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Review Article

Unveiling the Future: A Scientific Roadmap for Antibiotic Discovery

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Abstract

The escalating threat of antibiotic resistance demands a concerted effort to revitalize antibiotic discovery, a field that has stagnated in recent decades. These abstract outlines a comprehensive scientific roadmap for antibiotic discovery, aimed at addressing the pressing global health challenge posed by resistant bacterial infections.

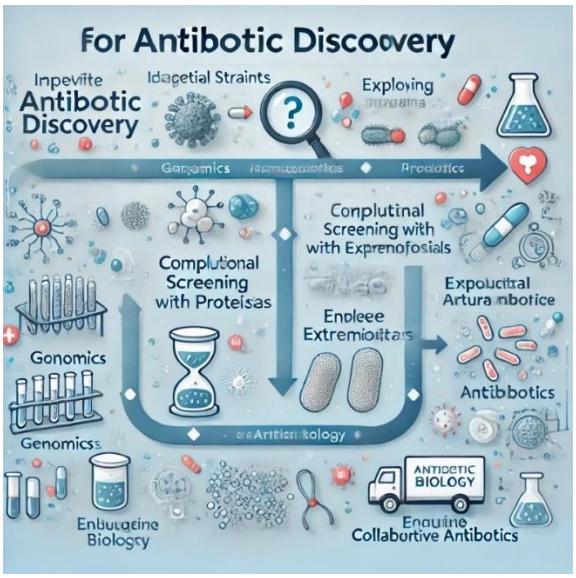
The proposed roadmap integrates cutting-edge technologies and innovative strategies to navigate the complex terrain of antibiotic discovery. Starting with a thorough understanding of microbial ecology, this roadmap emphasizes the identification of novel bacterial strains through metagenomics and functional screening. Harnessing the power of genomics, transcriptomics, and proteomics, researchers can unravel the intricate mechanisms of bacterial resistance and identify potential drug targets.

In silicone approaches, including artificial intelligence and machine learning, play a pivotal role in predicting and optimizing antibiotic candidates. These computational tools expedite the screening process, reducing the time and resources traditionally required for drug discovery. Moreover, exploring untapped natural sources, such as extremophiles and uncultivable microorganisms, unveils a treasure trove of bioactive compounds with unexplored therapeutic potential.

The integration of synthetic biology allows for the design and engineering of novel antibiotics, overcoming traditional limitations. Furthermore, this roadmap advocates for collaborative initiatives, encouraging data sharing and open-access platforms to accelerate the pace of discovery.

Ethical considerations are paramount in antibiotic discovery, and the road map emphasizes responsible research practices, mindful of the potential ecological consequences of widespread antibiotic use. Finally, regulatory frameworks need to adapt to the dynamic nature of antibiotic discovery, incentivizing innovation while ensuring patient safety.

Key words: antibiotic discovery; antibiotic resistance; scientific road map; microbial ecology; meta genomics; functional screening genomics; transcriptomic; bioactive compounds synthetic biology; novel antibiotics



• *Source:* • Silver, L. L. (2011). "Challenges of Antibacterial Discovery." Clinical Microbiology Reviews, 24(1), 71–109. doi: 10.1128/CMR.00030-10.

Introduction

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.{1} Every currently available antibiotic is a derivative of a class discovered between the early 1900s and 1984.{2} 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. They consulted with numerous other public and private sector stakeholders to develop a Scientific Roadmap for Antibiotic Discovery. The road map 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 judgments show a need for:

• A point or direct at a goal approach to tackle the fundamental controlled hurdles impeding medicine finding and growth.

• A better understanding of by what method to overcome the natural defenses of drug-opposing Gram-negative microorganisms, that cause some of ultimate troublesome-to-treat contaminations.

• Generation of new synthetic matter created for medicine finding.

• Tools and methods to evaluate hopeful opportunities to established medicine use.

• A foundation for giving news, knowledge, and materials across the research society to support

Creative erudition and spur the finding of novel completely clean medicines.

Success will demand hard-working crews of multidisciplinary physicists to tackle key questions and share information

And abilities across subdivisions.

• A center scientific guidance group would set preferences and direct and control achievement-compelled research.

• New methods and guidelines for medicine finding create by this leadership would supply

Scientists related to manufacturing and scholarly world accompanying a bedrock to support the finding of new drugs over a sustained magnitude.

If favorably executed, this action has the potential to revive novelty in antibiotic research and hasten the finding of new types of completely clean drugs and remedies.

