Meeting Summary: Scientific Priorities for Antibiotic Discovery and the Role of Networks

DISCUSSION DRAFT

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A note to participants

This document captures an informal small-group meeting held at The Pew Charitable Trusts in Washington, D.C. in Sept. 2014 to discuss scientific impediments to the discovery of new antibiotics. The meeting was the first in a series to bring together academic and industry experts—and ultimately government officials—to identify and prioritize research and identify potential funding models that would enhance and accelerate antibiotic innovation.

Participants in the first meeting identified four key scientific priorities for antibiotic drug discovery. These priorities are not independent of one another and there is no significance to the order of this list:

- Understand and overcome barriers to drug penetration and avoidance of efflux for Gram-negative bacteria;
- Generate new chemical matter for antibacterial screening;
- Model and predict antibiotic resistance; and
- Explore new paradigms for treatment of bacterial infections.

Pew will hold a second meeting in Jan. 2015 to identify both the resources needed, including the expertise, information, tools, and funding, to address key scientific priorities for antibiotic discovery and the specific actions, such as the establishment of a consortium, public private partnership, or other collaborative forum, that could effectively marshal necessary resources.

In advance of the January meeting, we ask for your review and feedback on the list of four key scientific priorities and the following meeting summary. In particular, we ask that you consider the following:

1. Does the list of scientific priorities developed at the meeting reflect your understanding of the top priorities for antibiotic discovery?
2. Would addressing these priorities have a significant impact on antibiotic discovery? Why or why not?
3. Do you think that progress on these priorities is possible? Why or why not?
4. What hurdles and/or gaps are impeding progress on these priorities?
5. What resources are needed (e.g., information, tools, expertise, communication, money) to make progress on these priorities?

We are relying on your expertise and guidance to identify the top scientific priorities for antibiotic discovery, clarify what barriers are preventing progress on these priorities, and determine how to turn ideas into action.

Introduction

While there has been much discussion on how to address economic and regulatory barriers to antibiotic development, less attention has been focused on how to answer the basic science questions that stymie antibiotic discovery. Over the past three decades, research avenues pursued by industry and academia have largely failed to produce novel antibiotic agents despite significant investment in discovery programs. A growing number of experts agree that targeted investments in key areas could rejuvenate antibiotic discovery. Yet, as major pharmaceutical companies have downsized or exited antibiotic research and development, the task of addressing scientific obstacles has fallen to small companies and academic laboratories, which often lack the necessary expertise and resources to effectively conduct drug discovery.

On September 9, 2014, the Pew Charitable Trusts brought together academic and industry experts to review and prioritize key scientific bottlenecks to antibiotic discovery. The group also discussed the merits of establishing a U.S.-based antibiotic discovery network to help find solutions to these challenges. This initial discussion will help guide the course of upcoming Pew-hosted meetings that will seek to identify specific actions to change the current paradigm for antibiotic discovery, facilitate better collaboration across academia and industry, and address the antibiotic discovery void.

Scientific priorities for antibiotic discovery

Pew asked meeting participants to pinpoint the most pressing scientific questions, which, if addressed, would transform antibiotic discovery. Much of the discussion focused around four priorities, briefly described here:

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

There is a clear need for more drugs to treat Gram-negative infections, but finding these agents is a challenge. More specifically, participants highlighted the need for chemical matter that can penetrate Gram-negative pathogens and avoid efflux.

Participants discussed the New Drugs for Bad Bugs TRANSLOCATION project, which focuses on the molecular basis of bacterial cell wall permeability, and is funded through the Innovative Medicines Initiative (IMI), a large public-private initiative between the European Union and the European Federation of Pharmaceutical Industries and Associations. While several participants agreed that it is too early to assess the potential impact of the IMI effort, a few participants suggested that if the U.S. were to extend this project, there would be an opportunity to build on IMI work and significantly advance the field. A U.S. effort could capture additional points of view, allow for a more organic development of a research plan, and help pool information from U.S. academic and industry researchers.

