BIOBUSINESS BRIEFS

MARKET WATCH

# Innovation in the preclinical antibiotic pipeline

Antibiotic resistance is high on the political agenda and improving the antibiotic R&D pipeline is one of the major action points. The Combating Antibiotic Resistant Bacteria Biopharmaceutical Accelerator (CARB-X) supports antibacterial projects through early preclinical development, with a 5-year budget totalling US$455 million (*Nat. Rev. Drug Discov.* **15**, 589–590; 2016). Since its inception in July 2016, 368 applications from around the world have been submitted. This pool of information provides a reasonable approximation of global preclinical antibiotic R&D activities and was used for this analysis. Of 368 submitted projects, we excluded funding requests for diagnostics and out-of-scope applications, leaving 254 applications for analysis (FIG. 1).

More than 50 small-molecule preclinical projects among the CARB-X submissions focused on at least one of the critical priority pathogens on the WHO global priority list that was recently published to guide antibiotic R&D, which are all extensively drug-resistant Gram-negative bacteria. The small molecules being investigated by these projects belong to new chemical and/or functional classes with no anticipated cross-resistance to existing classes (FIG. 1a). These projects exhibit considerable diversity, with several clusters (FIG. 1b) as well as a large group of projects classified as 'other'. The largest cluster are membrane-targeting agents, including compounds modelled on natural antimicrobial peptides. There is also a substantial cluster of agents that inhibit LpxC, the enzyme responsible for the first committed step in the biosynthesis of lipid A — a key component of the outer membrane of Gram-negative bacteria.

Another prominent trend is the strong focus on biologics, including antibodies, antibacterial vaccines, antibody–drug conjugates and other large molecules (FIG. 1a). Such pathogen-specific strategies are usually intended for pre-emptive use. Some of these biologics target bacterial virulence factors, and it is notable that there are also multiple small-molecule projects targeting bacterial virulence mechanisms in other ways. Phage-related products are also prominent (FIG. 1a). In contrast to earlier years, there are fewer projects with phage cocktails, and more genetic engineering efforts, using phages for delivery and phage products such as endolysins as starting points.

Innovation in antibiotics against Gram-positive bacteria is also needed for future resistance problems. Several novel chemical scaffolds and targets for Gram-positive bacteria are present in the pipeline (FIG. 1a). In contrast to the preclinical pipeline a decade ago, the decrease in the

