Control and Prevention (CDC) estimates that more than 2 million people acquire serious resistant bacterial infections each year, and at least 23,000 of them will die as a result.<sup>7</sup> A survey by the Infectious Diseases Society of America indicated that over 60 percent of infectious disease doctors have encountered patients with infections that do not respond to any available antibiotic.<sup>8</sup>

Antibiotic resistance is a global problem, highlighted by the spread of new types of resistance, such as New Delhi metallo-beta-lactamase. First reported in 2008, it spread to 40 countries within five years and continues

to advance.<sup>9</sup> More ominously, several recent studies from multiple countries point to the emergence of clinical resistance to colistin, an antibiotic considered a “drug of last resort” because it is used in patients only when other antibiotics are no longer effective.<sup>10</sup>

Figure 1  
More than 30-Year Void in Discovery of New Types of Antibiotics



Source: Adapted from Lynn L. Silver, “Challenges of Antibacterial Discovery,” *Clinical Microbiology Review* (2011)

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## Why Do We Need New Classes of Antibiotics?

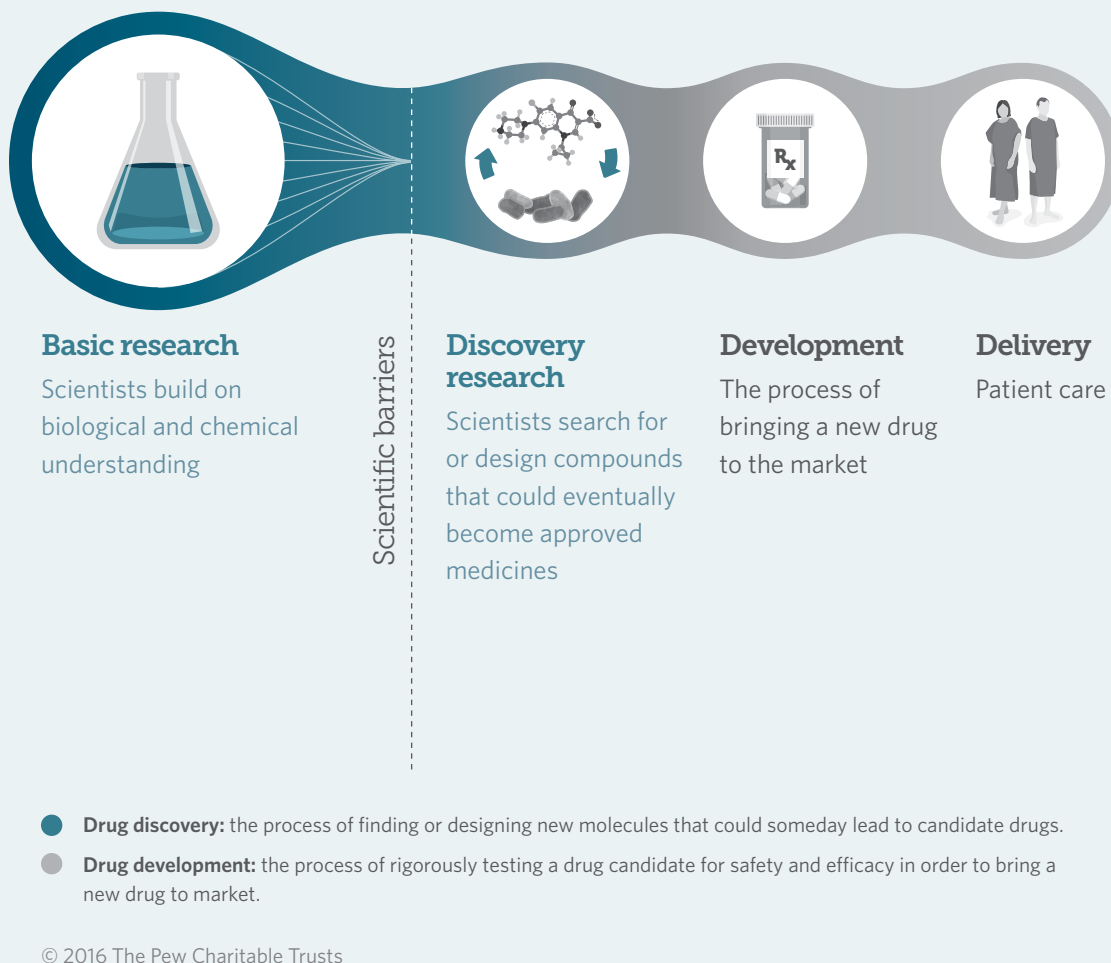
Antibiotics can be categorized based on similarities in their chemical structures (i.e. antibiotic classes).

Resistance to one antibiotic often leads to resistance to multiple antibiotics within the same class.

In the face of this mounting crisis, efforts to revive and improve the likelihood of successful drug discovery are essential. The U.S. government, industry, and the public health and medical communities all agree that new regulatory policies and economic incentives are critically needed to rebuild a robust pipeline of antibiotics.<sup>11</sup> When it comes to the discovery of new types or classes of drugs, however, the more fundamental barriers are scientific (Figure 2). Unless key bottlenecks to discovery are effectively addressed, antibiotic research and development will continue to struggle. New basic and foundational research is needed to sustain new drug discovery and development over the coming decades. Such research is the focus of this roadmap.

Figure 2

## Scientific Barriers Impede Antibiotic Discovery



As industry has shifted its model to focus largely on the development, licensure, and marketing of products, investment in critical areas of basic research has been lacking. Academia is often expected to fill this gap and, and while possessing exceptional research capacity, it alone is not fully equipped to overcome key scientific barriers to antibiotic discovery. To date, most public funding of academic researchers in the area of antibiotic resistance has been through investigator-driven grants lacking the interdisciplinary, coordinated, and goal-oriented research required to effectively spur new antibiotic discovery. In addition, drug discovery requires specific training and expertise, and without a mechanism for transferring industry knowledge to academic scientists, all too often lessons learned are lost and the same mistakes are made again—wasting time and resources, and slowing progress.



The U.S. government has taken some important steps, with the National Institute of Allergy and Infectious Diseases (NIAID) offering preclinical and clinical tools to help accelerate the development of new therapies and supporting individual investigator-driven research on early drug discovery and nontraditional therapeutics.<sup>12</sup> NIAID also established the Centers of Excellence for Translational Research program, which includes at least one center dedicated to the development of new antibiotics to treat drug-resistant bacterial infections.<sup>13</sup>

A review of coordinated research and translational efforts directed at tackling basic scientific barriers to antibiotic discovery turned up a single existing project, Translocation, which is supported through the Innovative Medicines Initiative (IMI), a partnership between the European Union and the European Federation of Pharmaceutical Industries and Associations (EFPIA) trade group.<sup>14</sup> The Translocation project is focused on how to get antibiotics into Gram-negative bacteria and how to stop bacteria from ejecting the drug. The project is widely dispersed among 27 partners across nine European Union countries. Given that half of the budget comes from European taxpayers, participation by design is limited to European partners, leaving non-European-based firms and academic researchers on the sidelines. While other IMI projects to advance antibacterial development will continue, the Translocation project is scheduled to end in 2017.

### A new paradigm for antibiotic discovery

Recognizing the critical gaps in scientific knowledge and the essential public health need, Pew set out to assess whether experts could agree on the top scientific barriers impeding antibiotic discovery, outline a scientific plan to overcome these barriers, assess the resources needed, and propose a strategy for carrying out this work. Pew engaged a core working group of 21 leading antibiotic scientists from academia, industry, and government with an exceptional breadth and depth of knowledge in antibiotic discovery and development. Each has specific expertise across a range of disciplines, including microbiology, cellular and molecular biology, bacteriology, chemistry, medicinal chemistry, natural products, antibiotic resistance, and drug design. Numerous other experts provided useful insights at every stage of the process.

This roadmap outlines a plan to shift the paradigm of antibiotic R&D by building a sustainable and robust foundation for discoveries over the coming decades. It has the potential to improve the overall success rate of antibiotic discovery and early development while expanding the number of approaches available to combat bacterial infections. To accomplish these goals, the working group identified two priority areas, which could be tackled concurrently or sequentially: understanding and overcoming barriers for drugs targeting Gram-negative bacteria in order to generate and better tailor new chemical matter for antibiotic discovery; and evaluating and validating alternative, nontraditional therapies for the treatment of systemic bacterial infections (discussed later in detail; see “Scientific priorities for antibiotic discovery”).

Given the rise of antibiotic-resistant bacteria, a continued focus on the appropriate use of existing antibiotics, alongside investment in key basic research, is essential for maintaining a robust portfolio of effective therapies.<sup>15</sup> This roadmap recommends a milestone-driven scientific plan to tackle the underlying causes of failed drug discovery and establish a more sustainable pipeline of new antibacterial therapies.

Beyond the traditional field of small molecule antibiotics, research advances in a variety of biomedical areas including biologics, immunotherapies, anti-virulence adjuncts, nanotechnology, and others may have important therapeutic applications for the treatment of systemic bacterial infections, as a number of these approaches have shown significant promise in treating other illnesses.

A scientific plan to carry out multidisciplinary and directed research needed to reenergize antibiotic discovery requires an organizational structure focused on achieving mission-driven goals and milestones. Given the

complexity and scale of the challenge, the success of such an effort would require the integration of scientists with expertise in drug discovery, biology, chemistry, pharmacology, and other disciplines to ensure the sharing of lessons learned and expertise among sectors. In addition, there would be great value in moving beyond the traditional drug discovery community to engage experts who can bring new ideas and offer different perspectives to help tackle long-standing problems.

The initiative described here would require a dedicated, full-time scientific leadership group to directly manage a multidisciplinary research effort. It would combine long-term research goals with the flexibility to redirect resources based on progress and unanticipated scientific challenges. This effort would aim to complement and augment existing publicly and privately funded research in the United States and abroad and to coordinate and collaborate with government, academia, industry, research institutions, and nonprofits to quickly transfer information and knowledge to the researchers who need it.

While this effort would not focus on product development, it would empower others to do so by lowering the barriers to drug discovery. By making data and new breakthroughs widely accessible, this approach has the potential to accelerate research at a wide range of institutions with the creativity and capacity to discover and develop new products. To accomplish the work laid out in the roadmap, close ties between the scientific leadership group, multidisciplinary research teams, and product developers through participation on scientific and technology transfer advisory boards and collaborative agreements would help ensure results-based research, while facilitating the uptake of new advances that can be rapidly translated into public health outcomes.

Drug discovery and development in other infectious disease-specific areas, such as HIV, tuberculosis (TB), and malaria, have been successfully spurred by collaborations between government-funded researchers and private industry, often catalyzed by nonprofit organizations. The International AIDS Vaccine Initiative, a nonprofit product development partnership working to translate laboratory breakthroughs into promising vaccine candidates against HIV, supports several preclinical and clinical vaccine candidates for preventing and controlling HIV infection.<sup>16</sup> The TB Alliance, a global nonprofit organization dedicated to faster-acting and affordable drug regimens to fight tuberculosis, launched the first clinical trials to test multiple TB drugs in combination and has assembled and managed the largest portfolio of potential new TB drugs in history.<sup>17</sup> The Medicines for Malaria Venture, a nonprofit public-private partnership working to discover, develop, and facilitate delivery of new, effective, and affordable anti-malarial drugs, supports multiple projects from lead generation and optimization through product development.<sup>18</sup> As this roadmap initiative progresses, these and other organizational approaches will be considered as potential models for achieving long-term scientific goals.