Participants considered the impact and value of a better understanding of the physiochemical properties required for compounds to penetrate the outer and cytoplasmic membranes of Gram-negative cells, avoid efflux pumps, and effectively reach their target. Participants also mentioned the need for more research on bacterial uptake pathways as a means of delivering antibiotics. There was some discussion of the potential for establishing “rules of entry” for compounds targeting Gram-negative bacteria to help inform lead selection and optimization as well as the design and construction of antibiotic-focused compound screening libraries. Such an effort would require sharing information, perhaps by establishing a repository for old protocols and other background material (published and unpublished) from prior industry screening campaigns in an easily accessible format. A clear understanding of what work has already been done would facilitate experts’ assessment of what additional knowledge is needed. Given that some chemical generalities have already been determined based on existing compounds, participants thought there was promise in testing whether these generalities could be applied more widely or used predictively. Furthermore, there was discussion of developing conditional rules for compounds based upon routes of entry or efflux avoidance.

Questions for further discussion

- *What information is required to address this priority? What is known and what is not known? What incentives are needed for industry and academia to share information more broadly?*
- *What evidence do we have to demonstrate whether it is possible to establish general rules or properties for drugs targeting Gram-negative bacteria? What would need to be done to assess the applicability and predictive nature of general rules developed based on existing compounds?*
- *What size of investment would be necessary to tackle the scientific priority outlined above?*
- *How would any U.S. investment in this issue complement and go beyond the IMI? What remains to be done that IMI is not already doing?*

Generate new chemical matter for antibacterial screening

Participants discussed where and how to find new antibiotics, focusing on two broad-based approaches: (i) screening natural products for compounds that can be used as drugs; and (ii) screening synthetic compound (and occasionally natural-product) libraries that can be modified through medicinal chemistry and computational drug design.

Over the past few decades, natural products screening largely fell out of favor in the pharmaceutical industry. Although natural products screening was initially fruitful, output waned once easily identifiable chemical classes had been mined, and companies largely abandoned this approach due to the resulting lack of new discovery. Conventional high throughput screening (HTS) efforts as well as whole-cell screens instead focused on synthetic chemical libraries, which predominantly contain Lipinski's Rule-of-5-compliant chemicals and are generally not well suited for antibiotic discovery. While inhibitors of molecular or enzymatic targets were identified through *in vitro* HTS and can be made more potent through medicinal chemistry, it was difficult to improve the ability of these compounds to reach the molecular targets within bacterial cells, particularly for Gram-negative bacteria. Thus, participants felt an understanding of Gram-negative entry and efflux would make it possible to develop better chemical libraries.

Participants considered whether further exploration of natural products could yield promising antibiotic compounds. While there have been advances in genomic analysis and technical improvements for growing difficult-to-culture organisms, challenges to identifying promising novel compounds in natural products' extracts limits drug discovery. Participants discussed the difficulty of finding good candidate compounds as well as the challenge of de-replication (i.e.

the rapid identification of known compounds present in a mixture), which are both critical for the discovery of novel natural products. Expertise in appropriate screening methodology (new and old), including hypersensitive whole cell screens, was highlighted as a critically important for finding novel compounds.

It was pointed out that any future effort on natural products chemistry should incorporate or complement existing partnerships and activities. For example, the International Biodiversity Conservation Group, which is jointly funded by the National Institutes of Health (NIH) and the National Science Foundation (NSF), supports public and private collaborative efforts and helps guide natural products drug discovery in ways that benefits local communities and organizations in source countries such as Costa Rica and the Philippines. Participants also emphasized that screening efforts should include a wide range of chemical sources and technologies, including further exploration of synthetic chemistry, computational modeling, and structure-based drug design.

There was discussion of how to access existing chemical libraries and revive old drug discovery platforms using new readouts and screening paradigms. A recurring topic that came up throughout the discussion was the lack of sharing across sectors and between disciplines. While industry has published on new molecular entities, screening methods are more often proprietary information. It was noted there does exist a body of published work on fermentation and protocols, but researchers may not go back and read this older material. Participants agreed that finding a way to disseminate information and lessons learned, perhaps through a common repository or failed projects forum, would be particularly useful for academics and small companies that too often try to reinvent the wheel.