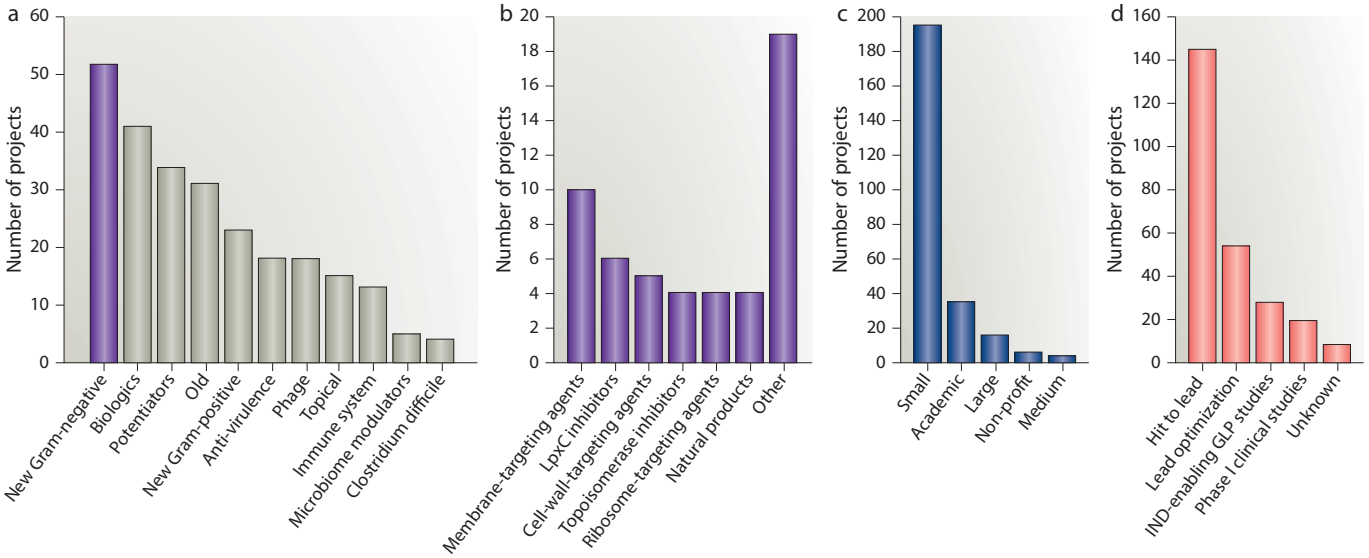


Figure 1 | **Analysis of CARB-X applications.** The data presented are derived from 254 applications received from August 2016 to January 2017. **a** | Project characteristics. New Gram-negative projects investigate novel small molecules that are active against at least one of the WHO critical priority pathogens, with potentially no cross-resistance for existing classes. Biologics include antibodies, antibody–drug conjugates, antibody-derived approaches and vaccines; 15 of these target Gram-negative pathogens. Potentiators include β-lactamase inhibitors, synergistic pencillin-binding protein (PBP)-binders, efflux pump inhibitors, resistance regulator inactivators, resistance preventers and membrane permeabilizers. Old projects include modification of old classes, combinations of old antibiotics and/or other off-patent drugs, and transporter conjugates. New Gram-positive projects investigate novel small molecules with activity against multidrug-resistant Gram-positive pathogens, with potentially no cross-resistance for existing classes. Anti-virulence projects investigate small molecules, including those targeted at biofilms and persisters, and inducers of autophagy; some biologics also target virulence factors. Phage projects include phage cocktails, engineered phages, phage delivery and phage-related approaches including CRISPR technologies and lysins. Topical projects are for superficial skin and wound infections. Immune system projects boost immune functions non-specifically. Microbiome projects are therapeutics containing defined or engineered bacteria. **b** | Characteristics of projects in the new Gram-negative category ($n = 52$). **c** | Developing institutions ($n = 254$). The academic category includes universities or other university-associated institutions; small companies have <500 employees (most have <100 employees); medium-sized companies have 500–5,000 employees and large companies have >5,000 employees. **d** | R&D stage of the applications. GLP, good laboratory practice; IND, investigational new drug.

number of submitted funding applications in the Gram-positive field may reflect the CARB-X focus on Gram-negative bacteria, but also the shift in global priority to Gram-negative bacteria and the availability of several current and future antibiotic options for infections caused by Gram-positive bacteria.

Overall, the analysis of this project sample shows reasonable convergence with the WHO critical priority pathogens and a promising trend of innovative projects that has not been seen in the clinical pipeline (see the WHO report in Further information). Although innovative projects are riskier than modifications of known chemical scaffolds, such innovative drugs are urgently needed against the most-resistant bacteria. Many innovative non-traditional approaches may not translate into a measurable benefit for patients in the near future, but may still provide valuable insights for future progress in treatment strategies. Finally, most projects were submitted by small companies (FIG. 1c) and were at the hit-to-lead stage (FIG. 1d). Given this, and that the attrition rates are extremely high for innovative approaches, more incentives and support are needed to maintain this positive momentum as these projects move towards clinical studies.

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**Competing interests statement**
The authors declare no competing interests.

**DATABASES**
**WHO. Global priority list of antibiotic-resistant bacteria to guide research, discovery, and development of new antibiotics:** http://www.who.int/medicines/publications/WHO-PPL-Short_Summary_25Feb-ET_NM_WHO.pdf
**WHO. Antibacterial agents in clinical development:** http://apps.who.int/iris/bitstream/10665/258965/1/WHO-EMP-IAU-2017.11-eng.pdf
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