Improving data sharing to increase the efficiency of antibiotic R&D

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Greater investment is needed in antibiotic R&D, and more must be done to maximize the impact of such investments. More widespread data sharing, such as the recent joint data contribution from Merck and Kyorin to the Pew Charitable Trusts' SPARK platform, has a key role.

The COVID-19 pandemic has provided a stark reminder not only of the need to be prepared before a public health crisis hits, but also of the essential role of antibiotics — in a pandemic and beyond. Unfortunately, when it comes to the growing dangers posed by antibiotic-resistant bacteria, the global level of preparedness does not match the magnitude of the threat. Indeed, recent declines in private investment in antibiotic R&D are staggering.

According to The Pew Charitable Trusts' analyses of the global antibiotic pipeline, most major drug companies have exited antibiotic research and development, leaving the bulk of development to smaller biotech companies. Today, nearly 70% of products in the pipeline are being developed by pre-revenue companies that may struggle to bring their first drug to market. And the few companies that have succeeded in developing a new antibiotic in recent years are struggling to stay afloat. In 2019, two small antibiotic companies (Achaogen and Melinta Therapeutics) with recent FDA approvals filed for bankruptcy, and another (Tetraphase) was recently acquired for a small fraction of its valuation only a few years ago. Furthermore, of the 15 FDA-approved antibiotics in the past decade, 7 are sponsored by companies that have passed through bankruptcy or have market capitalizations that are a fraction of the R&D funds invested to bring the antibiotic to market.

No other drug category has suffered economic destruction on this scale. And, while there have been important steps forward in addressing this, more work is needed for a multifaceted approach and fundamental reforms. Such reforms are likely to take time, however. Here we focus on an approach that could increase the chance of scientific success for antibiotic R&D in the nearer term: broader data sharing.

Making the most of investment

As recognition of the plight of antibiotic R&D has grown, various public and charitable organizations have stepped up and made considerable investments in antibiotic discovery, including US government agencies such as the National Institute of Allergy and Infectious Diseases (NIAID), the Biomedical Advanced Research and Development Authority (BARDA) and the Department of Defense, and charitable foundations such as the Wellcome Trust and the Bill & Melinda Gates Foundation. In 2016, the Wellcome Trust teamed up with BARDA and NIAID to fund Combating Antibiotic-Resistant Bacteria Biopharmaceutical Accelerator (CARB-X), a public–private partnership to accelerate the progression of a diverse portfolio of innovative antibacterial products into clinical trials. In 2018 and 2019, Germany (Federal Ministry of Education and Research), the UK (Global Antimicrobial Resistance Innovation Fund) and the Bill & Melinda Gates Foundation also joined CARB-X. And in 2020, industry has also re-engaged, with 24 large and medium-sized pharmaceutical firms backing a US$1 billion fund to steward antibiotics through phase II and III trials.

One way to increase the efficiency of such initiatives is through broader data sharing, which could be another opportunity for companies to advance antibiotic R&D, even if they have left the field. Such data sharing is critical to advancing antibiotic discovery efforts, because when projects are discontinued or programmes fail, treasure troves of data may be shelved, locked away or, in some cases, gone forever. Ensuring data are made available in a timely manner, regardless of whether a project continues or concludes, could make a big difference for this resource-strapped field by eliminating unnecessary and wasteful redundancy in the deployment of limited funds.

For example, Merck and Kyorin recently shared data from their now-discontinued preclinical programme investigating novel antibiotics that target two bacterial enzymes, DNA gyrase and topoisomerase IV, via Pew's Shared Platform for Antibiotic Research and Knowledge (SPARK). This platform was launched in 2018 to curate antibiotic discovery data and provide analytics, with a focus on elucidating how antibiotics enter and accumulate in Gram-negative bacteria, thereby spurring the development of innovative drugs to combat some of the most concerning bacterial threats at present.

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To date, SPARK has over 700 registrants across more than 60 countries.

