Preclinical antibiotic pipeline gets a pick-me-up

CARB-X, a public–private partnership aimed at bolstering the antibiotic pipeline, funded a diverse set of 17 early-stage drug development projects in its first year.

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The antibiotic pipeline is running dry. An analysis by the WHO of the development landscape for antibiotics aimed at the most dangerous bacterial pathogens found that just nine innovative products are currently in clinical trials. Given high trial failure rates — and warnings that antimicrobial resistance could kill 10 million people a year by 2050 — the need for novel products to test in clinical trials is dire.

To address this long-persisting problem, CARB-X launched last year to accelerate preclinical development projects. Backed by US$455 million over 5 years — from the Wellcome Trust and the Biomedical Advanced Research and Development Authority (BARDA) — the non-profit promised to fund hit-to-lead, optimization and preclinical projects for priority pathogens (*Nat. Rev. Drug Discov.* **15**, 589–590; 2016). One year on, the non-profit has funded "the largest and most diverse preclinical pipeline in the world," says CARB-X executive director, Kevin Outterson.

The portfolio currently includes 17 antibiotics — including 8 small molecules with new chemotypes and 5 non-traditional therapeutics (TABLE 1). CARB-X also funded work on one diagnostic.

"Any activity in this space has to be applauded, and so I'm delighted that it is ongoing and resourced," says Matthew Cooper, an antibiotic researcher at the Institute for Molecular Bioscience in Queensland, Australia, and programme leader at the Community for Open Antimicrobial Drug Discovery (CO-ADD). But other research and funding gaps remain, he adds, including support for academic institutions and basic research projects that search for and experiment with new chemical matter that can penetrate Gram-negative bacteria. "CARB-X is sucking up a lot of good assets that were pre-existing. This is fine. But what comes next?" he asks. "Where are the new chemotypes coming from?"

Priming the pipeline

Since CARB-X's inception, the non-profit has received 368 responses to its calls for proposals (see page 744). "We think of ourselves as knowing a lot about preclinical antibiotic R&D, and our experts thought that they knew most of the antibiotic projects going on in the world," says Outterson. "We were actually surprised by the number of small companies with interesting research projects that were in scope."

"What's not surprising is that most of these little companies are starving for funding, trying to build a company with duct tape and balsa wood," he adds.

"CARB-X really fills an important gap, especially in terms of supporting small companies," says Peter Beyer, senior advisor at the WHO and an author of their antibiotic pipeline review. Most of the clinical-stage candidates that the WHO identified as innovative are being developed by small companies, he adds, highlighting the importance of this sector.

Of the 17 drug discovery projects CARB-X supported in its first year, 12 focus on 'traditional' antibiotics — small-molecule, bacteria-killing drugs.

One-third of these projects are working on drugs with novel chemotypes and new mechanisms of action, offering high development risk but also high reward. For example, two small molecules inhibit LpxC, the enzyme that catalyses the synthesis of lipid A, a key component of the outer monolayer of Gram-negative bacteria. Another third are advancing new chemotypes for established mechanisms of action, such as new topoisomerase and gyrase inhibitors. The last third act via established chemotypes and on established mechanisms of action, with the lowest scientific and developmental risk but also offering the lowest potential antimicrobial resistance payout.

The eight traditional drugs with new chemotypes are the most exciting, says Cooper. If even one makes it to the market, he says, that would be a major advance for the field. "That hasn't happened in years."

CARB-X also funded work on five 'non-traditional' antibiotics, which face an even harder path to the market. Visterra's VIS705, for example, is an antibody–drug conjugate that delivers a one-two punch; the antibody component of the therapy binds to *Pseudomonas* to attract the host's immune system, and at the same time delivers an antimicrobial peptide with high specificity to kill the pathogen. Two anti-virulence projects aim to hobble bacteria by blocking bacterial factors that otherwise promote infection and damage the host (*Nat. Rev. Drug Discov.* **16**, 457–471; 2017).

Although a few anti-virulence factors have been approved for narrow use against Gram-positive bacteria, their utility for Gram-negative bacteria remains to be proved.

Because there is no established regulatory pathway for these non-traditional candidates, CARB-X is working with the FDA and the European Medicines Agency (EMA) to establish a drug development framework. "We want to help take some of the risk out of the equation by working on regulatory as well as scientific questions 5–10 years before anyone needs to have the answers," says Outterson.

On the basis of historic attrition rates, these first 17 projects are likely to yield only 1 or 2 approvals, says Outterson. "We're not going to succeed here unless we actually get a large number of candidates into clinical trials," he adds.

Consequently, CARB-X is working to expand its drug development pipeline. It is already poised to double its pipeline, and is set to issue a third call for proposals soon. "We are not done with any particular chemotype, mechanism of action or modality," adds Outterson.

Other incentives needed

Cooper remains concerned about the longer-term picture. "We need a discovery engine. We haven't had one that has worked for the past 40 years," he says.

Many large pharmaceutical firms have screened their small molecule decks for potent small molecules that can penetrate the outer membranes of Gram-negative bacteria, and have come up lacking (*Nat. Rev. Drug Discov.* **14**, 529–542; 2015). Last year, a report by the Pew Charitable Trust highlighted the need for new chemical matter as a top antibiotic priority.