Questions for further discussion

- *Why would any new screening venture work when most others have failed?*
- *Should the goal of a program focused on natural products be to find natural products to use as drugs or as chemical starting points?*
- *What organizational structure, resources, and expertise are needed to manage the generation of new chemical matter? How should efforts on natural products and synthetic compounds be coordinated?*
- *How much of this work is doable, but not being done—versus important, but not currently doable?*
- *What are the strengths and weaknesses of current natural products discovery efforts, and how would additional investment make a difference?*
- *What models could ensure that today's academic and industrial researchers have access to the cumulative knowledge from earlier research?*

Model and predict antibiotic resistance

Participants agreed on a number of criteria for good antibiotic target selection (e.g., essential, broadly conserved, no human homolog), including low resistance potential. They discussed the challenge of understanding and modeling drug resistance for current and new drugs. While there are a number of laboratory methods available for assessing rates of resistance, it is difficult to predict the future potential for resistant infections arising in the clinic. Participants discussed the usefulness of standardizing animal models for resistance selection and competitive fitness. The question was raised whether it is possible to accurately predict clinically relevant drug resistance.

Participants argued that structure-based drug design has been too focused on single enzyme targets, which are prone to rapid resistance development. There was discussion of how to identify promising targets that are less likely to mutate in response to drug pressure. Given that successful systemic antibiotics have multiple molecular targets or target the products of multiple genes, participants discussed the value of taking a multi-target approach. While it was agreed that such an approach likely holds promise, it was pointed out that academic researchers have, in large part, focused on single-target screening efforts.

Questions for further discussion

- *What is needed to develop good models to better predict resistance in the clinic? Are there predictive models for compounds that can be standardized?*
- *What is the evidence that addressing this priority is possible?*
- *How can academic thinking be refocused toward more promising drug targets and away from single-target screening efforts?*

Explore new paradigms for treatment of bacterial infections

While not something that could be condensed into a single scientific question, participants discussed the importance of considering and evaluating new paradigms and approaches, such as immunomodulators, vaccines, and bacteriophage therapy. A number of participants emphasized the value of engaging with multiple disciplines and exploring big shifts in thinking. Participants noted that large companies have approached antibacterial discovery with a very narrow scientific focus (i.e. traditional small molecule screening), but have taken on new approaches when it comes to other therapeutic areas such as HIV or oncology. Small companies and academia are pursuing work on new paradigms, but proof-of-concept experiments are still needed to demonstrate the potential for alternative therapies.

A few participants highlighted the importance of targeting persisters, which are not mutant cells, but microbes that are in a transient dormant state and able to tolerate antibiotics. The

presence of persister cells in the context of human infection can lead to longer antibiotic treatment courses and potential treatment failures. It was noted that chronic infections require a different type of compounds for treatment and would likely need to be used in combination with other drugs.

It was generally noted that one way to reduce drug resistance is to use more than one drug concurrently. Participants discussed the lack of basic scientific understanding and the challenge in modeling combination therapy and designing human trials for combination drugs. They agreed that in the short term, combination therapy is needed. It was pointed out that there is an IMI consortium, PreDICT-TB, which is focused on model-based preclinical development of drug combinations to address tuberculosis (TB) infections. This approach has not been applied to other bacterial infections, but some considered it a feasible approach.

While the focus of this discussion was on scientific barriers to drug discovery, participants acknowledged the regulatory challenges of combination therapy. In particular, participants expressed uncertainty regarding the regulatory approval pathway for antibiotic combinations. Participants pointed out that the U.S. Food and Drug Administration (FDA) has issued guidance for industry on approval of TB drug combinations and has worked with industry on approval of beta-lactam/beta-lactamase inhibitor combinations.

Questions for further discussion

- *What are the scientific barriers preventing uptake of new approaches on the part of industry (i.e. what proof-of-concept experiments need to be carried out and why have these experiments not been done)?*
- *What feedback and critique would be useful for small companies and academia working on new paradigms for treatment of bacterial infections? How should this information be shared?*
- *How should we allocate limited resources between existing paradigms and new ones?*
- *How should we evaluate antibiotic combinations? Where are the gaps in understanding?*
- *How do rapid diagnostics fit into this discussion?*