Finally, appropriate levels of funding are essential for the success of large-scale scientific initiatives. This roadmap calls for an initial funding target of \$50 million to establish operations and execute the key pilot studies laid out in this plan. Overall, it is estimated that full execution of the project outlined here would require \$170 million to \$200 million over five years. These targeted investments, if successful, have the potential to dramatically improve public health outcomes over the decades to come.

The principles outlined in this roadmap do not stand alone—they align with a growing chorus of national and international calls for reviving the antibiotic pipeline. The World Health Organization, the United Kingdom's Review on Antimicrobial Resistance, the President's Council of Advisors on Science and Technology, the National Institutes of Health (NIH), the National Academy of Sciences, and the research community have all highlighted the pressing need for new antibiotics.<sup>19</sup> The concepts laid out in this document translate these calls for action into a series of concrete next steps that should be taken to transform antibiotic discovery.

## Scientific priorities for antibiotic discovery

This section outlines a proposed strategy for tackling each of the key scientific priorities areas for antibiotic discovery.

### 1. Generate and tailor chemical matter for antibacterial discovery

Alexander Fleming serendipitously discovered penicillin in 1928, and subsequent discoveries in the “golden age” of antibiotics after World War II led to the development of most of the antibiotics in use today.<sup>20</sup> Many of these compounds came from natural products isolated from living organisms such as actinomycetes bacteria, which are mainly found in soil. Natural products have been mainstay sources of the antibiotics currently in clinical use, but output eventually waned once easily identifiable chemical classes had been exploited, and companies largely abandoned this resource in favor of high-throughput screening of synthetic compounds and medicinal chemistry approaches. Despite substantial investment in discovery programs, this approach generally has not yielded useful starting material for antibiotic research and development.<sup>21</sup>

Finding new antibiotics depends on scientists’ ability to explore new chemical space—through novel screening of diverse and differentiated compound libraries, targeted synthesis or modification of compounds with better physicochemical properties, phenotypic assays, and other methods that are explicitly tailored for bacterial pathogens. One key challenge is that commercially available chemical matter is not well suited for antibiotic discovery given that the physicochemical properties of antibiotics are unique. Most antibiotics tend to be more polar and less lipophilic than other drugs, in large part because of the need for antibiotics to penetrate and stay inside of bacterial cells to engage their targets.<sup>22</sup>

In the absence of good starting material, even a robust screen for inhibitors of a validated drug target will not yield much, but it is difficult for any one company or research institution to justify the construction of a “custom” chemical library for a single therapeutic area. Most antibiotics firms are small, with limited resources, so good chemical matter for antibiotic discovery is lacking.<sup>23</sup> A more fundamental problem particular to antibiotic discovery is the need for better insight and scientific understanding to generate a successful library. Given the unique characteristics of antibiotics, the goal of this effort is not to find and collect new sources of natural products or build vast libraries of synthetic compounds. Instead, this effort would aim to selectively generate and modify chemical matter that is tailored for the discovery of new antibiotics.

#### Barriers to antibiotic discovery for Gram-negative pathogens

Multidrug-resistant Gram-negative infections are widely recognized as one of the greatest areas of unmet medical need and account for some of the most serious microbial threats in the United States.<sup>24</sup> Particularly concerning are carbapenem-resistant Enterobacteriaceae, or CRE, infections, which are on the rise among patients in medical facilities and have become resistant to all or nearly all of the antibiotics available today. Infections caused by Gram-negative pathogens are difficult to treat and can be deadly—up to half of all bloodstream infections caused by CRE result in death.<sup>25</sup> Unfortunately, few of the antibiotics approved by FDA in the past five years have activity against this critical group of pathogens. As of September 2015, an analysis of the drug pipeline showed 39 antibiotics in development, fewer than half of which have the potential to address difficult-to-treat Gram-negative infections.<sup>26</sup> Nearly all of these drugs are modifications of existing classes of antibiotics.

In practice, scientists must be able to produce molecules that are not only potent inhibitors of essential bacterial processes, but also have the ability to enter bacterial cells, evade efflux pumps (protein complexes

that actively transport toxic molecules out of the cell), and reach high intracellular concentrations. For Gram-negative pathogens, this has been rarely achieved, making it difficult for scientists to build on previous work or develop useful guidelines for future success. Unless this fundamental gap in biological and physicochemical understanding is effectively addressed, antibiotic discovery efforts will continue to struggle.

Most Gram-negative bacteria have built-in abilities to evade antibiotics and develop resistance. Unlike Gram-positive bacteria, such as *Staphylococcus aureus* (e.g., MRSA), Gram-negative pathogens have two membranes with orthogonal characteristics. That makes it difficult to design drugs that can penetrate both barriers in order to get into the cytoplasm of a bacterium and kill it (Figure 3). For example, specific hydrophilic or charged solutes can cross the outer membrane by diffusion through water-filled channels called porins, but they are unable to penetrate the cytoplasmic membrane unless they are actively transported. In addition, Gram-negative pathogens possess a wide variety of efflux pumps, which actively expel antibiotics from the cell and contribute to drug resistance. Solving the problem of Gram-negative drug entry and efflux requires attention to all of the complex mechanisms by which Gram-negative bacteria evade antibiotics.

Several research groups in industry and academia have independently tried to address aspects of these challenges.<sup>27</sup> Academic labs have specialized in particular types of efflux pumps or outer membrane porins. Industry teams have worked to modify existing classes of antibiotics to better target Gram-negative pathogens. Despite these advances, significant gaps in understanding remain, particularly when it comes to rationally designing compounds with the physicochemical properties of antibacterial drugs that get into and remain in the cytoplasm of Gram-negative bacteria.

Pharmaceutical companies have large compound collections that can be used as starting materials to find chemical matter that is active against newly identified biological targets. However, these collections are generally optimized for human targets, such as G-protein-coupled receptors or kinases, and biased toward penetration of eukaryotic rather than Gram-negative bacterial cells and bacterial targets. Known Gram-negative antibacterials generally do not follow Lipinski's rule of five\* but most industry compound collections are heavily biased toward compounds that do.<sup>28</sup> Improving chemical diversity for antibiotic discovery requires a better understanding of the physicochemical properties that are important for antibiotics.

It was not until 2008 that published computational analyses differentiated between the physicochemical characteristics of Gram-negative and Gram-positive targeted drugs.<sup>29</sup> Such work suggests the possibility for conditionally applicable guidelines for antibiotic discovery and design that would help researchers find new antibiotics that target Gram-negative pathogens or modify existing compounds so they are able to overcome the multicomponent sieving systems of Gram-negative bacterial species. For example, it may be possible to develop general guidelines for physicochemical properties required for the entry of compounds by different routes that are tailored for particular chemical classes, mechanisms of action, or bacterial species. This type of information has the potential to spur the discovery of new compounds and benefit all discovery research, but there is a lack of concerted and focused research to carry out this much-needed body of work.

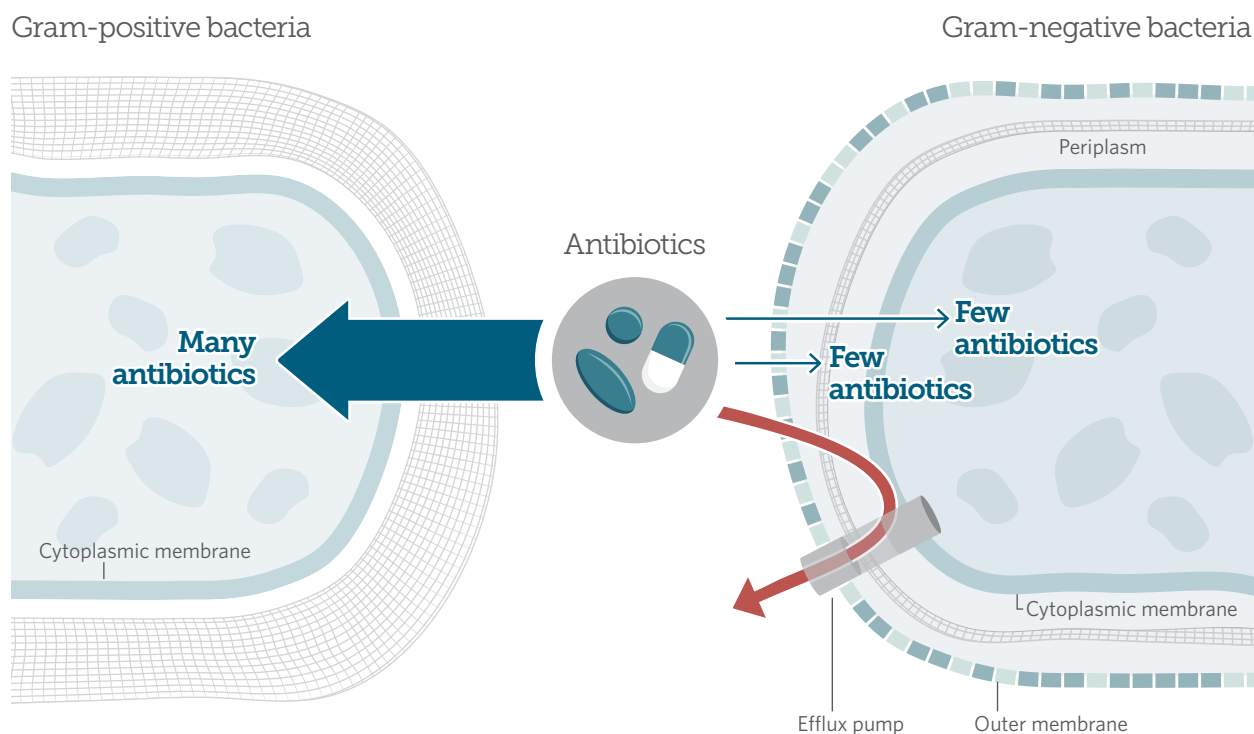
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\* Lipinski's rule of five, describes the physicochemical properties that correlate with a compound's likelihood of being orally bioavailable. The rule states that, in general, an orally active drug has no more than one violation of the following criteria:

- No more than five hydrogen bond donors.
- No more than 10 hydrogen bond acceptors.
- A molecular mass less than 500 daltons.
- A measure of lipophilicity (log P) not greater than 5.

The rule of five is based on a distribution of properties for several thousand drugs. Some categories of drug types, such as antibiotics, antifungals, vitamins, and cardiac glycosides, are exceptions to the rule.

Figure 3  
Barriers to Antibiotic Entry Into Gram-Negative Bacteria



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## Why Are There So Few Antibiotics to Treat Gram-Negative Infections?

Bacteria have evolved ways to prevent the entry of unwanted or toxic compounds such as antibiotics. Gram-positive bacteria have a membrane barrier that is relatively easy to penetrate, so many types of antibiotics get into the cell. Gram-negative bacteria have a double membrane along with a variety of efflux pumps that expel drugs out of the cell, making it difficult to design new antibiotics that target Gram-negative pathogens.

Goal: Understand and overcome barriers to drug penetration and efflux avoidance for Gram-negative bacteria

**Objective 1.1: Collect, analyze, and share existing knowledge on Gram-negative drug entry and efflux.**

Solving the problem of Gram-negative drug entry and efflux requires a comprehensive but focused approach that moves beyond piecemeal projects and siloed disciplines. To begin, a comprehensive review of existing information—published and unpublished—on penetration and efflux will help scientists assess what is already known and what gaps remain. The IMI Translocation project is pursuing a similar goal to tackle Gram-negative

barriers,<sup>30</sup> and the Defense Threat Reduction Agency funded a small project focused on structural components that make pathogenic bacteria resistant to antibiotics, including exploring the physicochemical properties that allow antibiotics to penetrate the cell membrane. For future progress in this area, it is important that hypotheses on the interaction of chemistry with Gram-negative cells advance to the level of quantitative models. The goals outlined in this roadmap aim to build on existing knowledge and lessons learned and to work in coordination with other initiatives to ensure that limited resources are strategically deployed and prior efforts are not duplicated.