A few efforts are under way to find these compounds. Cooper's CO-ADD, for example, screens synthesized compounds for free, and without intellectual property restrictions, to identify hits with antimicrobial activity (*Nat. Rev. Drug Discov.* **14**, 587–588; 2015). Millions of compounds have been made in academic and industry labs around the world, but have never been tested for antimicrobial activity, he explains, potentially representing a wealth of untapped chemical diversity. Since launching in 2015, they have screened over 250,000 compounds, and found over

Table 1 | **The CARB-X pipeline**

Drug name	Sponsor	Properties	Indication	Status
Traditional antibiotics				
LPS*‡	Oppilotech	Targets LPS synthesis	Gram-negatives	Hit to lead
Debio1453*‡	Debiopharm	Narrow-spectrum FabI inhibitors	*Neisseria gonorrhoeae*	Lead optimization
FG-LpxC*‡	Forge Therapeutics	LpxC inhibitor	Gram-negatives	Lead optimization
AKAO- LpxC*‡	Achaogen	LpxC Inhibitor	*Pseudomonas aeruginosa*	Preclinical
VNRX-PBP*	VenatoRx	β-Lactamase resistant PBP inhibitor	Enterobacteriaceae	Hit to lead
Gyrox*	Bugworks Research	Gyrase–topoisomerase inhibitor	Gram-negatives	Lead optimization
NBTI*	Redx Pharma	Dual-acting topoisomerase inhibitor	*Acinetobacter*, *P. aeruginosa* and Enterobacteriaceae	Lead optimization
Helical AMP*	EligoChem	Helical antimicrobial peptide	Gram-negatives	Lead optimization
SPR741	Spero Therapeutics	Potentiator	Gram-negatives	Preclinical
ETX0282 CPDP	Entasis Therapeutics	Oral combination	Gram-negatives	Preclinical
Sulopenem	Iterum Therapeutics	Oral and intravenous penem	Gram-negatives	Phase I
TP-6076	Tetraphase Pharmaceuticals	Next-generation tetracycline	*Acinetobacter* and Enterobacteriaceae	Phase I
Non-traditional antibiotics				
Gram-negative lysins‡	ContraFect	Recombinant lysin protein	*P. aeruginosa*	Hit to lead
PEI‡	Antabio	*Pseudomonas* elastase; virulence modifier	*P. aeruginosa*	Lead optimization
T3SS inhibitor‡	Microbiotix	Type III secretion system inhibitor; virulence modifier	*P. aeruginosa*	Lead optimization
VIS705‡	Visterra	Antibody–drug conjugate	*P. aeruginosa*	Lead optimization
CD201‡	Cidara Therapeutics	Bifunctional immunotherapy	*Acinetobacter*, *P. aeruginosa* and Enterobacteriaceae	Preclinical

LPS, lipopolysaccharide; PBP, penicillin-binding protein. *New chemotype. ‡Novel mechanism of action. Pipeline as of 1 October 2017.

120 hits. But more funding so that academic groups can run with any hits that come out of these types of projects is needed, says Cooper.

Another platform approach for discovering new antibiotics relies on a new means of growing bacteria that were previously thought to be unculturable, and exploring whether the natural products these bugs produce have antibacterial activity. The approach is being pioneered by NovoBiotic Pharmaceuticals, and uses an 'iChip' to grow isolated bacteria *in situ* in their natural environment (*Nat. Rev. Drug Discov.* **14**, 153–154; 2015).

Others are hoping that in-depth analyses of the genomes of microorganisms could yet point the way to novel clusters of genes that produce antimicrobials. Warp Drive Bio has been mining bacterial genomes since 2012 to find such leads, and last year handed over a novel aminoglycoside antibiotic with activity against Gram-negative infections to its partner Sanofi for further preclinical and clinical validation.

The Innovative Medicines Initiative (IMI) public–private partnership ENABLE project has also been building a collaborative Gram-negative antibacterial discovery engine. Earlier this year it identified and characterized a new class of antibacterials that use a distinct mechanism of action to perturb DNA gyrase.

On the other end of the drug development spectrum, there are calls for market entry rewards on the order of $1 billion for companies that bring innovative new antibiotics to market (*Nat. Rev. Drug Discov.* **13**, 711–713; 2014). Available antibiotics are cheap, and any new antibiotics that are eventually approved will need to be used as infrequently as possible to delay the emergence of new resistance mechanisms. The antibiotic market is consequently unappealing, especially when compared with the potential profit margins for oncology or chronic disease drugs. A large market-entry pull incentive might increase market appeal, say advocates, potentially translating into renewed investment in antibiotic research, discovery and development.

But for Tom Frieden, president of the global health initiative Resolve and former director of the US Centers for Disease Control and Prevention (CDC), the focus on antibiotics is just one piece of a large and complex puzzle. "CARB-X, and any programme that can further this development are important," he says. "But we also need research to develop rapid diagnostics to distinguish drug-resistant from drug-susceptible infections, new vaccines and better ways to prevent infections from spreading, particularly in hospitals," he says.