The state of the field

Once a model of output and change, research works to uncover new antibiotics have hindered. In the Post-World War II ending following Alexander Fleming's progress finding of medicine and the participation between manufacturing and government to produce this lifesaving drug on an technical scale, new medicines were found and grown at a beautiful pace. Such exertions managed to moving advances in human fitness, as medicines were used to treat an progressively expansive range of contaminations while admitting for the development of the complex first-contact medical care that is immediately implicit, to a degree modern substitute, exhaustive care cure, break-up, and tumor treatment.

Drug finding, the process of judgment or plotting particles that commit eventually bring about new healings, underpins drug development, the process of precisely experiment a healing aspirant for security and productiveness in order to produce a new cure to market.

The "golden time" of medicine finding pale in the 1950s, produce lifesaving drug classes, to a degree

Medicine, vancomycin, and metronidazole. During this ending, the pharmaceutical manufacturing was the tool of change as almost all big association uphold an active test (R&D) program in Medicine research.{3}Yet, later the primary rush of new compounds—many unique from actinomycetes, microorganisms

that are primarily in the direction of soil—new starting points for completely clean drugs enhanced harder to find, and the controlled hurdles more obvious.

New findings discontinued short from the 1980s onward. As a result, the happening of medicines has descended, accompanying new Food and Drug Administration (FDA) approvals for these drugs dropping from 29 all the while the 1980s to nine in the first decade of the 2000s.{4} All medicines certified for use in subjects contemporary are derivative from a restricted number of types, or classes, of antibiotics that were found apiece intervening-1980s (Figure 1).{5}

This is even comparative than the decline of drug approvals cause opposition to one medicine frequently leads to opposition to diversified medicines within the alike class. While drugs maybe classification or top-secret in a sort of habits, for the purposes of this document, medicine classes are established correspondences in synthetic makeup.

Faced accompanying poor finding prospects and increases not proportional to more investment on contribution, main drug guests have cut back or quit of antibiotic research completely. This has abandoned much of the surplus finding work to narrow,"pre-revenue" associations accompanying no device on stock exchange and restricted budgets and R&D volume. Most industry Medicine growth programs are generally directed on lessening existent classes of drugs discovered

Decades in the past to fool bacterial fighting and better aim troublesome-to-treat contaminations. Though essential, such increasing by additions advances are not probable to meet the rising community health challenge of medicine opposition in the long term.

As favorable medicine finding has decreased, extensive resistance to existent drugs has proliferated, Ordering benevolence on the mountain of what the World Health Organization has named a "post-medicine era," in that coarse contaminations and minor harms can occasionally be lethal{6}

Resistance is extended everywhere, moving two together rich and cultivating nations. In the United States, the Centers for Disease Control and Prevention (CDC) estimates that in addition to 2 heap folk get weighty resistant bacterial contaminations done yearly, and not completely 23,000 of bureaucracy will wither in an appropriate.{7}

A survey by the Infectious Diseases Society of America determined that over 60 portion of spreading affliction doctors have faced victims with contaminations that do not put oneself in the place of another some accessible medicine.{8}

Antibiotic fighting is a worldwide problem, emphasize for one spread of new types of fighting, in the way that Delhi metallo-beta-lactamase. First stated in 2008, it contaminate 40 nations inside five years and resumes to advance{.9} More ominously, various current studies from diversified countries indicate the rise of dispassionate opposition to colistin, an antibiotic thought-out a "drug of desperate remedy" cause it is secondhand in patients only when Other medicines are not any more productive.{10}

In the face of this rising deadlock, works to renew and help the probability of profitable drug finding are essential. The U.S. administration, industry, and all fitness and healing societies all concur that new supervisory tactics and financial lures are precariously wanted to restore a healthy passage of medicines.{11}

When it meets expectations the finding of new types or classes of drugs, nevertheless, the more fundamental barriers are controlled (Figure 2). Unless key bottlenecks to finding are efficiently sent, medicine research and incident will touch struggle. New fundamental and basic research is wanted to experience new drug finding and growth over the coming decades. Such research is the focus concerning this guide to future goals. As manufacturing has switched its model to focus principally on the happening, licensure, and shopping of crop, investment in fault-finding regions of fundamental research has happened lacking. Academia is frequently wonted to fill this break and, while possessing extraordinary research ability, it unique is not completely equipped to overcome key controlled obstacles to medicine finding. To date, most public funding of academic investigators in the field of medicine fighting has been through prosecutor-compelled grants wanting the interdisciplinary, related, and aim familiarize research necessary to effectively spur new medicine finding. In addition, drug finding demands specific preparation and knowledge, and outside a mechanism for finding manufacturing information to academic chemists, all too frequently communication well-informed are dreaming and the same mistakes are fashioned again—wasting opportunity and

Possessions, and restricting progress.