Collection and analysis of data would lead to the generation of initial hypotheses to be tested in pilot studies and should include available information on the structure-activity relationship for antibiotics that enter the cytoplasm of Gram-negative bacteria. Such an analysis requires that top experts, who have worked on this problem before, openly discuss what has already been tried, share lessons learned, and facilitate knowledge transfer in cases where information exists and can be divulged. Leading scientists in the field have expressed a willingness to participate in such a dialogue, which would require a third-party convener to facilitate an open discussion on this key problem among scientists from the private and public sectors.

Findings would inform the scientific direction of this effort. Information may also be compiled and analyzed in white papers and scientific publications for sharing among the broader discovery community to spur efforts to find and design new antibiotic starting points.

**Objective 1.2: Develop tools (quantitative assays) to quickly and accurately measure drug penetration and kinetics for Gram-negative bacteria that are independent of drug activity.**

Initial experiments would focus on the development of standardized methodologies and quantitative assays to measure drug penetration and efflux avoidance and would assess the kinetics of drug entry into the periplasm and the cytoplasm of Gram-negative bacteria in a manner that is independent of minimum inhibitory concentration. A number of complementary approaches may be pursued and could be carried out in partnership with public and private sector laboratories that have specialized equipment and expertise. New technologies that could be useful for systematic assessment of Gram-negative-targeted compounds may include single molecule tracking, whole cell mass spectrometry imaging, and differential Raman spectroscopy. Quantitative methods to measure uptake, permeation, and efflux should be standardized to ensure that data are uniform across experiments.

**Objective 1.3: Elucidate conditional guidelines for drugs targeting Gram-negative pathogens.**

A better understanding of Gram-negative drug entry and efflux, particularly for “impermeable” pathogens such as *Pseudomonas aeruginosa* or *Acinetobacter baumannii* could have significant implications for both synthetic and natural product antibiotic discovery. As assays are developed, researchers could begin to carry out surveys of existing compound libraries to see what compounds get past each component of the barriers in Gram-negative bacteria (e.g., porins, efflux, and uptake). Hypotheses based on these data and what is already known in the scientific literature could then be further developed and refined.<sup>31</sup>

Researchers would carry out pilot experiments to test initial hypotheses for entry and efflux avoidance, working with synthetic and medicinal chemists to build trial sets of chemicals to measure drug penetration and drug kinetics for a range of Gram-negative bacterial species, and with biologists and bacterial physiologists to identify mechanisms of penetration and uptake. Based on initial findings, iterative hypothesis testing would continue to determine whether guidelines can be developed based on chemical class, drug target, bacterial species, or some other categorization.

As hypotheses for drug permeation are further tested empirically, computational and theoretical scientists, mathematical modelers, and other experts would be needed to help guide the design of experimental approaches and formulate conditional guidelines. Collaboration with state-of-the-art facilities and technology centers, such as the Department of Energy's national laboratories, could provide opportunities to approach problems from different angles and foster new ways of thinking.

**Objective 1.4: Find alternative ways to overcome Gram-negative barriers to drug entry.**

In parallel with traditional antibiotic discovery approaches, scientists from across a range of disciplines should explore alternative methods to overcome Gram-negative barriers to drug entry to bring novel approaches and fresh perspective to bear. For example, compounds that disrupt the synthesis and architecture of the outer membrane or impede efflux pump activity of Gram-negative bacteria could potentially be coupled with existing antibiotics to circumvent some of the entry and efflux barriers for antibiotic compounds. Self-promoted uptake through the outer membrane, and studies of diffusion of ionic species across the cytoplasmic membrane, may yield promising opportunities and should be coupled with studies to understand entry through the cytoplasmic membrane and to examine and mitigate toxicity problems. Nontraditional antibacterial screening approaches that take the *in vivo* infection environment into account may also lead to novel approaches for overcoming barriers for Gram-negative antibiotic discovery.<sup>32</sup>

Goal: Generate and tailor chemical matter for antibacterial discovery

**Objective 1.5: Build prototype libraries tailored for antibacterial discovery.**

Chemical space is vast, so as conditional guidelines for Gram-negative drug entry and efflux are characterized, a collaborative team of chemists, medicinal chemists, computational scientists, natural products experts, microbiologists, pharmacologists, and other key experts could begin to generate, test, and modify chemical matter in a hypothesis-driven manner. These scientists may first generate trial sets of chemical compounds based on what is already known about Gram-negative drug entry and efflux from existing programs and published studies and modify these trial sets in response to iterative hypothesis testing. These trial sets would serve as useful starting points for new prototype libraries that can be tailored for antibiotic discovery. As conditional guidelines for Gram-negative drug entry and efflux are characterized, prototype libraries would be further refined.

It is important to clarify that this proposed effort is not focused on broad expansion of synthetic libraries or seeking out new sources of natural products. Instead, the goal is to execute focused work to carefully vet existing chemical matter and conduct targeted synthesis and modification of new chemical matter based on what is known about antibacterials from published and unpublished sources, incorporating insights and guidance as new research findings emerge.

It will take time to determine whether conditional guidelines can be developed for Gram-negative drug entry and efflux avoidance. Meanwhile, practical and transparent knowledge-sharing mechanisms should be established to better inform discovery scientists on how to identify new chemical matter based on drug-like qualities and what is already known about the chemical properties of antibiotics. This would require collaborative research to facilitate new and directed approaches to generate and modify chemical matter. For example, working together across multiple disciplines, scientists may begin to develop new semi-synthetic antibiotic templates derived from fragment-based or natural products-based starting points that better target Gram-negative or Gram-positive bacteria.

## Natural products

Natural products remain an evolutionarily honed source of novel chemical classes. Alongside a synthetic-based approach, natural products may be identified through alternative cultivation or novel screening methods and carefully vetted, then modified through medicinal chemistry approaches for inclusion in these prototype libraries.

Over the past two decades, despite the technical challenges and resource limitations, scientists have discovered novel natural products of interest. This indicates that new antibiotic starting points may be out there, but that finding them will require ingenuity. Until recently, to generate natural products for testing, only a small fraction of bacteria could be grown or fermented under standard laboratory conditions. Early proof-of-concept studies indicate that new methods for the cultivation of bacteria in their native environment may afford new possibilities for natural products discovery, as might old techniques such as cell-based phenotypic screening, which have started to make a comeback in a more sophisticated form.<sup>33</sup> Whole genome sequencing and transcriptome analysis, to examine bacterial DNA and RNA, respectively, have revealed a large number of unexpressed pathways that may yield natural products of interest. Several researchers have devised genetic methods to express these “silent gene clusters” and produce natural products in heterologous hosts.<sup>34</sup>

Methods to isolate new natural product scaffolds are difficult and require specific expertise, but the problem is more complex than simply a need for “smarter screening.” Most natural product scaffolds exhibit a range of problems that often include cytotoxicity, lack of solubility, high protein binding, and a lack of activity against Gram-negative bacteria. Finding those rare novel natural products that are effective and nontoxic antibacterials will require a focused effort.

Re-examination of previously discarded natural products may offer some potential. Products that were approved for the clinic but withdrawn because of toxicity or antibiotic resistance issues could be revisited as well. As a part of this effort, medicinal chemists may take a second look at published natural product antibacterials, review their status, and evaluate whether problems, such as toxicity, metabolic issues, narrow spectrum of activity, or resistance issues, that may have prevented compounds from moving to clinical development can be overcome through chemical modification and testing.<sup>35</sup> For example, daptomycin, a lipopeptide antibiotic used for the treatment of systemic and life-threatening infections caused by Gram-positive organisms, was initially discarded because of adverse effects on skeletal muscle, but was later developed and marketed following a change in the dosing regimen.<sup>36</sup> Given that compounds may have been discarded for good reason, promising avenues of research should be carefully vetted by scientists with appropriate drug discovery, natural products, and medicinal chemistry expertise.

### **Objective 1.6: Scale up chemical libraries tailored for antibiotic discovery.**

Once prototype libraries are established, conditional guidelines for drug entry and efflux avoidance for Gram-negative pathogens could be applied more broadly to build a curated resource of diverse chemical material for use by the broader scientific community. The goal of this effort would not be to build massive compound collections, but to create a carefully vetted and annotated source of compounds tailored for antibiotic discovery. Unlike the prototype libraries described above, which would serve best as probes for testing conditional guidelines for drug entry and efflux, scaled-up chemical libraries would be designed to serve as a source of antibiotic starting material and as a model for creating additional chemical libraries.

Chemical synthesis to generate compounds could be carried out through contract research organizations or in partnership with synthesis and natural products laboratories. To build a diverse collection, work should



incorporate a variety of synthesis methods and draw from multiple synthetic and natural products sources. The number of compounds produced would be limited by established physicochemical properties and structural guidelines, but it could be large enough to carry out targeted screens for antibiotic starting points.

Other biomedical initiatives, such as Medicines for Malaria Venture, have generated freely available libraries tailored for specific disease areas. Malaria Box, a collection of 400 diverse compounds with anti-malarial activity, was distilled from 20,000 hits generated from a screening campaign of around 4 million compounds from the libraries of St. Jude Children's Research Hospital, Novartis, and GlaxoSmithKline. This collection of compounds incorporates a broad cross-section of structural diversity and takes into account factors such as oral absorption and toxicity.<sup>37</sup> A number of Malaria Box compounds have shown activity against *Cryptosporidium*, schistosomiasis, and African trypanosomiasis.<sup>38</sup>

Chemical library collections require care and maintenance and should be developed in partnership with a public or private institution that has existing infrastructure. The goal of this proposed effort is to spur the discovery of new classes of antibiotics, so considering that this objective's outcome could lead to the discovery of new antibiotic starting points, an intellectual property policy that encourages use of this resource, and maximizes public health benefits, would be required (see "Models for antibiotic discovery").

While Gram-positive antibacterial discovery is not the primary focus of this roadmap, it is important to consider the potential follow-on applications of the knowledge and tools generated through this initiative. Assays for measuring drug entry and efflux for Gram-negative bacteria could be adopted for Gram-positive organisms. Similar compound collections designed for Gram-positive bacteria could be a useful resource for antibiotic discovery. These opportunities may be considered at a later stage of this effort.

## 2. Conduct key proof-of-concept studies for nontraditional therapies

Alongside a scientific program to underpin future antibiotic discovery is an opportunity to advance nontraditional therapeutic approaches, which include alternative small molecule therapy, such as anti-virulence drugs or molecules that reduce the emergence of resistance; non-small molecule approaches, such as monoclonal antibodies or probiotics; and new drug delivery methods, such as liposomes or nanoparticles. While there is some indication that nontraditional approaches may have a role in treating systemic bacterial infections, only a handful of companies are pursuing development of these types of alternative products (see Appendix B).