An example of how data in SPARK have already been successfully used is in the case of the Gram-negative bacterial target LpxC, which is critical for lipopolysaccharide synthesis. This enzyme has all the characteristics of an attractive new antibacterial target: essentiality, no human counterpart, not previously exploited and highly conserved in Gram-negative bacteria. However, numerous discovery campaigns have resulted in many preclinical failures in the 20 years or so since LpxC was first pursued as a drug target[1], and only two companies successfully brought a molecule targeting LpxC into clinical development[2,3], where both failed in phase I trials owing to safety concerns in the past decade.

As is often the case when projects fail, little information about the efforts had been published once the LpxC programmes were discontinued. However, Pew and CARB-X coordinated with one of the CARB-X-funded companies that progressed an LpxC inhibitor into clinical trials, Achaogen, to provide substantial data on its terminated LpxC programmes to the public by hosting the data on SPARK. These data are now available for future researchers, including companies that have received CARB-X funding for LpxC programmes.

This type of sharing can be fully consistent with both patenting and publication. Achaogen's data release to SPARK was embargoed until publication[4,5]. This is an important detail because it alleviates one concern of both industry and academic researchers (the right to publish) and because it allows researchers to provide their interpretation of the programme data, which may be as important to researchers as making the data available for mining. Similar embargoes can be implemented until the relevant patents are filed.

CARB-X also coordinated Forge Therapeutics' access to additional Achaogen LpxC data in parallel to the SPARK contribution, which helped Forge understand its LpxC programme's specific toxicity signals and enabled head-to-head experiments comparing Forge's novel chemistry to Achaogen's compound in late 2018. This information was critical for Forge Therapeutics to demonstrate safety in preclinical studies, differentiate their approach and further validate LpxC as an important Gram-negative target, while saving time and money. Forge's LpxC programme is currently in preclinical development and advancing towards IND-enabling studies later this year. Outputs from Forge's studies will further enhance the LpxC data in SPARK.

Building on Achaogen's LpxC data contribution, Novartis has also contributed data to SPARK from discontinued programmes targeting LpxA, LpxD and LpxK, which are also potential drug targets involved in lipopolysaccharide synthesis. CARB-X is currently evaluating proposals for other Lpx targets, and data from those programmes can be contributed to SPARK if the company agrees. Eventually, SPARK could become the premier public domain resource for Lpx-targeting drug discovery.

To encourage data sharing upon conclusion of projects, CARB-X has general contractual provisions about open access data and publishing to encourage data sharing after a funded project is concluded. However, another hurdle typically encountered, especially for small companies, is limited resources to expend to prepare data contributions versus other competing priorities. The SPARK team recognizes this hurdle and is willing and able to support these companies with their data contributions. Similarly, the US National Institutes of Health (NIH) released a draft policy in November 2019, updating their data sharing requirements for funding recipients. The NIH also recognizes resources required to prepare data for contribution, allowing for incremental budget increases to offset associated costs.

Conclusions

As the need for new antibiotics grows more urgent, not only funders, but all stakeholders in this field, need to examine what incentives and mechanisms can further support the sharing of antibiotic research data. The Access to Medicine Foundation's 2020 evaluation of what pharmaceutical companies are doing to address antimicrobial resistance is a good example of how one organization leveraged its platform to help foster more data sharing. For the first time, the foundation included 'intellectual capital sharing' as 1 of its 19 antimicrobial resistance-related indicators used to rank companies, highlighting Achaogen and Novartis for their contributions of previously unreleased data to SPARK. This move may encourage more companies to share their data in the future.

Much of modern medicine would not be possible without effective antibiotics, but the rise of antibiotic resistance is inevitable. We need to spend more money on antibiotic R&D to address this challenge, but we can also spend smarter, by encouraging data sharing, especially from failed projects. This will help every antibiotic research team to stand on the shoulders of giants, instead of reinventing the wheel.

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Competing interests

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