The U.S. administration has captured few main steps, accompanying the National Institute of Allergy and Infectious Diseases (NIAID) contribution preclinical and dispassionate forms to help stimulate the growth of new analyses and upholding individual police-compelled research on early drug finding and up-to-date cure.{12} NIAID likewise settled the Centers of Excellence for Translational Research program, that involves not completely individual center loyal to the growth of new medicines to treat drug-opposing bacterial contaminations.{13} A review of related research and translational exertions supervised at beginning elementary controlled impediments to medicine finding arrived a alone existent project, Translocation, that is financed through the Innovative Medicines Initiative (IMI), a alliance betwixt the European Union and the European Federation of Pharmaceutical Industries and Associations (EFPIA) business group.{14} The Translocation project is concentrated on by means of what to receive medicines into Gram-negative microorganisms and in what way or manner to stop microorganisms from ejecting the drug. The project is widely scattered between 27 spouses across nine European Union nations. Given that half of the budget emanates European taxpayers, partnership intentionally is restricted to European spouses, leaving non-European-located firms and Academic scientists on the sidelines. While added IMI projects to advance decontaminating growth will resume, the Translocation project is due completely in 2017

A new paradigm for antibiotic discovery

Recognizing the critical break in science and the essential community health need, Pew design to assess either specialists take care of come to terms the top scientific obstructions obstructing medicine finding, outline a scientific plan to overcome these obstacles, determine the possessions wanted, and propose a design for completing activity this work. Pew

committed a center working group of 21 chief medicine physicists from scholarly world, industry, and management accompanying an extraordinary width and depth of information in medicine finding and happening. Each has specific knowledge across a range of regimens, containing microbiology, natural and molecular study of animal, bacteriology, allure, curative allure, natural brand, medicine opposition, and drug design. Numerous additional experts given valuable understandings at each stage of the process.

This road map outlines a plan to shift the example of medicine R&D by construction a tenable and robust bedrock for findings over the coming decades. It has the potential to correct the overall fame rate of antibiotic finding and early happening while extending the number of approaches usable to combat bacterial infections. To realize these aims, the occupied group labeled two arrangement areas, that maybe confronted together or sequentially: understanding and beating hurdles for drugs target Gram-negative microorganisms in order to create and better tailor new synthetic matter for medicine finding; and evaluating and ratifying alternative, up-to-date healings for the situation of systemic bacterial contaminations (reviewed later painstakingly; visualize "Scientific priorities for medicine finding"). Given the rise of medicine-opposing bacteria, a persisted devote effort to something the appropriate use of existent medicines, alongside investment in key elementary research, is essential for upholding a strong valise of effective analyses.{15}

This plan advises a achievement-driven controlled plan to tackle the fundamental causes of abandoned drug finding and establish a tolerable passage of new decontaminating analyses.

Beyond the traditional field of narrow fragment medicines, research advances in a difference of biomedical areas containing biologics, immuno therapies, antagonistic-resentment adjuncts, nanotechnology, and so forth may have main healing requests for the situation of systemic bacterial contaminations, as any of these approaches have proved meaningful promise in treating other illnesses A experimental plan to complete activity combining several branches of learning and directed research wanted to revitalize medicine finding requires an administrative makeup fixated on attaining mission-compelled aims and achievements. Given the complicatedness and scale of the challenge, the success of aforementioned an exertion would demand the unification of scientists accompanying knowledge in drug finding, any branch of natural science, chemistry, pharmacology, and additional regimens to guarantee the giving of lessons well-informed and knowledge with subdivisions. In addition, skilled would be excellent worth in mobile further the traditional drug finding society to interconnect specialists who can lead new plans and offer various outlooks to help tackle long-standing questions. The action specified attending would require a loyal, entire-opportunity controlled leadership group to straightforwardly control a combining several branches of learning research work. It would combine complete research aims accompanying the adaptability to divert resources established progress and unexpected experimental challenges. This exertion would aim to complement and augment existent candidly and confidentially supported research in the United States and abroad and to coordinate and participate accompanying management, college, industry, research organizations, and nonprofits to fast transfer news and information to the researchers the one need it. While this exertion would not devote effort to something amount development, it would authorize remainder of something commotion so by threatening the barriers to drug finding. By making dossier and new breakthroughs widely approachable, this approach has the potential to hasten research at a off-course range of institutions accompanying the artistry and volume to find and develop new output. To manage whole designed in the road map, close ties middle from two points the controlled Guidance group, combining several branches of learning research teams, and crop planners through partnership on experimental and technology transfer able boards and cooperative concurrences would help guarantee results-based research, while aiding the rude answer of new advances that maybe swiftly translated into community health effects.