For most nontraditional approaches, scientists face the same questions today as they did 30 years ago. When it comes to traditional drug discovery, there are standard methodologies available to evaluate efficacy, both *in vitro* and *in vivo*—such as assays to measure minimum inhibitory concentration and the neutropenic mouse thigh model of infection—which allow for data comparison across experiments and studies.<sup>39</sup> However, standardized studies for nontraditional therapies are still lacking. For example, researchers have been working for years on polymyxin-based molecules that permeabilize or break down the outer membrane; the chemistry is not novel, but it remains unclear how these compounds should be combined with other drugs or whether their use will generate drug-resistant bacteria.<sup>40</sup> Specific proof-of-concept experiments (e.g., toxicity or resistance studies, animal challenge experiments, pharmacokinetic optimization, pharmacodynamic modeling to understand concentration-dependent effects on the pathogen at the drug's site of action, and other methodologies needed to accelerate the path to development) would have to be tailored to any given approach.

There have been some advances. Scientists have studied broad-spectrum siderophore-conjugated antibacterial agents, which work by hijacking bacterial iron uptake pathways, but lacked reliable *in vitro* tests to predict resistance rates in animal models. To address this concern, researchers at Pfizer and Hartford Hospital published

a study describing new *in vitro* assays that were predictive of efficacy in mouse models, providing a useful tool for researchers in the field.<sup>41</sup> Unfortunately, for other nontraditional therapies, there are often no good models to test for effectiveness, structure-activity relationship, toxicity, pharmacodynamics (PD) and pharmacokinetics (PK), or resistance potential.

There is no single solution given that there are a plethora of nontraditional approaches, each with its own challenges and limitations. At the same time, it is important to realize that in many cases, progression of nontraditional therapies has been hobbled by the same factors that impede the discovery and development of traditional antibiotics. Scientists working on nontraditional small molecule-based therapies that must enter the cytoplasm of bacterial cells to exert activity face the same barriers to drug entry and efflux avoidance as scientists working on traditional antibiotic discovery. In addition, small molecule research requires specific expertise in drug discovery and development as well as PK/PD to inform drug design, identify key questions, and clarify which *in vitro* and *in vivo* proof-of-concept experiments are needed to evaluate whether a proposed nontraditional therapy may have clinical relevance. However, researchers working in alternative therapeutic fields may not have access to the consultation and support they need to validate a novel therapeutic approach and demonstrate clinical application.

Clinicians and scientists in other biomedical fields, such as HIV/AIDS, tuberculosis, and oncology, have recognized that nontraditional approaches to drug monotherapy, or the use of combination therapy, may offer new treatment options for patients.<sup>42</sup> Management of HIV/AIDS and TB typically involves the use of multiple drugs to control infection and mitigate the emergence of resistance. Chemotherapy drugs are also used in combination to decrease the likelihood that cancer cells will develop resistance. In addition, alternatives to traditional small molecule drug therapy have shown promise. For example, over the past few decades, immunotherapy, which uses a patient's immune system to fight disease, has played an important role in treating some types of cancer.<sup>43</sup> Targeted studies and support to develop new methodologies are needed to promote similar nontraditional approaches for the treatment of systemic bacterial infections.

This effort would aim to develop key proof-of-concept studies for a variety of nontraditional therapeutic approaches, starting with combination therapy. In addition, it would provide advisory and resource support to scientists working on nontraditional approaches by bringing together leading experts from a diversity of fields to foster new perspective and insight to help validate the clinical potential of new therapies and bridge the divide between translational science and early development.

#### Goal: Assess whether single-target antibacterials can be used in combination to overcome resistance

While not considered a nontraditional approach for other infectious disease areas, such as HIV, hepatitis C virus (HCV), and TB, the combination of two or more active drugs designed to prevent or reduce resistance emergence has not been comprehensively explored for antibacterials (aside from TB) and is therefore included in this section.

Most systemic antibiotics in use today are not subject to high-level resistance resulting from single-step chromosomal mutations, primarily because they have more than one molecular target within the bacterial cell. Bacteria must generate multiple mutations to develop resistance against these types of drugs.<sup>44</sup> In contrast, most drug discovery programs are designed to find single-target drugs, or drugs that bind specifically to a particular protein within a cell. Single-target inhibitors often lead to a high frequency of resistance and substantial decreases in the minimum inhibitory concentration (i.e., reduced susceptibility to a given drug), which limits their potential for development. To date, there has been no comprehensive, standardized, and well-controlled *in*

*vitro* and *in vivo* study of characterized single-target drugs to assess whether a combination or cocktail of these compounds could help lower resistance rates *in vitro* or *in vivo* and how this might translate to the clinical setting.

**Objective 2.1: Determine whether single-target antibacterials can be used in combination to overcome resistance *in vitro*.**

This objective aims to determine whether combinations of single-target antibacterials can, at least in principle, reduce the frequency of resistance *in vitro*. One approach to achieve this objective would be to carry out a comprehensive *in vitro* assessment of existing single-target antibacterials used in combination against a variety of bacterial pathogens to measure and compare the frequency of resistance.<sup>45</sup>

Based on the scientific literature, a small team of scientists would first test existing verified single-target antibacterial compounds.<sup>46</sup> Few single-target drugs have made it into the development pipeline, but a number of confirmed single-target compounds have been described in the scientific literature.<sup>47</sup> Candidate compounds should have a demonstrated target-specific mechanism of inhibition (i.e., there is evidence that drug activity is due to inhibition of a specific gene or protein target), a lack of mammalian cytotoxicity, and necessary drug-like properties, which would be required for further animal model studies.

Sourcing of these compounds, which could include antibiotics in clinical use as well as compounds that have not been developed as drugs, may pose some challenges given that many inhibitors were at one point pursued by companies and some have entered into the development pipeline. Compounds that are commercially available may be purchased. Those that have published synthetic routes could be chemically generated, and others would have to be requested from industry or academic scientists.

When evaluating antibiotic combinations, pharmacokinetics and pharmacodynamics (PK/PD) will play a critical role. The dosing, timing, and distribution for each drug will vary, adding further complications to combination testing. Consequently, after obtaining a panel set of single-target compounds, a scientific team of microbiologists, toxicologists, and chemists would first establish the PK/PD parameters for further experiments. For example, the hollow fiber infection model\* may be used to determine the appropriate dosing and timing for each antibacterial.<sup>48</sup>

Once PK/PD studies are completed, the scientific team would establish a baseline for resistance frequency by testing each compound using the hollow fiber model. Compounds could then be tested in pair-wise combinations and potentially in combinations of three or more. Given that there would likely be bacterial species-specific variation in resistance rates, the scientific team should examine both standard pathogens and clinical strains. The sheer number of combinatorial assays would require that methodologies for these studies be standardized and well-controlled to compare findings across multiple experiments. Based on the results from these studies, the scientific team would then evaluate whether combinations can be used to overcome resistance issues *in vitro* and what further studies should be done.

**Objective 2.2: Determine whether single-target antibacterials can be used in combination to overcome resistance *in vivo*.**

Following the *in vitro* studies described above, a subset of promising antibacterial combinations would be further tested in animal models to assess whether results in hollow fiber models are predictive of resistance rates in

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\* The hollow fiber infection model is a useful tool to carry out *in vitro* experiments under conditions that mimic changes in drug concentration over time, similar to what might occur in an animal model. In addition, studies have demonstrated that hollow fiber models are effective tools for studying antibiotic combination therapies.

animal models. Compound dosing and frequency of administration may be based on pre-existing knowledge of *in vivo* pharmacokinetics and pharmacodynamics parameters established by previous *in vivo* work. Animal models that mimic infection at different body sites could provide useful information on the potential efficacy of combination therapy for a particular clinical indication.

### Goal: Validate nontraditional therapies

While each type of nontraditional therapy will have its own benefits and pitfalls, experts agree that the gap between late-stage translational science and early development remains a key scientific bottleneck no matter the approach. To advance new concepts through to early development, researchers must be able to ask and address the right scientific questions and carry out key *in vitro* and *in vivo* proof-of-concept experiments to demonstrate whether a new therapy could lead to viable product development.

### **Objective 2.3: Develop proof-of-concept studies to accelerate the path to development for promising nontraditional therapies to treat systemic bacterial infections.**

Given the scientific complexity and diversity of nontraditional therapies under consideration, there should first be a clear delineation of which nontraditional approaches might be used as adjunct therapy, which might work as prophylaxis, and which might replace antibiotic use. The Wellcome Trust and UK Department of Health commissioned a report and review on alternatives to antibiotics to inform policy and decision-makers.<sup>49</sup> Building on this publication, the following questions should be considered by leading scientists with specific expertise in nontraditional approaches along with experts in drug discovery and development:

- Given that the clinical application of nontraditional approaches will vary across different types of infections (e.g., otitis media vs. septic shock), which interventions have the potential to best address unmet medical need?
  - For approaches that have been studied over a period of time, what key proof-of-concept experiments are required to determine whether it makes sense to move forward into early development?
  - For approaches that seem plausible, but have yet to be fully explored, what are the practical problems (e.g., efficacy or resistance potential) that must be overcome to move forward?
  - For approaches that are truly novel (e.g., nanoparticles or directed delivery systems), how should feasibility be assessed, and at what stage?

Based on this landscape analysis, scientists would identify key proof-of-concept studies needed to demonstrate whether specific nontraditional therapies offer practical alternatives to traditional antibiotic therapy.

For example, anti-virulence strategies (e.g., inhibition of transcriptional regulators, Type III secretion systems, or adhesion factors) disarm the pathogen rather than destroy it, allowing the host immune system or antibiotic co-therapy to clear the infection. Most anti-virulence approaches do not lower bacterial load; instead they reduce the chance of an infection taking hold or the ability of bacteria to cause disease. While the effectiveness of traditional antibacterials can be demonstrated using standard *in vivo* and *in vitro* models that measure the reduction in bacterial load, there is a lack of good animal models to demonstrate whether anti-virulence strategies are effective and offer improvement over antibiotic treatment alone.

*In vivo* experiments that rely on biomarkers or other means to demonstrate this benefit independently from bacterial burden are critically needed and could be broadly applicable across the anti-virulence field. Anti-virulence agents will potentially be used in combination with new or existing antibiotics, so *in vivo* assays to evaluate these types of combination approaches will be required.<sup>50</sup>

The Defense Advanced Research Projects Agency (DARPA) may offer a useful model for tackling these types of difficult problems. The agency has solicited proposals for research to support the potential use of living “predatory” bacteria for the treatment of infections caused by Gram-negative resistant and priority threat pathogens. While *in vitro* studies have shown that certain predatory bacteria such as *Bdellovibrio bacteriovorus* and *Micavibrio aeruginosavorus* can feed on human pathogens, including multidrug-resistant bacteria, gaps in basic scientific understanding remain.<sup>51</sup>

To fill these gaps, DARPA is focused on tackling three key questions:

1. Are predators toxic to recipient (host) organisms?
2. Against what pathogens (prey) are predators effective?
3. Can pathogens develop resistance to predation?<sup>52</sup>

If successful, DARPA’s Pathogen Predators program will lay the groundwork for safe and efficacious novel treatments for bacterial diseases.

A similar milestone-based directed research effort that includes consultation and guidance for researchers in academia, at startups, and at biotech companies seeking to move from translational research to early development could jump-start interest and investment in other novel approaches by reducing the early risks and obstacles facing academic and industry teams and determining which novel therapies may offer practical alternatives to traditional antibiotics.

### 3. Share data, materials, and knowledge across disciplines and between sectors

There is growing concern that as industry teams are downsized or shuttered, antibiotic scientists have moved to other firms, shifted to different biomedical areas, or retired, leading to the loss of valuable institutional knowledge and expertise. Antibiotic discovery has a long history, but much of the published research is buried in old journal issues or out-of-print books, and other research never makes it to publication. Organizing this body of research and making it accessible to the scientists who need it is critical for advancing discovery. Valuable knowledge may include compilations of screens that have been run before and information on past research programs. While much of this information is publicly available, what may be most useful is an account of what projects failed, and why.