Additional themes that emerged

Throughout the meeting, a number of additional themes emerged, including the need to develop and implement a plan of action to translate common understanding of scientific barriers to antibiotic discovery into tangible steps to address those barriers. A number of participants emphasized the need to define and clarify how academia and industry could partner to optimize their efforts and how to engage experts across disciplines. Throughout the discussion, participants expressed deep concern over how to capture or record valuable industry expertise as antibiotic programs are downsized or terminated and as experienced

industrial researchers leave the field. The importance of addressing the future of young antibiotic discovery researchers and providing opportunities for training, guidance, and mentorship were also highlighted. One topic that was brought up early on in the discussion, but not explored in-depth, was the concept that diagnostics and drug discovery, particularly for narrow-spectrum antibiotics, are not separable so there should be some consideration of the degree to which the two can be integrated.

Discussion of a network-based approach

Antibiotic Discovery – UK

During the second half of the discussion, participants had an opportunity to learn about and discuss Antibiotic Discovery- United Kingdom (AD-UK)—a network of academic and industry experts working to integrate knowledge transfer across research groups, disciplines, and sectors—and explore the merits of establishing a US-based antibiotic discovery network. Representatives from AD-UK discussed their informal, collective-based approach to rebuild antibiotic discovery in universities and industry and promote education and research on new approaches. For example, the network called for a new Cross-Research Council Antimicrobial Resistance Initiative on the part of the UK Medical Research Council (MRC), which led to an MRC call for applications in 2014. In an effort to expand on a global scale, AD-UK has helped establish AD-Spain and is in discussions with a number of other countries. AD-UK representatives described not only some of the benefits, but also some of the challenges in taking this approach, such as the importance of holding regular in-person meetings and the need for sustained funding.

Consideration of a US-based network

There was some coalescence around creating an informal network in the U.S., similar to the AD-UK model, as a starting point to address scientific priorities. Participants acknowledged that such a network does not currently exist and could provide a useful forum for ideas exchange at relatively low cost. It was noted that in the U.S., there are a number of groups driving discussions around antibiotic resistance and that better coordination is needed. Given this fragmentation, a neutral body could help facilitate this network, bring meetings together, and help catalyze action.

While an informal network may not be able to execute solutions, participants considered how such an exchange might lead to more formalized activities that could help tackle some of the scientific challenges addressed earlier in the discussion. Such a network would have the power of the crowd and could serve as a forum for getting things done, whether that be signing on to letters to government agencies or serving as a resource for information. Several participants supported the recommendation that the network be structured into active working groups, composed of individuals with similar interests, to allow for a greater degree of collaboration and push conversations towards focused, tangible outputs, such as white papers or other publications. A web-based presence could potentially provide an open-access platform for mentorship and advice, information on funding opportunities, or other resources. It was generally agreed that direction and tangible goals would be required for such a network given limited time and resources.

Questions for further discussion

- *What are the benefits and drawbacks of establishing a U.S.-based informal network?*
- *What are the incentives for participation?*
- *What would a network add that does not already exist?*
- *What specific activities could a network carry out?*

Additional mechanisms for addressing scientific priorities

As mentioned above, an informal network, at least informed by—if not connected to—the AD-UK model could be a first step in catalyzing action on priority questions impeding antibiotic discovery. It was pointed out that establishing an informal network would be a way to demonstrate the antibiotic discovery community's willingness to come together and advocate for more substantial action.

The following potential activities were briefly discussed and may be explored in more detail going forward:

Establishing consortia or partnerships

An overall challenge that researchers have faced is the lack of communication between academia and industry. Establishing a partnership or consortium around antibiotic discovery could be one way to better leverage knowledge and expertise across academia and industry, enhance information flow, and connect experts across sectors and disciplines. This structured approach to information and resource-sharing could increase efficiencies of effort and foster greater collaboration across sectors. Participants discussed the value of setting common goals and having a governance structure in place.

While a formal public-private partnership or consortium-based approach might be less nimble than an informal network, multi-sector collaborations to accelerate biomedical research have demonstrated success in other biomedical areas. These partnerships vary significantly in breadth, focus, governance, and operational structures depending on set goals.

There was discussion of an antibiotic discovery partnership focused more broadly on pre-competitive research that could facilitate information-sharing across sectors and disciplines with the goal of catalyzing increased antibiotic development activity. The question was raised as to what constitutes precompetitive research—basic biology, biomarkers, drug targets, or even leads.

