PUBLISHED: 25 APRIL 2017 | VOLUME: 2 | ARTICLE NUMBER: 17071

editorial

Counter resistance

If we are to be successful in keeping priority pathogens at bay in the long term, global responses to antimicrobial resistance should embrace and fund innovative therapeutic strategies that are developed in the basic microbiology laboratory.

The global threat posed by antimicrobial resistance (AMR) continues to demand the attention of health bodies and policy makers. March 2017 witnessed the announcement by the United Nations (UN) secretary-general António Guterres of the formal launch of the *ad hoc* Interagency Coordination Group on AMR, following on from the UN High-Level Meeting on Antimicrobial Resistance that was held in September 2016 (see 'Resistance ascends the political summit'[1]). The group is comprised of high-level representatives from relevant UN agencies, international organizations and select experts on AMR from various sectors. Its aim will be to provide guidance on the most effective and sustainable approaches to tackle AMR at a global level, although precisely what will be on the agenda remains to be seen.

Preceding the first meeting of the Interagency Coordination Group, March also saw publication of a global priority pathogen list of antibiotic-resistant bacteria (http://go.nature.com/2nJ8JaF) by the World Health Organization (WHO) — one of the group's member agencies. The aim for the list is to help focus research and development of new antibiotics, and raise political and public health awareness. The list was developed by a panel of experts based on a range of criteria and is stratified into three priority tiers: on the critical-priority list are carbapenem-resistant *Acinetobacter baumannii* and *Pseudomonas aeruginosa*, as well as *Enterobacteriaceae* that are resistant to carbapenems and third-generation cephalosporins; on the high-priority list are vancomycin-resistant *Enterococcus faecium*, methicillin- and vancomycin-resistant *Staphylococcus aureus*, clarithromycin-resistant *Helicobacter pylori*, fluoroquinolone-resistant *Campylobacter* and *Salmonella* spp., and *Neisseria gonorrhoea* resistant to fluoroquinolones and third-generation cephalosporins; on the medium-priority list are penicillin-tolerant *Streptococcus pneumoniae*, ampicillin-resistant *Haemophilus influenzae*, and fluoroquinolone-resistant *Shigella* spp. Notable by their absence were multidrug-resistant (MDR) and extensively drug-resistant (XDR) *Mycobacterium tuberculosis*, which the WHO noted were not included in the review process as tuberculosis (TB) "is already a globally established priority for which innovative new treatments are urgently needed". This exclusion is curious, and unnecessarily rankled TB researchers and campaigners (http://go.nature.com/2o9bwgr), as simply including TB in the analysis and assigning it to a tier need not have detracted attention, or funds, from the other pathogens listed. The WHO panel recommend a future focus on the discovery and development of new antibiotics against these MDR and XDR Gram-negative bacteria, especially drugs that are targeted at the paediatric population, and for oral formulations in the case of community diseases with high morbidity.

While the call to discover and develop new antibiotics against these bacterial pathogens is a no-brainer, the emergence of resistance does not, in all cases, necessarily mean that a weapon now blunted must be removed from the armoury for good; swords can be re-sharpened. Interest has grown recently in devising strategies to reverse or overcome resistance and enable a drug that is ineffective to kill once again. In a recent example, Alain Baulard and colleagues developed compounds that could help to overcome resistance against the second-line TB drug ethionamide (ETH)[2]. ETH requires bioactivation by *M. tuberculosis* to convert it from prodrug to active form, making ETH vulnerable to mutations occurring in *ethA*, which encodes the monooxygenase responsible for activating the prodrug. Baulard and colleagues found that the spiroisoxazoline compound SMARt-420 could trigger a cryptic, second ETH bioactivation pathway by binding to the transcriptional repressor EthR2, thereby increasing expression of *ethA2*, which can also convert ETH into its active form, overcoming resistance mutations in *ethA* and reducing bacterial load in the lungs of mice.

Another anti-resistance example is provided in this issue of *Nature Microbiology*, with the demonstration by Eric Brown and colleagues that an anti-protozoal drug can sensitize Gram-negative pathogens — including those resistant to colistin — to antibiotics typically restricted to targeting Gram-positive bacteria[3]. In a screen for non-lethal compounds that perturb the Gram-negative bacterial outer membrane, the authors found that pentamidine, which is used for the treatment of pneumocystis pneumonia and West African trypanosomiasis, potentiated the activity of rifampicin, novobiocin and erythromycin against *Escherichia coli*. Furthermore, in a systemic murine infection model for infection with *A. baumannii*, pentamidine potentiated the effects of novobiocin, with 100% survival of mice treated at doses much lower than the equivalent therapeutic doses in humans. Even for colistin-resistant *A. baumannii*, 10 out of 11 mice were rescued by pentamidine in combination with novobiocin, with total clearance of bacteria from the spleen, suggesting promise as a potential adjuvant for treating infections by bacteria that are becoming resistant to last-line antibiotics.

Beyond using adjuvants, others have sought to genetically undo resistance. For example, Udi Qimron and colleagues previously provided proof of principle that phage can be used to deliver wild-type alleles of genes that then act in a dominant fashion to resensitize the cell to antibiotics[4]. The same group have also used phage to deliver a functional CRISPR–Cas system into the genome of a resistant bacterium, which upon expression destroys antibiotic-resistance-conferring plasmids, thereby sensitizing the cells to the drug once more[5].

If we are to rise to the challenge posed by antibiotic-resistant bacteria, whether on a priority list or not, then a range of imaginative strategies, including those for reversing or overcoming resistance, will need to be conceived in the basic microbiological research laboratory and then nurtured as they grow to become useful new tools. While tackling the serious structural problems associated with antimicrobial development, manufacture and stewardship, members of the Interagency Coordination Group on AMR would be wise to recognize the important role that fundamental research will have in providing the groundwork on which we can build a new therapeutic armoury. ❐

References

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