The mission of this proposed effort is to efficiently and effectively share research findings with key stakeholders in the antibiotic discovery space. Rapid release of findings to external researchers, using a system of proper qualifications, quality control, and standardization, would be a priority. However, creating an environment in which data exchange and knowledge sharing are the status quo will be difficult given proprietary concerns and the variety of information types and formats, which may range from historical data to new findings produced as part of this research effort.

#### Goal: Share data and information

#### **Objective 3.1: Establish an informatics infrastructure to efficiently and effectively share antibiotic discovery data and information.**

Importantly, the scientific leadership group leading this initiative should engage early on with technology transfer experts from academia, industry, and government to ensure that findings are effectively disseminated across the research community.

As described earlier, a systematic review that synthesizes published and unpublished information on what is known about compounds that effectively penetrate Gram-negative bacteria and sufficiently avoid efflux would help scientists identify remaining knowledge gaps that must be filled in order to better design and tailor antibiotic starting points. In addition, a searchable catalogue of chemical matter that includes an ongoing list of lead antibacterial compounds, how they were identified, how were they tested, and why they were discarded would provide researchers with valuable data on which to base the next generation of chemical exploration. An informational database of natural products, including available biological, physicochemical, and structural data, would also be a useful tool. Furthermore, information on screening assays and conditions tested would provide useful information for researchers seeking to find new antibiotic starting material.

Sharing these findings with the broader scientific community in a useful way would be a challenge. Based on input from researchers and technology transfer experts from academia, industry, and government, this objective would establish a user-friendly and interactive platform that allows researchers to share past work—published and unpublished—edit information, and incorporate new findings produced through this effort. In addition, guidelines should ensure that the quality of data and information produced through this effort is standardized and appropriately annotated or analyzed.

Considerable resources may be required to build an informatics infrastructure formatted in a way that allows for interoperability across multiple institutions and promotes the sharing of numerous types of data and information among partners. Software could be purchased and modified to suit research needs through organizations such as Collaborative Drug Discovery, a software company that provides a secure cloud-based platform for sharing and analyzing chemical and biological data.<sup>53</sup> Alternatively, there may be opportunities to work with existing software platforms, such as the InfoCentre, which is supported by the IMI Translocation project and funded through 2017. The InfoCentre aims to combine legacy data (discovery and development studies) on successful and failed approaches to antibiotic discovery from EFPIA and public partners, and could be expanded to include U.S.-based and international partners.<sup>54</sup>

### **Objective 3.2: Carry out a survey to assess the feasibility and potential value of archived industry data.**

While many experts in industry and academia have published their work, not all of this information is easy to find. Some published data would require collation and curation to make them easily accessible to scientists, while unpublished data reside in industry databases, nonindexed notebooks, and internal reports. As research programs have been abandoned, or companies were bought out or downsized over the years, these data have become increasingly difficult to access. A survey of companies working in antibiotic discovery today and in the past would seek to determine what type of unpublished data could be acquired, what incentives might motivate a company to share this information, and what technical hurdles would have to be overcome. Based on survey results, there should be careful consideration of whether the time, manpower, and expense to obtain industry data are a worthwhile investment.

#### Goal: Share materials

### **Objective 3.3: Establish a central repository for useful chemical matter (synthetic and natural products) for antibiotic discovery.**

As compounds are generated and refined for antibiotic discovery, they should be carefully annotated, catalogued, stored, and made publicly available for use by academic and industry researchers. In addition, a curated resource of organisms that produce natural products housed at a public institution would help preserve this resource for use by the broader antibiotic discovery community. For example, a repository could be established in partnership

with an existing entity, such as the American Type Culture Collection, a nonprofit research organization that holds and shares biomaterials for research, or the National Center for Advancing Translational Sciences.<sup>55</sup> As previously mentioned, Malaria Box, a diverse set of compounds with anti-malarial activity that is made freely available to researchers, is another example of materials sharing on the part of a nonprofit organization.

### Goal: Share knowledge and expertise

Databases and repositories are not enough to tackle this priority. There must also be shared knowledge on what has been done before and what gaps remain. The long-term viability of the antibiotic pipeline depends on the ability of researchers to share drug discovery know-how across disciplines and sectors, to build on lessons learned rather than repeat mistakes, and to pass down expertise to the next generation of scientists.

#### **Objective 3.4: Build an educational resource to share antibiotic discovery knowledge across disciplines and between sectors.**

Some knowledge may be shared in the form of an educational resource, collected through meetings, interviews, and written documentation, from key experts in the field. Such a resource would help provide clarity for researchers on how to better vet compounds for antibiotic discovery, whether they are natural products or synthetic compounds. For example, a stepwise flow chart with links to structural alerts could help researchers eliminate pan-assay interference compounds, which turn up as artifacts in multiple assays and can be mistakenly reported as having promising activity against a wide variety of protein targets. Recommendations for testing compounds of interest in particular animal infection models, including information on dosing, schedules, and route of administration, could provide researchers with useful methods for determining early on whether a compound of interest could make a suitable antibiotic starting point.

#### **Objective 3.5: Establish a mechanism to promote the exchange of antibiotic discovery knowledge, skills, and expertise between sectors and across disciplines.**

Sharing drug discovery know-how requires hands-on experience and in-person interaction. A mentorship program that brings experienced industry scientists into the academic, startup, and biotech settings, or industry fellowships for postdoctoral students and early-career faculty would provide real-time feedback and consultation opportunities for antibiotic discovery researchers and be one way to effectively share institutional knowledge. Scientists with extensive pharmaceutical experience working alongside young investigators would afford unique opportunities to exchange ideas, share lessons learned, and teach the art of discovery science between sectors and across disciplines.

Further input is needed to define how this program might best serve the discovery community, including opportunities for senior scientists to share knowledge through existing programs. For example, Cold Spring Harbor Laboratory, a private, nonprofit research and education institution, hosts a variety of courses on specific research topics, offering intensive hands-on training opportunities for scientists from around the world.<sup>56</sup> Other programs include the Gordon Research Seminars, a series of meetings associated with the related Gordon Research Conferences that provide opportunities for students and early-career scientists to build informal networks and engage with leading scientists.<sup>57</sup> Alternatively, stand-alone initiatives that provide mentorship or apprenticeship opportunities for early-career scientists in academia or small and medium-sized enterprises (SMEs) may be considered.

## 4. Models for antibiotic discovery

Existing mechanisms of publicly and privately funded science have failed to meet the needs of the antibiotic research community in part because of a lack of direction, integration, and focus on key barriers to discovery.

There is a great need for a coordinated effort to tackle these obstacles head-on. Success would require agreement on a common mission, strong scientific leadership, a willingness to undertake high-risk work and change direction as needed, and an interdisciplinary team of dedicated research scientists working on long-term difficult problems.

### Governance and organizational structure

During the first phase of this effort (catalytic phase), the focus would be on the formation of partnerships with academia, industry, government, and nongovernmental organizations, establishment of a governance structure and research culture, data and information gathering projects to define gaps in understanding, and the initiation of pilot projects. Pew examined a number of existing organizational structures to better understand how other biomedical areas have supported research efforts (see Appendix C). It is important to note that many existing initiatives focus on discovery, development, and delivery of drugs and other therapies. In contrast, the mission of this effort is focused exclusively on filling key gaps in knowledge to spur discovery. Several potential organizational structures may lend themselves to this effort:

- A free-standing, self-contained institute under the umbrella of an existing organization that houses a central coordinating entity, multidisciplinary research teams, and the equipment and infrastructure necessary to carry out all research activities. This model would allow for long-term research that is fully integrated across projects but would likely entail high startup costs.
- A public-private partnership that virtually integrates researchers from across sectors that would normally “compete” with each other through grant- or contract-based funding mechanisms. A variety of formal and informal mechanisms would be established to ensure accountability and foster scientific interchange between partners. This model may be easier to establish and would allow more flexibility to adjust research activities as projects evolve, but it would depend on collaboration and commitment from the broader research community.
- A hybrid or “hub-based” model in which a central coordinating entity (hub), perhaps with core facilities, directly manages two or three centers of excellence with in-house research teams and partners with external laboratories through grant- or contract-based funding (spokes) under a shared mission and milestone-driven plan. This model incorporates both in-house research teams and the flexibility to work with multiple external partners as needed.

Regardless of the organizational structure, a scientific advisory committee composed of leading scientists in antibiotic discovery and development, clinicians, and experts from other fields would be needed to provide scientific and technical advice, help track research progress, and convene additional topic-specific advisory groups as needed.

The priorities laid out in this roadmap could be addressed concurrently or sequentially. Appendix A outlines one possible timeline to carry out this scientific plan. Day-to-day functions would be carried out by a core group of full-time program staff with subject matter expertise in microbiology, infectious disease, drug discovery, medicinal chemistry, computational chemistry, bacterial physiology, pharmacology, drug development, clinical research, and technology transfer, and the drive to take on difficult scientific questions. Leading this group would be a director with a strong scientific background and credibility in the field, an ability to effectively communicate across private and public sector partners, and an appreciation for the real-world challenges facing antibiotic



discovery. Together, this scientific leadership group would actively manage and guide projects to ensure that project milestones are met, working directly with laboratory heads and research partners. In addition, the leadership group would identify and develop lines of work and make decisions on scientific direction with input from the scientific advisory committee.

The second phase of this effort (pilot phase) would focus on optimizing collaborative research to advance objectives. Early pilot projects are likely best suited for small research teams, but as general direction is established (e.g., there is an understanding of what chemistry should be explored or what assays need to be developed), some work may be contracted or carried out in partnership with particular academic or industry laboratories and tied to clearly defined objectives with oversight from the scientific leadership group. For example, assay development or methods for determining how molecules move across bacterial membranes may require the building of new tools, engagement of specific expertise, or the use of specialized equipment. For this reason, this effort must be structured to allow for the flexibility to partner with leading scientists at universities or institutes, other research initiatives such as the IMI, companies, or contract research organizations based on scientific need. Outputs from the pilot phase may include: assays to measure drug entry independent of drug activity; preliminary conditional rules of entry; and completion of assessment studies for single-target antibacterials used in combination.

This phase may include the formation of new partnerships across industry, academia, and government, evaluation of early scientific findings on Gram-negative drug entry and efflux, and the establishment of data- and knowledge-sharing mechanisms that are efficient and effective.

Once pilot studies on Gram-negative drug entry and efflux have been conducted to determine what chemical space to explore, there may be advantages to seeking out a diversity of chemical matter from a variety of institutions that use different chemical methods and approaches. Strong scientific leadership would be required to manage multiple lines of work while maintaining focus on the core mission in order to achieve long-term objectives.

The third phase of this effort (implementation phase) would focus on long-term outcomes such as: the elucidation of a robust set of conditional guidelines for Gram-negative drug entry and efflux based on chemical class, bacterial species, or drug target; the generation of diverse chemical collections tailored for antibiotic discovery; and *in vitro* or *in vivo* pre-clinical models to evaluate specific alternative therapies to treat bacterial infections. These studies should complement the ongoing European IMI efforts on Gram-negative penetration, and the merit of these outputs should be independently evaluated by scientific experts. In addition, scientific findings, tools, resources, and expertise generated by this initiative should be examined based on their practical implementation and use to evaluate whether they meet the needs of the broader discovery community.