Questions for further discussion

- *What elements of the top scientific priorities could be addressed through a consortium-based effort? What are some common goals that might be addressed pre-competitively?*
- *What should be considered pre-competitive research for antibiotic discovery?*
- *What would incentivize industry and other stakeholders to engage in an antibiotic discovery consortium or public-private partnership?*
- *What assets would each of these stakeholders bring to the table?*
- *How much would it cost and who would pay for it?*

Creating an antibiotic discovery institute

Several participants highlighted the critical value of regular in-person discussions and informal meetings between researchers. Providing a physical space that brings together cross-disciplinary and cross-sector expertise to collaboratively address antibiotic discovery could be one way to significantly advance the field, but would have high startup costs.

Participants discussed how opportunities to exchange personnel between academic and industry labs through an infectious disease institute and made possible by fellowships would facilitate better understanding of the drug pipeline and improve antibiotic discovery efforts. Such an institute could serve as an anchor for an informal U.S.-based network.

Questions for further discussion

- *What would be the scope of an antibiotic discovery institute?*
- *What resources and expertise would be needed to establish an institute?*
- *How much would it cost and who would pay for it?*
- *How would an institute remain sustainable over time?*

Next steps

This initial discussion will help guide the course of upcoming Pew-hosted meetings that will seek to identify specific actions to change the current paradigm for antibiotic discovery, facilitate better collaboration across academia and industry, and address the antibiotic discovery void.

Appendix A: Participant List

Karen Bush, Indiana University Bloomington
Anthony Coates, St George's, University of London
Chris Dowson, University of Warwick
Alice Erwin, Erwin Consulting
David Hooper, Massachusetts General Hospital
Deborah Hung, Broad Institute
Ann Kwong, InnovaTID Pharmaceuticals
Richard Lee, St. Jude Children's Research
Kim Lewis, Northeastern University
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Appendix B: Agenda

Tuesday, September 9, 2014
11:30 am – 3:30 pm

The Pew Charitable Trusts
901 E Street NW, 3rd Floor
Oklahoma Room
Washington, DC 20004

Small Group Discussion Goals and Outcomes

Goals:

1. Establish a preliminary list of top 3-5 scientific questions impeding antibiotic discovery;
2. Learn about and discuss Antibiotic Discovery-UK, a network of academic and industry experts working to integrate knowledge transfer across research groups, disciplines, and sectors; and
3. Explore the merits of establishing a US-based antibiotic discovery network; and
4. Identify next steps for shaping upcoming meetings.

11:00-11:30 a.m.	**Registration – coffee and lunch served**
11:30-11:40 a.m.	**Welcome and overview** • **Allan Coukell**, Senior Director, Health Programs, The Pew Charitable Trusts
11:40-11:45 a.m.	**Outline of goals and expectations for this meeting** • Abby Dilley, Vice President of Programs, RESOLVE
11:45-11:50 a.m.	**Participant introductions**
11:50 a.m.-12:00 p.m.	**Scientific questions that impede antibiotic discovery** • Dr. Lynn Silver, Founder and Principal, LL Silver Consulting, LLC
12:00-1:30 p.m.	**Identification and discussion of top scientific questions** *Small group discussion* **Discussion Question** Blue-sky thinking: What are the top 3-5 unanswered scientific questions (rate-limiting steps) impeding antibiotic discovery?
1:30-1:45 p.m.	**Coffee Break**

1:45-2:15 p.m. **Prioritization of top 3-5 scientific questions**
Small group discussion

Discussion Question
Can we reach preliminary consensus on the top 3-5 unanswered scientific questions?

2:15-2:35 p.m. **A Network-based Approach for Catalyzing Research in the UK: Overview of Antibiotic Discovery-UK**

- Sir Anthony Coates, Professor of Medical Microbiology, St George's, University of London
- Dr. Chris Dowson, Professor of Microbiology, University of Warwick

Discussion Question
What are the advantages of taking a network-based approach to tackle some of the challenges for antibiotic discovery?

