BIOBUSINESS BRIEFS

Roche taps potential antibiotics mine with Warp Drive Bio

Roche has entered into a strategic collaboration with Warp Drive Bio to mine bacterial genomes for novel antibiotics. The terms of the agreement, worth up to US\$387 million, include an option for Roche to have a worldwide license to develop certain classes of antibiotics that emerge from the collaboration.

Numerous pharmaceutical companies have halted or de-emphasized their investments in antibiotic R&D, owing in part to the difficulty of identifying novel chemical scaffolds using target-based or phenotypic screening methods (*Nat. Rev. Drug Discov.* **14**, 529–542; 2015). Only 2 new classes of antibiotics (daptomycin and the oxazolidin-2-ones) have been developed in the past 50 years; the remaining new antibiotics fall into existing classes based on their core chemical structure, most of which were identified during the 1940s and 1950s by screening cultures of soil-dwelling bacteria from the Actinomycetaceae family (actinomycetes) for secreted antimicrobial compounds.

The usefulness of new compounds from existing classes is limited, as antimicrobial resistance mechanisms are often pan-class. “The bottleneck for antibiotics discovery and development has been our lack of ability to produce lead compounds,” says Kim Lewis, a professor at Northeastern University, Boston, USA.

Genome mining, a natural products-based strategy that is being pursued by Warp Drive and others, relies on the identification of bacterial gene clusters that are not expressed under standard laboratory conditions and that encode enzymes involved in the biosynthesis of natural products. The identification of clusters is followed by *in silico* chemical prediction and/or expression of the cluster in cultured bacteria. The rise of genome mining has been possible due to the low cost of DNA sequencing and the advances in computational biology. “Today there are quite powerful computational methods that allow you to predict at least the core chemical structure of compounds,” says Jörn Piel, a professor at ETH Zürich, Switzerland, who mines the genomes of bacterial symbionts of marine animals to find

bioactive molecules. Other companies, such as Lodo Therapeutics, are looking to the human microbiome for new therapeutics.

Warp Drive has chosen to stick with actinomycetes. “We believe that actinomycetes are a tremendous source of chemistry that is medically relevant,” says Daniel Gray, senior director of genomic engineering and discovery at Warp Drive. The database of 135,000 actinomycete genomes that they’ve built comes from “legacy pharma collections that we’ve acquired over the past 5 years to make our own aggregate strain collection,” he explains.

For self-protection, bacteria that produce antibacterial compounds also express molecules that provide resistance to these agents, which can include decoys or additional copies of the antibacterial target itself. Resistance mechanisms are therefore often encoded in the same gene cluster as the antimicrobial agent so that they are expressed simultaneously. Warp Drive is using this observation to identify antibiotic-producing gene clusters. The genomic resolution of Warp Drive’s database is key: “by having the entire genomic sequence we can really pinpoint the boundaries of a particular cluster,” says Gray. Capturing the entire cluster also ensures that the full complement of genes that produce the antimicrobial are identified, which means that the correct chemical structure can be predicted.

“Going after silent operons — ultimately I think it has to work,” says Lewis. “Our sampling capability so far has been extremely small in comparison to the size of the biosphere.” The issue then becomes identifying which of those compounds can be developed into antibiotics suitable for human use. “One must not underestimate the effort required to find those ‘gems’ among the newly identified, presumably previously ‘silent’ gene clusters,” says Tom

“Going after silent operons — ultimately I think it has to work”

Dougherty, a researcher at Harvard Medical School, Boston, USA, who has been involved in many antibiotic discovery programmes. Although numerous antibiotics, mostly from existing classes, have been discovered in the past 20 years, “solubility, poor antimicrobial spectrum, no improvement in activity over existing molecules, mammalian cell toxicity, poor fermentation yields, purification problems and many other factors eliminated the vast majority of compounds from further consideration for development,” he highlights.

Synthetic chemistry could have an important role here. Penetration, particularly into Gram-negative bacteria, has been a major obstacle. Recently, ‘rules of penetration’, analogous to Lipinski’s ‘rule of five’ on physicochemical characteristics that are associated with oral bioavailability, have been developed (*Nature* **545**, 299–304; 2017) (*mBio* **8**, e01172-17; 2017). “Some of these rules are opposite to what I thought — they’re very interesting,” says Lewis. The definition of these rules could help build focused libraries for screening and identify useful scaffolds from genome mining pursuits. “In your structure–activity relationship studies, you can be thinking not only about target binding but also about penetration to that target,” Lewis emphasizes.

The identification of new classes of antibiotics would be a major step forward in the battle against antimicrobial resistance, and genome mining could provide such an advance. “Considering the wealth of unexplored microbes and biosynthetic gene clusters out there, it’s all new territory — it’s really exciting,” says Piel.

Megan Cully