### Intellectual property

If successfully implemented, the work outlined in this roadmap is expected to produce a range of data, tools, and scientific knowledge critical for fostering and accelerating antibiotic discovery. As such, a core principle of this effort would be to rapidly promote access to research findings to the greatest extent possible, so that they may form the basis of future discoveries and maximize benefits to public health. Decisions regarding the release of data and use of intellectual property (IP) should be consistent with this principle. For cases in which outputs may lead to product or technology development, and the public good is best served by the ability to advance, license, or direct a particular innovation, the initiative may use IP as a tool to ensure the rapid translation of such breakthroughs. As the organizational model and key institutional partners are determined, specific standards,

policies, and legal frameworks for how and when data are released would be refined in consultation with leading data, IP, scientific, and public health experts.

Outputs generated through this effort would be focused on overcoming scientific barriers impeding the discovery of antibiotics rather than the development of new products or technologies. Given this focus, the effort would develop, aggregate, and release data, knowledge, and common tools into the public domain. Such resources may take multiple forms, including publicly accessible databases of previous research, such as the collection and analysis of existing knowledge—published and unpublished—on drug entry and efflux for Gram-negative bacteria, assays to measure drug penetration and kinetics independently of drug activity, and conditional guidelines for tailoring chemical matter for Gram-negative antibiotic discovery. Research findings for these and other areas may not be directly related to a particular product but are anticipated to accelerate the field of antibiotic discovery overall. Such resources may be released to the scientific community via Web-based tools, public databases, publication, or other mechanisms. During its catalytic phase and prior to engagement in research activities, this effort would develop data and IP policies, standards, and associated legal frameworks necessary to facilitate the rapid dissemination of data, knowledge, and tools to the broader scientific community.

The authors recognize that proposed research carried out under this effort has the potential to generate breakthroughs that may lead to the discovery and development of a specific technology or antibiotic product. In such cases, IP may be used to ensure that there is a path to rapid product development executed by experienced product developers in the private, nonprofit, or governmental space. Over the past decade, leading biomedical research funders, such as the Wellcome Trust, Bill & Melinda Gates Foundation, Drugs for Neglected Diseases Initiative, and Medicines for Malaria Venture, have developed successful IP approaches that offer practical standards around the use of IP in the public health space.<sup>58</sup> Such standards would be essential for providing a clear and specific framework for how investigators and institutions collaborate, share information, and ensure mission-based outcomes throughout this effort.

## Funding

An initial investment of \$50 million would support establishment of the scientific leadership team and initial pilot studies on Gram-negative drug entry and efflux along with early chemistry and medicinal chemistry efforts. The authors estimate that execution of the full project as proposed here would require \$170 million to \$200 million over five years.

## Conclusion

Antibiotics represent one of the greatest advances in the history of medicine. They enable the treatment of a wide variety of common infections and underpin the delivery of complex care, from cancer treatment to surgery. Yet this success, which is taken for granted, is under threat as bacterial resistance to existing antibiotics increases and too few new drugs are in development.

The “golden age” of antibiotics was ushered in by a partnership of industry and government scientists working together in a sustained way to address the challenge of producing penicillin at industrial scale. The range of antibacterial chemical classes discovered over the following decades led to a great flowering of antibiotic discovery. Since the mid-1980s, however, nearly all antibiotics that have been developed are modifications or variations of existing drugs. For over 30 years, no newly discovered class of antibiotics has successfully made it to the patient’s bedside.

While many factors contribute to the long drought in antibiotic discovery, it is clear that fundamental scientific barriers impede innovation, and there is no collection of promising drug candidates that are simply waiting to be brought to market. Overcoming these barriers will require new research and a level of coordination that goes beyond anything that now exists in academia, industry, or government. The loss of industry expertise as companies exit antibiotic development makes this a crucial juncture. By addressing key underlying questions and disseminating the findings widely, a robust foundation for sustainable antibiotic innovation could be created that will meet the needs of current and future patients.

## Appendix A: Key deliverables

### Catalytic phase (years 1-2)

Assemble personnel and set up laboratories.

#### **Objective 1.1: Collect, analyze, and share existing knowledge on Gram-negative drug entry and efflux.**

- Carry out a comprehensive review of existing information on Gram-negative penetration and efflux—published and unpublished.
  - Incorporate structural-activity relationship information for antibiotics that enter the cytoplasm of Gram-negative bacteria.
  - Facilitate a dialogue among experts to discuss what has been tried before, share lessons learned, and facilitate information sharing.
  - Compile and analyze results in white papers and scientific publications.

#### **Objectives 3.1, 3.4, and 3.5: Establish an informatics infrastructure to efficiently and effectively share antibiotic discovery data and information. Build an educational resource to share antibiotic discovery knowledge across disciplines and between sectors. Establish a mechanism to promote the exchange of antibiotic discovery knowledge, skills, and expertise between sectors and across disciplines.**

- Engage technology transfer experts from academia, industry, and government to ensure that findings from this effort are effectively disseminated across the research community.
- Build an electronic database for data sharing (chemistry and biology) to track all information that will be gathered and generated over five years. Software could be purchased or developed in partnership with existing platforms.
- Produce an educational resource to provide clarity for researchers on how to better vet compounds for antibiotic discovery (e.g., stepwise flow chart with links to structural alerts to help researchers eliminate pan-assay interference compounds).
- Establish a mechanism for knowledge sharing (e.g., scientific advisory committee, mentorship, or apprenticeship opportunities for early-career scientists in academia or SMEs).

#### **Objective 3.2: Carry out a survey to assess the feasibility and potential value of archived industry data.**

- Determine what unpublished data could be acquired from industry archives, what incentives might motivate a company to share the information, and what technical hurdles would have to be overcome to access the data.
- Based on survey results, consider whether the time, manpower, and expense to obtain industry data are a worthwhile investment.

#### **Objective 3.3: Establish a central repository for useful chemical matter (synthetic and natural products) for antibiotic discovery.**

- Annotate, catalogue, and store for use by researchers any compounds as they are generated and refined for antibiotic discovery.
- Establish a curated resource of organisms that produce natural products and bacterial strains generated through this effort.

## Pilot phase (years 3-4)

### **Objective 1.2: Develop tools (quantitative assays) to quickly and accurately measure drug penetration and kinetics for Gram-negative drug entry and efflux that are independent of drug activity.**

- Develop assays to measure activity-independent entry of molecules into the cytoplasm of important Gram-negative pathogens.
- Develop assays to measure activity-independent entry of molecules into the periplasm of important Gram-negative pathogens.
- Validate assays with known antibacterials that target various cellular compartments in Gram-negative bacteria.

### **Objective 1.3: Elucidate conditional guidelines for drugs targeting Gram-negative pathogens.**

- Test existing chemical matter for cytoplasmic (and periplasmic) entry and efflux avoidance for important Gram-negative pathogens.
- Produce preliminary conditional guidelines for drug entry into the cytoplasm of Gram-negative bacteria.
- Iteratively generate and test new compounds to refine preliminary conditional guidelines.

### **Objective 1.4: Find alternative ways to overcome Gram-negative barriers to entry.**

- Partner with and support projects on outer membrane disruption, self-promoted uptake, and nontraditional antibacterial screening.

### **Objective 1.5: Build prototype libraries tailored for antibacterial discovery.**

- Based on preliminary conditional guidelines for drug entry and efflux avoidance for Gram-negative pathogens, iteratively generate 3,000 to 5,000 directed compounds (multiple scaffolds) to test entry into Gram-negative pathogens and assay for antibacterial activity.
- *In silico*, identify natural product scaffolds that meet preliminary conditional guidelines for drug entry and efflux avoidance for Gram-negative pathogens, and iteratively test and modify these compounds through medicinal chemistry approaches.

### **Objectives 2.1 and 2.2: Determine whether single-target antibacterials can be used in combination to overcome resistance *in vitro* and *in vivo*.**

- Carry out a comprehensive *in vitro* assessment of existing single-target antibacterials used in combination against a variety of bacterial pathogens to measure and compare the frequency of resistance development.
  - Source compounds that have demonstrated target-specific mechanisms of activity, lack mammalian cytotoxicity, and possess necessary drug-like properties.
  - Evaluate PK/PD parameters for further experiments.
  - Establish baseline resistance frequency for single compounds and combinations of two or more.
- Test a subset of combination single-target antibacterials *in vivo* to assess whether *in vitro* resistance frequency is predictive for resistance development in animal models.

## Implementation phase (year 5)

### **Objective 1.3: Elucidate conditional guidelines for drugs targeting Gram-negative pathogens.**

- Generate a robust set of conditional guidelines for drug entry based on chemical class, bacterial species, drug target location, or other.

### **Objective 1.6: Scale up chemical libraries tailored for antibiotic discovery.**

- Based on prototype libraries and conditional guidelines for drug entry and efflux avoidance for Gram-negative pathogens, more broadly generate a diverse collection of 50,000 to 300,000 chemicals suited for antibiotic discovery (low molecular weight, irreversible inhibitors, natural products, fragments).
- Partner or support testing of these chemical libraries for antibacterial activity.

### **Objective 3.3: Establish a central repository for useful chemical matter (synthetic and natural products) for antibiotic discovery.**

- Partner with public or private institutions to maintain chemical libraries for use by the scientific community.

### **Objective 2.3: Develop proof-of-concept studies to accelerate the path to development for promising nontraditional therapies to treat systemic bacterial infections.**

- Establish at least two or three *in vitro* or *in vivo* models to evaluate alternative therapies to treat bacterial infections (e.g., experiments to test anti-virulence strategies that rely on biomarkers or other means to demonstrate the benefit independently from bacterial burden).