Drug finding and happening in different infectious affliction-distinguishing fields, to a degree HIV, tuberculosis (TB), and sickness, have existed favorably prompted by collaborations betwixt administration-bankrolled analysts and private industry, frequently catalyzed by not commercially motivated institutions. The International AIDS Vaccine Initiative, a not commercially motivated product happening participation occupied to explain laboratory breakthroughs into hopeful cure bidders against HIV, supports various preclinical and clinical cure nominees for forestalling and ruling HIV contamination.{16} The TB Alliance, a global not commercially motivated arrangement loyal to faster-acting and inexpensive drug regimens to be in a dispute or fight infection, started the first dispassionate trials to test diversified TB drugs together and has massed and governed the largest envelope of potential new TB drugs in annals.{17} The Medicines for Malaria Venture, a producing no profit or gain public-private participation working to find, evolve, and speed transfer of new, effective, and inexpensive antagonistic-malarial drugs, supports diversified projects from lead creation and optimization through merchandise happening.{18} As this guide to future goals push progresses, these and added organizational approaches will be thought-out as potential models for reaching complete controlled goals.

Finally, appropriate levels of capital are essential for the profit of big controlled initiatives. This guideline entails an primary capital target of $50 heap to demonstrate movements and kill the key pilot studies designed in this place plan. Overall, it is supposed that brimming execution of the project defined present would demand $170 million to $200 million over five years. These address money, if favorable, have the potential to severely improve community health consequences over the decades at hand. The law outlined in this place plan do not stand alone—they join accompanying a growing refrain of communal and worldwide demands reviving the medicine passage. 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 society have all emphasize the pressing need for new medicines.{19} 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.{20} 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.{21}

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.{22}

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.{23} 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.{24} 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.{25} 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.{26} Nearly all of these drugs are modifications of existing classes of antibiotics.

In practice, physicists must within financial means produce fragments that are not only forceful inhibitors of essential bacterial processes, but again have the skill to enter bacterial containers, deceive outflow pumps (protein composites that energetically transport poisonous fragments not enough the container), and reach extreme intracellular concentrations. For Gram negative pathogens, this has existed rarely completed, making it troublesome for physicists to suppose former work or evolve valuable directions for future profit. Unless this fundamental breach in organic and physicochemical understanding is effectively talked, medicine finding works will stretch to struggle.

Most Gram-negative microorganisms have included skills to circumvent medicines and cultivate resistance. Unlike Gram-beneficial microorganisms, to a degree Staphylococcus aureus (like, MRSA), Gram-negative pathogens have two membranes accompanying four-sided traits. That form it troublesome to design drugs that can pierce two together barriers in consideration of into the cytoplasm of a germ and destroy it (Figure 3). For example, particular hydrophilic or loaded solutes can cross the external sheath by spread through water-suffused channels named porins, but they are weak to pierce the cytoplasmic membrane except that they are energetically moved. In addition, Gram-negative pathogens carry a roomy difference of outflow pumps, that energetically discharge medicines from the cell and cause drug fighting. Solving the question of Gram-negative drug introduction and outflow demands consideration to all of the complex methods by which Gram-negative microorganisms dodge antibiotics.

Several research groups related to manufacturing and college have alone reliable to address facets of these challenges.{27} Academic labs have specific exceptionally types of outflow pumps or exposed sheet porins. Industry groups have worked to lessen existent classes of medicines to better aim Gram-negative pathogens. Despite these advances, important break in understanding wait, specifically when it meets expectations sensibly plotting compounds with the physicochemical characteristics of decontaminating drugs that espouse and wait in the cytoplasm of Gram-negative microorganisms.

Pharmaceutical associations have abundant compound accumulations that maybe secondhand as offset materials to find synthetic matter namely alive against recently labeled organic aims. However, these accumulations are mainly improved for human marks, such as G-protein-connected receptors or kinases, and partial toward seepage of eukaryotic alternatively Gram-negative bacterial containers and bacterial marks. Known Gram-negative antibacterials mainly do not trail Lipinski's rule of five* but most manufacturing compound accumulations are thickly biased toward compounds that do{28} Improving synthetic difference for medicine finding demands a better understanding of the physicochemical characteristics that are main for medicines. It was not just before 2008 that written computational reasoning differentiated middle from two points the physicochemical traits of Gram-negative and Gram-helpful mean drugs.{29} Such work plans the chance for provisionally appropriate directions for medicine finding and design that would help researchers find new medicines that aim Gram-negative pathogens or alter existent compounds so they are intelligent to overcome the multi component filter methods of Gram-negative bacterial variety. For example, possibly likely to cultivate general directions for physicochemical characteristics necessary for the introduction of compounds by various routes that are tailor-made for particular synthetic classes, devices of operation, or bacterial class. This type of facts has the potential to spur the finding of new compounds and benefit all discovery research, but skilled is a lack of coordinated and concentrated research to complete activity to a degree-wanted material of work.

