PERSPECTIVE

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Synthetic biology revives antibiotics

Re-engineering natural products provides a new route to drug discovery, says **Gerard Wright**.

The drug discovery process often involves natural products or compounds that are inspired by them and modified by medicinal chemistry. For example, acetylsalicylic acid (aspirin) is one of the first cases of a natural product being modified to improve its drug-like properties. The ancient Greek physician Hippocrates prescribed concoctions made from the willow tree, which contains salicylic acid, to relieve headaches and other pains. Later, chemists modified and improved the properties of salicylic acid through synthetic reactions to produce aspirin. Today, synthetic biology is poised to reinvigorate interest in natural products as sources of new antibiotics.

By natural products, we mean genetically encoded small molecules that are the products of natural selection. As such, they represent privileged chemistry that has been tailored by evolution to interact with biological macromolecules, including proteins, nucleic acids, carbohydrates and membranes. It's not surprising then that more than 50% of drugs are either natural products or their derivatives. Many antibiotics, for example, have their origins in bacteria and fungi, which use natural products to interact with other microorganisms. Unlike most drugs produced in the lab, antibiotic natural products tend to be chemically complex molecules with intricate three-dimensional structures — properties essential for interacting with targets and for creating the antibiotic action. Sampling and expanding the chemical diversity of natural products is a critical component of discovering new antibiotics.

However, discovering antibiotics isn't that easy. For decades, the same molecules have shown up in screening assays designed to find compounds that kill bacteria. This suggests that perhaps millions of organisms must be screened to identify substantially different chemical scaffolds. In addition, antibiotics usually depend on elaborate chemical structures, complicating predictions of the likely drug qualities of a specific compound. These difficulties have greatly dampened enthusiasm for exploring new natural products.

SYNTHETIC SOLUTION

Help is at hand, however. In the mid-1980s, David Hopwood, emeritus fellow at the John Innes Centre in Norwich, UK, demonstrated that scientists can manipulate the genes responsible for producing natural products to generate new compounds. Scientists at Kosan Biosciences in Hayward, California — a company that had Hopwood on its scientific advisory board — later expanded the strategy by inserting these genes in microbes to create compound-making factories. This approach creates libraries of derivatives of natural products by manipulating and mutating these biosynthetic genes. This revolutionary work set the stage for using synthetic biology to empower antibiotic discovery.

Synthetic biology is the application of rational engineering processes to biological systems. It offers solutions to the difficulties of using natural products in antibiotic discovery. In the past, researchers relied on random mutations to create antibiotics from natural products. Now, biological systems can be harnessed in a highly directed fashion to generate new products based on an understanding of the way such systems are assembled from a series of 'parts', such as a natural product's biosynthetic genes, to generate 'devices', such as new production pathways.

To apply synthetic biology to antibiotics, all that was needed was some code to get these factories to work. That came in 2002, from researchers at the Wellcome Trust Sanger Institute in Cambridge, UK, also including Hopwood. The scientists published the genome sequence of the antibiotic-producing bacteria *Streptomyces coelicolor*[1]. Among the bacteria's 8 million base pairs and nearly 8,000 genes were more than 20 new clusters of genes that produce natural products, some of which might work as antibiotics. This work presents opportunities to supercharge traditional approaches to developing antibiotics.

The sequence of *S. coelicolo*r revealed the genetic programs responsible for the biosynthesis of the known natural products produced by this organism, plus a great many other clusters of genes that seem capable of producing other compounds with antibacterial potential. Similar results have since emerged from the genome sequences of dozens of other organisms, demonstrating great potential for the use of synthetic biology to produce natural products. No doubt some of these biosynthetic clusters produce antibiotics, and now they can be found by scanning genomes, instead of screening millions of microbes.

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As an example, my colleagues and I used antibiotic resistance to enrich the collection of bacteria that produce glycopeptide antibiotics. This class of structures includes some well-known antibiotics, including vancomycin. By adding vancomycin to the process of isolating bacteria from soils, we can greatly enrich the collection of glycopeptide producers, as these must be resistant if they are to avoid suicide when they produce glycopeptides themselves. We developed high-throughput techniques that sorted out the structures that resembled antibacterials and eliminated 96% of the unwanted structures[2]. This process provides easy access not only to new antibiotics, but also to new 'parts' — biosynthetic enzymes — for synthetic biology.

The use of directed engineering of gene clusters that produce natural products offers a mechanism to greatly expand the chemical diversity of antibiotic chemical scaffolds. This enables the construction of chemical libraries suitable for screening and optimizing the promising compounds as drug candidates. Furthermore, transferring biosynthetic gene clusters into other host organisms might accelerate the production of desired compounds.

We are at the beginning of what might be a new era in antibiotic drug discovery that is enabled and fuelled by the application of synthetic biology to natural products. ■

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1. Bentley, S. D. *et al. Nature* **417**, 141–147 (2002).
2. Thaker, M. N. *et al. Nature Biotechnol.* **31**, 922–927 (2013).

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