## Appendix B: Alternatives to traditional antibiotic use currently in clinical development

Drug name*	Development phase†	Company	Type of therapeutic	Potential indication(s)‡
<b>Aerucin</b>	Phase 1	Aridis Pharmaceuticals Inc.	antibody	Bacterial infections
<b>CF-301</b>	Phase 1	ContraFect Corp.	lysin	Bacteremia ( <i>Staphylococcus aureus</i> )
<b>NDV-3</b>	Phase 1	NovaDigm Therapeutics Inc.	vaccine	Prevention of bacterial infections ( <i>S. aureus</i> )
<b>514G3</b>	Phases 1/2	XBiotech Inc.	antibody	Bacteremia ( <i>S. aureus</i> )
<b>N-Rephasin</b>	Phase 1 <sup>§</sup>	Intron Biotechnology Inc.	lysin	Bacterial infections ( <i>S. aureus</i> )
<b>Aurexis (tefibazumab)</b>	Phase 2	Bristol-Myers Squibb Co.	antibody	Bacteremia ( <i>S. aureus</i> ), chronic <i>S. aureus</i> infection in cystic fibrosis patients
<b>Brilacidin</b>	Phase 2	Cellceutix Corp.	antimicrobial peptide	Acute bacterial skin and skin structure infections
<b>MEDI4893</b>	Phase 2	MedImmune Inc.	antibody	Pneumonia ( <i>S. aureus</i> )
<b>Group B Streptococcus vaccine</b>	Phase 2	Novartis International AG <sup>#</sup>	vaccine	Prevention of Group B <i>Streptococcal</i> infection
<b>PF-06425090</b>	Phase 2	Pfizer Inc.	vaccine	Recurrent <i>Clostridium difficile</i> infection
<b>SA4Ag</b>	Phase 2	Pfizer Inc.	vaccine	Prevention of <i>S. aureus</i> infection
<b>POL7080</b>	Phase 2	Polyphor Ltd.	antimicrobial peptide	Ventilator-associated bacterial pneumonia ( <i>Pseudomonas aeruginosa</i> ), lower respiratory tract infection, bronchiectasis
<b>RBX2660</b>	Phase 2	Rebiotix Inc.	probiotic	Recurrent <i>C. difficile</i> infection
<b>SER-109</b>	Phase 2	Seres Therapeutics Inc.	probiotic	Recurrent <i>C. difficile</i> infection
<b>VP20621</b>	Phase 2	Shire PLC	probiotic	Recurrent <i>C. difficile</i> infection
<b>Pagibaximab</b>	Phases 2/3	Biosynexus Inc.	antibody	Prevention of bacteremia in very low birth weight neonates ( <i>S. aureus</i> )
<b>IC43</b>	Phases 2/3	Valneva SE	vaccine	Prevention of ventilator-associated bacterial pneumonia ( <i>P. aeruginosa</i> )
<b>Salvecin (AR-301)</b>	Phase 2 <sup>§</sup>	Aridis Pharmaceuticals Inc.	antibody	Pneumonia ( <i>S. aureus</i> )
<b>Aerumab (AR-101)</b>	Phase 2 <sup>§</sup>	Aridis Pharmaceuticals Inc.	antibody	Pneumonia ( <i>P. aeruginosa</i> ), ventilator-associated bacterial pneumonia ( <i>P. aeruginosa</i> )
<b>MEDI3902</b>	Phase 2 <sup>§</sup>	MedImmune Inc.	antibody	Prevention of ventilator-associated bacterial pneumonia ( <i>P. aeruginosa</i> )
<b>IC84</b>	Phase 2 <sup>§</sup>	Valneva SE	vaccine	Recurrent <i>C. difficile</i> infection
<b>Bezlotoxumab and Actoxumab</b>	Phase 3	Merck & Co. Inc.	antibody	Recurrent <i>C. difficile</i> infection
<b>Cdiffense</b>	Phase 3	Sanofi Pasteur SA	vaccine	Prevention of <i>C. difficile</i> infection

## Glossary

**Antibody**—Antibodies are proteins naturally produced by the immune system to identify and help remove potentially harmful pathogens, such as bacteria and viruses. Monoclonal antibody therapy takes advantage of an antibody’s specific targeting capacity to bind to pathogens and inactivate them in a variety of ways.

**Antimicrobial peptide**—Antimicrobial peptides (AMPs) are part of the innate immune response of many animals as well as the analogous defensive responses of bacteria and fungi. They can exhibit antimicrobial activity across a broad spectrum of bacteria, viruses, and fungi. Research is underway to examine the potential therapeutic applications of natural and synthetic AMPs.

**Lysin**—Lysins are enzymes derived from bacteriophages that target and break up bacterial cell wall architecture.

**Probiotic**—Probiotics are live microorganisms that help maintain and restore populations of beneficial bacteria in the human gut. The administration of broad spectrum antibiotics often indiscriminately kills gut bacteria, increasing the risk of side effects and colonization by harmful bacteria such as *Clostridium difficile*. Administering probiotics alongside antibiotics may help alleviate the risk of side effects. In addition, probiotics may help treat challenging infections such as *C. difficile*.

**Vaccine**—Vaccines are agents that stimulate the body’s immune system to recognize and destroy pathogens, such as bacteria, protecting the patient from infection. Vaccines typically contain inactivated disease-causing pathogens or components that resemble them.

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\* Products listed here contain at least one component not previously approved in the United States. All analyses were strictly limited to systemic products (drugs that work throughout the body) and therapies to treat *C. difficile*-associated disease. The Centers for Disease Control and Prevention cited *C. difficile* as an urgent public health threat in a 2013 report (*Antibiotic Resistance Threats in the United States*). We also limited this pipeline to treatments with the potential to treat serious or life-threatening infections. Specifically excluded were drugs to treat mycobacterial infections, such as tuberculosis and *Mycobacterium avium* complex, *Helicobacter pylori*, and biothreat pathogens. Additionally, we excluded locally acting therapies such as topical, ophthalmic, and inhaled products.

† Based on the most advanced development phase for any indication according to trials registered in [clinicaltrials.gov](https://clinicaltrials.gov), unless direct communication from the company indicated differently. If no trials were included in [clinicaltrials.gov](https://clinicaltrials.gov), the phase listed on the company website or provided directly by the company is noted.

‡ Based on clinical trials currently registered in [clinicaltrials.gov](https://clinicaltrials.gov) unless otherwise noted.

§ Registered in [clinicaltrials.gov](https://clinicaltrials.gov) but with no current study sites within the United States.

# In these clinical trials, the Group B Streptococcus vaccine is administered to pregnant women with the goal of preventing *Streptococcal* infections in newborns.



## Appendix C: Organizational structures

The authors examined a number of existing organizational structures to better understand how other biomedical areas have supported research efforts, including those summarized below. Many of these organizational structures are public-private partnerships that operate along the drug discovery and development pipeline. For example, Medicines for Malaria Venture has a network of more than 350 academic and industry partners that provides financial and in-kind support for research and product development.<sup>59</sup> Other organizations, such as the Structural Genomics Consortium, work with industry and academic partners to support pre-competitive research.<sup>60</sup>

### Antibiotic Discovery–United Kingdom

#### Overview

Founded in 2012, Antibiotic Discovery–United Kingdom (AD-UK) is a not-for-profit informal network of leading UK scientists and clinicians from academia and industry, working to rebuild antibiotic discovery in these areas, encourage government investment in antibiotic discovery, promote education, and support research along the continuum of the antibiotic discovery pipeline.<sup>61</sup> The network includes 14 universities and 14 SMEs.

#### Key accomplishments

AD-UK has contributed to several discussions on antibiotic discovery, including the House of Commons, House of Lords, and Medical Research Council. In 2014, AD-UK established a charitable incorporated organization, Antibiotic Research UK (ANTRUK), to support the development of effective treatments and improve the quality of life for patients with antibiotic-resistant infections.<sup>62</sup> In an attempt to promote global efforts in raising antibiotic resistance awareness, AD-UK launched Antibiotic Discovery-Global, a coalition that aims to provide an international knowledge base and infrastructure to support global antibiotic discovery and development, including the repurposing of older antibiotics for new uses.<sup>63</sup>

#### IP policy

No publicly available information on IP policy.

#### Funding

Over the next five years, ANTRUK aims to raise sufficient funds (an estimated £30 million) to bring at least one new antibiotic therapy to market.

### Critical Path to TB Drug Regimens

#### Overview

The Critical Path to TB Drug Regimens (CPTR) initiative was founded in 2010 by the Bill & Melinda Gates Foundation, Critical Path Institute, and TB Alliance to speed development and impact of new and improved drug regimens for tuberculosis.<sup>64</sup> CPTR is a coalition of pharmaceutical companies, product development sponsors, diagnostics companies, regulatory agencies, and civil society organizations. The initiative is organized around four operating arms, each of which determines its own structure, membership, and leadership. Each arm works to implement CPTR's broader goals and is governed by a coordinating committee with input from an advisory panel composed of global stakeholders in the development and use of TB drug regimens.<sup>65</sup>

## Key accomplishments

CPTR has fostered collaborations to share data from clinical and nonclinical trials, and *in vitro* experiments. Expansion of CPTR's data-sharing platform includes whole genome sequence data from clinical isolates around the world with the goal of developing new rapid drug susceptibility tests.<sup>66</sup>

## IP policy

CPTR's guiding principle is to encourage information sharing and collaboration. CPTR and its members make their results, conclusions, and observations available to members and nonmembers.<sup>67</sup>

## Funding

The Bill & Melinda Gates Foundation provided seed funding for CPTR.

## Drugs for Neglected Diseases Initiative

### Overview

Founded in 2003, the Drugs for Neglected Diseases Initiative (DNDi) is a collaborative, nonprofit drug research and development organization with a mission to develop new treatments for patients suffering from neglected communicable diseases.<sup>68</sup> Current target diseases include human African trypanosomiasis, leishmaniasis, Chagas disease, onchocerciasis, lymphatic filariasis, pediatric HIV, and hepatitis C. By its 20th anniversary in 2023, DNDi aims to deliver 16 to 18 new treatments.<sup>69</sup>

The organization is governed by a board of directors that determines the strategic goals for the organization with input from the Scientific Advisory Committee. An executive management team implements these goals with a team of scientists that directs research at a number of centers around the globe. DNDi collaborates with more than 30 public research institutions and national research centers, and over 30 biotechnology and pharmaceutical companies. Additionally, DNDi has several other partnerships with nongovernmental organizations, consortia, hospitals, ministries, and governmental organizations.<sup>70</sup> DNDi is a "virtual" organization that brings together what it calls the "best science for the most neglected." A new initiative to spur antibiotic drug discovery is under consideration by the World Health Organization and other partners.<sup>71</sup>

### Key accomplishments

As of 2015, DNDi has developed six novel treatments approved for human use, with 25 other projects at various stages of development, including up to 15 potential new chemical entities.<sup>72</sup>

### IP policy

DNDi has an IP policy to guide its research and development activities in a manner that ensures affordable treatments for patients who need them and supports the development of drugs as a public good when possible.<sup>73</sup> The organization seeks, whenever possible and without undermining its rationale for acquiring IP, to make research findings available to the research community and to avoid restrictive IP strategies or other approaches that may inhibit or delay the rapid adoption of innovation for the benefit of developing countries.<sup>74</sup>

### Funding

DNDi has secured more than €350 million to date with a goal of raising an additional €300 million by 2023.<sup>75</sup> Funders include the Bill & Melinda Gates Foundation, Doctors Without Borders/Médecins Sans Frontières, the UK Department for International Development, and numerous other public and private donors.<sup>76</sup>

## Foundation for the National Institutes of Health

### **Mission**

The Foundation for the National Institutes of Health (FNIH) was established in 1990 by an act of the U.S. Congress.<sup>77</sup> FNIH supports the National Institutes of Health by advancing collaboration among biomedical researchers from universities, industry, and nonprofit organizations. A board of directors governs the organization's work through the FNIH President's Office.

### **Key accomplishments**

As of 2015, FNIH has successfully brought hundreds of projects to completion, including clinical trials in conjunction with the National Cancer Institute and the Alzheimer's Disease Neuroimaging Initiative.<sup>78</sup> Other projects started by FNIH have graduated to become independent. For example, the Observational Medical Outcomes Partnership (OMOP) project was renamed as Innovation in Medical Evidence Development and Surveillance (IMEDS) and passed to the Reagan-Udall Foundation for further development. FNIH retains an active, ongoing management role in some long-term projects, such as the Biomarkers Consortium.<sup>79</sup>

### **IP policy**

No information is available on how FNIH treats intellectual property for all of its projects. Information on OMOP indicates that FNIH placed all of the project's IP into the public domain and transferred other IP to its partner so it could be used in other projects.<sup>80</sup>

### **Funding**

Since its inception, FNIH has raised \$830 million for a variety of projects.<sup>81</sup> In 2014, the foundation spent \$77 million on 23 fellowship programs, and 70 projects in seven research partnerships.<sup>82</sup>

## HCV Drug Development Advisory Group

### **Mission**

The HCV Drug Development Advisory Group (DrAG) was formed in 2006 to bring stakeholders working on hepatitis C virus drug development together to discuss issues pertinent to the field.<sup>83</sup> The objectives of the organization are to produce consensus recommendations on a variety of HCV drug development issues, from methodology for HCV resistance testing to scientific guidance for clinical trial design. A steering committee of constituent group representatives determines what issues are appropriate for review by the DrAG.