2:35-3:20 p.m. **Discussion of a Network-based Approach in the US**
Small group discussion

Discussion Questions
How could a US-based network help address the top scientific questions facing antibiotic discovery?

What goals (narrow or broad) might a US-based network work to achieve?

Who should be a part of a US-based network for antibiotic discovery? What are the incentives to participate?

3:20-3:30 p.m. **Wrap-up and next steps**

3:30 p.m. **Adjourn**

Appendix C: Scientific questions based on previous discussions

Questions Based on Previous Discussions (last updated 9/3/14)

SCIENTIFIC QUESTIONS (focus of September 9 meeting hosted by Pew)
How do we get drugs into Gram-negative bacteria? Can we conduct SAR to predict entry and efflux?
How do we discover/develop drugs for intracellular targets?
What makes a good novel target and are there any targets left to be discovered/exploited?
Where is new chemical matter coming from (natural products or synthetic small molecules)?
Do we need new broad-spectrum or narrow-spectrum antibiotics? Will narrow-spectrum drugs have a lower tendency to select for resistance than broad-spectrum drugs?
How do we better understand the transition between *in vitro* and *in vivo* activity (protein binding, drug distribution, clearance, metabolism, etc.)?
How can we best model resistance development *in vitro* and *in vivo*? What are the best ways to look for resistance development to new agents so that the next generation of drugs can be designed to overcome novel mechanisms?
How can we model combination therapy? How do we conduct clinical trials that can model combination therapy to overcome resistance?
How do we encourage multi-modality therapy? For example, how can we take advantage of innate immunity or the microbiome to treat bacterial infections? What about antibacterial vaccines, phage therapy, immunostimulants, adjuvants, antivirulance therapy, probiotics, and their combinations?
How will understanding of the microbiome affect our ability to think beyond traditional antibiotics?
Can we better exploit hits from natural product screens or conduct these screens in better ways? Who is producing microbial natural product broths/extracts for screening?
What role do dormant persister bacterial cells have in acting as a potential source of antibiotic-resistant bacteria?
Can we develop or introduce new antibiotic-screening paradigms? Can we share old and/or established screening paradigms?
If we had excellent (cheap, accurate, rapid, and easy-to-use point-of-care) diagnostics, would we still need new drugs?

KNOWLEDGE TRANSFER QUESTIONS
How do we reverse the enormous brain drain from the antibiotic discovery field?
How can we utilize the brain drain from pharmaceutical drug discovery porgrams to train academic scientists in the ways that work or don't work in the search for new drugs?
How can we retain and transfer scientific knowledge—especially given the dissolution of microbiology groups in industry and elsewhere?
How do we ensure sustainable knowledge transfers between academia and industry in a feasible way?
How do we encourage better and more sustainable cross-sector (academia/industry) and cross-disciplinary (chemistry/microbiology/physiology/tech transfer) communication?

ECONOMIC QUESTIONS
How do we want to realign funding priorities? Should we fund basic science questions rather than academic drug discovery?
How can we forecast clinical and commercial needs for antibiotics 10 years out?
Does the market ascribe appropriate value to antibiotic? If not, why not? Is this true for all antibiotics or just a subset?
Are there barriers to companies charging their customers a price that reflects the value of their antibiotics? If so, what are potential mechanisms for overcoming those barriers?
When will we be able to charge what antibiotics are truly worth?
How can we change the profit motive to focus antibiotic discovery on health needs rather than market needs?
How can we retain interest in antibiotic discovery and development in large companies?
How can successful medium-sized companies focused on antibiotics survive and continue to invest in drug discovery/development?
How can we draw more funding to the basic science that needs to get done?
What would it take to set up a Manhattan Project for Gram-negatives?
Can public private partnerships such as the Innovative Medicines Initiative (IMI) deliver?
Are there enough scientists capable of conducting meaningful drug discovery research to make a public-private partnership venture successful? Will this take major input from the private sector for the research to yield something of value?

REGULATORY QUESTIONS
How would a LPAD (Limited Population Antibacterial Drug) regulatory pathway work in the real world?
How do we co-develop narrow spectrum drugs and diagnostics? Should clinical development pathways for these products rely on historic endpoints and superiority? If not, what changes are needed to better encourage innovation and protect public health?