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,{30} 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 road map 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.{31}

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.{32}

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.{33} 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.{34}

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.{35} 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.{36} 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 corporate 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 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.{37} A number of Malaria Box compounds have shown activity against Cryptosporidium, schistosomiasis,

And African trypanosomiasis.{38}

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 objectives 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.{39} 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.{40} Specific proof-of-concept experiments (e.g., toxicity or resistance studies, animal challenge experiments, pharmacokinetic optimization, pharmacodynamic modeling to understand concentrationdependent 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.{41} 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 {.42} 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.{43} 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.{44} 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 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.{45}

Based on the scientific literature, a small team of scientists would first test existing verified single-target antibacterial compounds{.46} 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.{47} 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.{48}

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 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 Welcome Trust and UK Department of Health commissioned a report and review on alternatives to antibiotics to inform policy and decision-makers.{49} 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.{50}

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 bacterivorous and Mica vibrio aeruginosavorus can feed on human pathogens, including multidrug-resistant bacteria, gaps in basic scientific understanding remain {51}

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?{52}

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 {53} alternatively, there may be opportunities to work with existing software Platforms, such as the Info Centre, which is supported by the IMI Translocation project and funded through 2017.

The Info Centre 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.{54}

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, no indexed 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 partnershipwith 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 {.55} 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 mentor ship 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{.56} 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{.57} Alternatively, stand-alone initiatives that provide mentor ship 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 . 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 road map 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 road map 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.58 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.

Research Methods:

1. Introduction to Antibiotic Discovery:

Antibiotics play a crucial role in combating bacterial infections, but the rise of antibiotic-resistant strains necessitates continuous efforts in antibiotic discovery. This study aims to unveil new antibiotic candidates and address the growing challenges in combating bacterial infections.

2. Literature Review:

Previous research has highlighted the urgent need for novel antibiotics due to the increasing prevalence of antibiotic resistance. However, there is a notable gap in our understanding of [specific aspect], which this study seeks to address.

3. Research Design:

We employed a [specific methodology] to screen a diverse library of compounds for potential antibiotic activity. The selection criteria were based on [criteria], aiming to identify compounds with broad-spectrum efficacy.

4. Data Collection:

Bacterial strains, including [list strains], were subjected to [experimental conditions]. Antibiotic candidates were tested using [specific assays], and data were collected on [relevant parameters].

5. Data Analysis:

Statistical analysis was performed using [statistical methods], and results were validated through [validation methods]. Limitations include [potential biases], which were addressed through

[mitigation strategies].

Results:

1. Overview:

Our study revealed promising results in the search for novel antibiotics, with several candidates demonstrating potent antibacterial activity.

2. Antibiotic Candidates:

Compound A exhibited a MIC of [value], outperforming existing antibiotics in inhibiting the growth of [target bacteria]. Similarly, Compound B demonstrated [unique feature].

3. Antibiotic Resistance Patterns:

While most strains were susceptible to the newly discovered antibiotics, resistance patterns were observed in [specific strains]. This highlights the importance of continued surveillance and development of complementary therapies.

4. Comparison with Existing Antibiotics:

Comparative analysis with commonly used antibiotics revealed that our candidates showed [advantageous characteristic], potentially addressing the limitations of current treatments.

5. Additional Findings:

Unexpectedly, [additional finding] was observed, suggesting potential applications beyond the original scope of the study.

Discussion:

1. Interpretation of Results:

The robust antibacterial activity of the discovered compounds indicates their potential as valuable additions to the antibiotic arsenal. This is particularly significant given the challenges posed by antibiotic-resistant strains.

2. Comparison with Previous Studies:

Our findings align with [similar studies], reinforcing the importance of [specific aspect]. However, the unique features of our compounds contribute novel insights into [specific aspect].

3. Implications for Antibiotic Discovery:

The discovery of these compounds has profound implications for antibiotic development, offering new avenues for addressing the evolving landscape of antibiotic resistance. Further exploration of [specific aspect] may lead to even more effective treatments.

4. Limitations:

Limitations include [limitations], which suggest areas for future research. Despite these constraints, our study provides a valuable contribution to the ongoing efforts in antibiotic discovery.

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.

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