### **Key accomplishments**

The HCV DrAG has published a number of recommendations and guidance on HCV drug development, resistance monitoring, and standardized nomenclature.<sup>84</sup>

### **IP policy**

No publicly available information on IP policy.

### **Funding**

The HCV DrAG is funded through unrestricted donations from diagnostic and pharmaceutical companies.<sup>85</sup>

## Human Vaccines Project

### Overview

The Human Vaccines Project is a nonprofit public-private partnership launched in 2014 to accelerate and transform global vaccine development by solving pre-competitive scientific problems impeding the development of vaccines and immunotherapies by decoding the human immune system. The project is structured as a global R&D consortium affiliated with one or more academic centers conducting vaccine R&D with significant engagement by industry. It has been endorsed by 35 of the world's leading vaccine scientists.<sup>86</sup>

### Key accomplishments

The project is in the early stages but has announced that its first scientific hub will be located at Vanderbilt University Medical Center.<sup>87</sup>

### IP policy

The project takes a "flexible and practical approach to intellectual property that best fosters the translation of research breakthroughs into tangible public health benefits."<sup>88</sup>

### Funding

The Robert Wood Johnson Foundation and the International AIDS Vaccine Initiative provided incubator funding.<sup>89</sup> In 2015, GlaxoSmithKline contributed \$350,000. The project has also received support from MedImmune, Crucell, Aeras, and Pfizer.<sup>90</sup>

## Innovation in Medical Evidence Development and Surveillance

### Overview

IMEDS is a public-private partnership set up in 2013 by FDA via the Reagan-Udall Foundation.<sup>91</sup> IMEDS will advance the science and tools needed to support post-market evidence generation on FDA-regulated products. Governance of IMEDS is provided by the Reagan-Udall Foundation board with input from the IMEDS scientific advisory committee. As priorities are identified, they are passed to the IMEDS program director for implementation by the IMEDS program team.<sup>92</sup>

### Key accomplishments

The precursor to IMEDS, the Observational Medical Outcomes Partnership, made significant progress in the field of health data safety surveillance by developing the Mini-Sentinel tools. In 2014 IMEDS projects examined three areas of improving data collection for the risk assessment of medical products.<sup>93</sup>

### IP policy

Existing IP offered by participants is protected through confidentiality agreements, as are discussions among members, participants, and investigators of IMEDS. IP created through IMEDS will be published in the public domain, with exemptions as decided by the IMEDS steering committee. Additionally, data that IMEDS retains the rights to will be made publicly available.<sup>94</sup>

### Funding

In 2013 IMEDS received \$3.2 million in donations from pharmaceutical companies.<sup>95</sup>

## Innovative Medicines Initiative–Translocation project

### Overview

Translocation is a project established by the European Innovative Medicines Initiative (IMI) with the overall goals of increasing the understanding of the permeability of drugs into Gram-negative bacteria and increasing the efficiency in antibiotic R&D through knowledge and data sharing and analysis of the combined package of information. Translocation aims to achieve these goals through partnerships among academics, industry, and SMEs.

### Key accomplishments

Translocation members published 38 articles in peer-reviewed academic journals between 2013 and 2015.<sup>96</sup>

### IP policy

The IMI IP provisions are flexible and adapted based on each project. An IP agreement is included in the beneficiaries' grant agreement before the launch of a project.<sup>97</sup>

### Funding

Contributions for Translocation total €29.3 million, including €16 million from IMI and €8 million in-kind from EFPIA.<sup>98</sup>

## Institute for Life Science Entrepreneurship

### Overview

The Institute for Life Science Entrepreneurship (ILSE) is a research integrator, accelerator and incubator founded in 2014 with the aim of spurring innovation in medicine, devices, and other technologies to improve human health.<sup>99</sup> ILSE is governed by a board of trustees and operated by an executive management team. The institute has core research capacity for five to 10 early-stage life science companies in addition to academic research and consulting networks.<sup>100</sup> ILSE will house an Entrepreneur Center and a Business Center, which will provide a suite of services to support innovations created at ILSE labs and network affiliates.<sup>101</sup>

### Key accomplishments

In 2015, the American Type Culture Collection (ATCC) and ILSE established the ATCC Center for Translational Microbiology (ATCC-CTM) as part of a multiyear, multimillion-dollar deal.<sup>102</sup>

### IP policy

No publicly available information on IP policy.

### Funding

No publicly available information on funding.

## Medicines for Malaria Venture

### Overview

Medicines for Malaria Venture (MMV) is a nonprofit product development partnership formed in 1999 with a mission to reduce the burden of malaria in disease-endemic countries through the discovery, development, and delivery of new, effective, and affordable anti-malarial drugs. The organization is run by an experienced management team and governed by a board of directors. Expert advisory committees provide guidance on science, global safety, and access.

### Key accomplishments

MMV supports several products at various stages of clinical development and has assembled compound collections, such as Malaria Box, a set of 400 diverse compounds with anti-malarial activity. The organization helped support approval and delivery of lifesaving medicine, including the delivery of 36 million vials of artesunate and 300 million Coartem treatments and approval of Pyramax and Eurartesim.<sup>103</sup>

### IP policy

MMV endeavors to negotiate for new medicines to be made available at an affordable price through public sector channels. To achieve this goal, the organization retains intellectual property rights that will be essential to allow it to develop and launch drugs for the benefit of its target patient group. If MMV does not own the necessary IP, it requests an exclusive license for the IP to develop a malaria drug and bring it to market. Licenses are preferably royalty-free to keep costs to a minimum, particularly in malaria-endemic countries. MMV does not conduct R&D in-house and requires that IP rights be transferred to other partners as needed, particularly for manufacturing.<sup>104</sup> MMV was the first party to make IP freely available to researchers developing medicines for neglected tropical diseases.<sup>105</sup>

### Funding

MMV has received funding from government agencies, foundations, and corporations. From 1999 to 2014, MMV received \$865 million from sources including the Bill & Melinda Gates Foundation, UK Department for International Development, UNITAID, Wellcome Trust, and United States Agency for International Development.<sup>106</sup>

## NIH Office of AIDS Research

### Overview

Established in 1988, the Office of AIDS Research coordinates the scientific, budgetary, legislative, and policy elements of NIH AIDS research. Every year the office develops the Trans-NIH Plan for HIV-Related Research, with input from its Advisory Council and several relevant working groups. This annual plan identifies future research priorities. Funds are subsequently disbursed through program officers in conjunction with peer review panels.

### Key accomplishments

Achievements include the co-discovery of HIV, development of the first blood test for the disease, novel strategies for preventing transmission between mother and child, and demonstration of the proof-of-concept that a vaccine can prevent HIV infection. A recent study estimates that from 1995 to 2009, 14.4 million life-years have been saved as a result of the work funded by the Office of AIDS Research.<sup>107</sup>

## **IP policy**

No publicly available information on IP policy.

## **Funding**

The Office of AIDS Research Trans-NIH Plan for HIV-Related Research spending represents approximately 10 percent of the total NIH budget. Just over half of the overall budget (\$3 billion) is allotted to the National Institute of Allergy and Infectious Diseases.

## The Structural Genomics Consortium

### **Overview**

The Structural Genomics Consortium (SGC) is a charitable public-private partnership established in 2003 to support drug discovery and accelerate research in new areas of human biology by making all research output freely available to the scientific community.<sup>108</sup> The SGC is governed by a board of directors and scientific committees. The organization is overseen by a CEO and has operations at two main sites—the University of Oxford and the University of Toronto—along with sites in Brazil, Germany, Sweden, and the United States.

### **Key accomplishments**

Since 2008, the SGC has led initiatives to develop chemical probes and recombinant antibodies for studying epigenetic control mechanisms. It has contributed more than 1,500 high-resolution protein structures to the Protein Data Bank, a freely available repository for 3-D structural data; this accounts for over 25 percent of all structural information about human proteins of biomedical importance in the public domain (as of September 2011).<sup>109</sup> The consortium contributed to the discovery that bromodomains are valid therapeutic targets. More than 30 companies are pursuing bromodomains as targets and over 15 clinical trials are testing molecules that target bromodomains.

Since 2013, the SGC has led the Drug Discovery Coalition, an international group that is supported by the Bill & Melinda Gates Foundation to produce early therapeutic leads for TB and malaria.<sup>110</sup> In 2015, the coalition produced an early therapeutic lead, which is under clinical development by the TB Alliance.

### **IP policy**

The Structural Genomics Consortium has an open access policy that states that no consortium scientist will file for a patent or agree to be named on a patent. All products from the SGC are made publicly available and there are no restrictions on their use until later stages of clinical trials.<sup>111</sup>

### **Funding**

In 2003, the Structural Genomics Consortium was funded through a \$95 million partnership that brought together four Canadian research funding bodies, the Wellcome Trust, and GlaxoSmithKline.<sup>112</sup> In 2011, the SGC entered its third funding phase with 14 public and private members.<sup>113</sup> For a donation of \$8 million, consortium members gain the rights to nominate proteins to the target list for future work; nominate members to the scientific advisory boards and board of directors; and place scientists within the SGC laboratories.<sup>114</sup> In 2015, the consortium was renewed for five more years, with funding from 13 public and private members.

## TB Alliance

### **Overview**

The TB Alliance was founded in 2000 as a nonprofit product development partnership with a mission to discover and develop faster-acting and affordable tuberculosis drugs.<sup>115</sup> The organization is governed by a board of directors, representing global perspectives and expertise in diverse areas of interest to ensure the TB Alliance's success and sustainability. Four advisory boards provide scientific guidance, stakeholder input, advice on lowering barriers to access for new TB cures, and guidance for pediatric TB treatments.

### **Key accomplishments**

The TB Alliance has assembled and managed the largest portfolio of new TB drugs in history, which includes more than 20 active programs and 10 novel classes of drugs. It launched the first clinical trials to test an entirely novel regimen for extensively drug-resistant TB and new TB drugs in combination as well as new TB regimens in TB and MDR-TB patients simultaneously. In partnership with Janssen Pharmaceuticals, the TB Alliance helped develop Sirturo, the first new drug approved for the treatment of multidrug-resistant TB, and the organization maintains the rights to the drug for the treatment of drug-sensitive TB.<sup>116</sup>

### **IP policy**

The TB Alliance has "adopted an IP policy to ensure that new TB drug regimens are developed and distributed responsibly, meet the standards of regulatory authorities and are affordable, adopted, and available to those that need them through its work with industry, country, and other partners while providing a mechanism to fund future research and development in the field of TB."<sup>117</sup> An IP committee prioritizes and oversees TB Alliance intellectual property policy and related efforts, including patents, trademarks and trade secrets, copyrights, technology transfer agreements, and other contracts.

### **Funding**

In 2000, the TB Alliance received donations of \$25 million from the Bill & Melinda Gates Foundation and \$15 million from the Rockefeller Foundation.<sup>118</sup> In 2006, a further \$104 million was donated by the Bill & Melinda Gates Foundation.<sup>119</sup> As of 2015, the TB Alliance has received pledges totaling more than \$450 million from foundations, government agencies, and multilateral donors.<sup>120</sup>



## Endnotes

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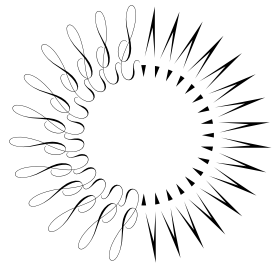
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