IN BRIEF

CARDIOVASCULAR DISEASE

GPR146 inhibition protects against atherosclerosis

Human genetic studies have established the orphan G protein-coupled receptor gene, *GPR146*, as a regulator of plasma cholesterol levels. In line with these findings, Yu et al. report that depletion of GPR146 in mice substantially reduces circulating LDL-cholesterol and triglyceride levels, through activation of ERK signalling and promotion of SREBP2 activity. The lipid-lowering effects of GPR146 depletion protected mice against atherosclerosis in an LDL receptor (LDLR)-independent manner, reducing lesion area by up to 90%. Injection of $LDLR^{-/-}$ mice with an AAV-delivered shRNA targeting GPR146 lowered plasma total cholesterol levels.

ORIGINAL ARTICLE Yu, H. et al. GPR146 deficiency protects against hypercholesterolemia and atherosclerosis. *Cell* **179**, 1276–1288 (2019)

INFECTIOUS DISEASE

Reversing resistance to MRSA

Strategies to tackle the growing threat of methicillin-resistant *Staphylococcus aureus* (MRSA) are urgently needed. Through a cell-based, high-throughput screen, El-Halfawy et al. identify MAC-545496, which inhibits glycopeptide-resistance-associated protein R, a regulator of the cell-envelope stress response that is an important virulence factor and determinant of antibiotic resistance. MAC-545496 reversed β-lactam resistance in a community-acquired MRSA strain, inhibited biofilm formation, abrogated intracellular survival in infected macrophages and attenuated virulence in a *Galleria mellonella* larvae infection model.

ORIGINAL ARTICLE El-Halfawy, O. M. et al. Discovery of an antivirulence compound that reverses β-lactam resistance in MRSA. *Nat. Chem. Biol.* https://doi.org/10.1038/s41589-019-0401-8 (2019)

CANCER

Decoy receptor targets lung cancer

The cardiotrophin-like cytokine factor 1 (CLCF1)–ciliary neurotrophic factor receptor (CNTFR) signalling axis has been identified as a potential therapeutic target in lung adenocarcinoma (LUAD). Here, Kim et al. engineer a high-affinity soluble decoy receptor (eCNTFR–Fc) that sequesters CLCF1 and neutralizes its activity. eCNTFR–Fc was particularly effective in cell lines and patient-derived xenograft models carrying oncogenic *KRAS* mutations. In a highly aggressive genetically engineered mouse model of LUAD, eCNTFR–Fc decreased tumour burden and increased survival comparably to cisplatin, but without toxic side effects.

ORIGINAL ARTICLE Kim, J. W. et al. Antitumor activity of an engineered decoy receptor targeting CLCF1–CNTFR signaling in lung adenocarcinoma. *Nat. Med.* **25**, 1783–1795 (2019)

NEURODEGENERATIVE DISORDERS

Lowering mutant huntingtin protein

Harnessing the power of autophagy to degrade disease-causing proteins may have potential for drug discovery. Using small-molecule microarray-based screening, Li et al. identify compounds that interact with mutant huntingtin (mHTT) and the autophagosome protein microtubule-associated protein 1A/1B light chain 3 (LC3). By interacting with the expanded polyQ tract in mHTT, these mHTT–LC3 linker compounds specifically directed mHTT, but not wild-type HTT, to autophagosomes. The compounds rescued mHTT toxicity in neurons derived from induced pluripotent stem cells from patients with Huntington disease (HD) and reversed HD-relevant behavioural phenotypes in fly and mouse models of HD.

ORIGINAL ARTICLE Li, Z. et al. Allele-selective lowering of mutant HTT protein by HTT–LC3 linker compounds. *Nature* **575**, 203–209 (2019)

ANTIBIOTICS

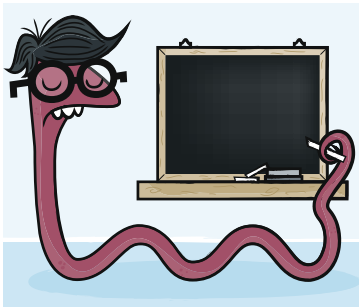
Learning from worms to kill Gram-negative bacteria

New options to combat antibiotic-resistant Gram-negative bacteria are a critical priority, but the protective nature of their outer membrane (OM) makes finding small-molecule drugs to target these pathogens particularly challenging. Imai, Myer et al. have now identified a new antibiotic that shows in vivo activity against important Gram-negative pathogens in animal models by screening the microbiomes of nematode worms that infect and kill insects.

Imai, Myer and colleagues reasoned that bacteria that may also benefit from antimicrobials active against Gram-negative bacteria with low toxicity to animals and good pharmacokinetic characteristics could be a promising source of antibiotics. Following this logic, they focused on a group of bacteria that have a symbiotic relationship with nematodes. These bacteria, such as *Photorhabdus* and *Xenorhabdus*, are part of the nematode gut microbiome, and one of their roles is to fend off Gram-negative bacteria once a nematode has invaded its insect prey.

The authors selected 67 *Photorhabdus* and *Xenorhabdus* strains, and screened them for antimicrobial compounds against *Escherichia coli*. A concentrated extract from *Photorhabdus khanii* HGB1456 harboured a novel active antimicrobial, darobactin (M_r 966), a heptapeptide cyclized with two unusual aromatic–aliphatic linkages. Analysis of the *P. khanii* genome revealed that darobactin is ribosomally synthesized by an operon named *dar*, including *darE*, which encodes a radical SAM enzyme that seems to be responsible for the linkages.

Mechanistic studies showed that darobactin's activity results from broadly activating envelope stress pathways, leading to membrane blebbing, swelling and lysis. Sequence analysis of darobactin-resistant mutants revealed that darobactin's direct target is BamA, an OM protein.



Credit: N.Smith/Springer Nature Limited

Darobactin directly binds to BamA and inhibits its activity — mediating the folding and insertion of nascent porins from the periplasm to the OM — in vitro (K_d = 1.2 μM and IC_{50} = 0.68–1 μM). This antimicrobial stabilizes BamA's closed gate conformation, which probably prevents substrate exit into the OM.

Darobactin showed activity against key drug-resistant pathogens, such as *E. coli* and *Klebsiella pneumoniae*, but was essentially inactive against gut commensals, including those important for human health. In single-dose pharmacokinetic analysis from intraperitoneal injection (50 mg kg^{-1}) in vivo, darobactin achieved good exposure, maintaining blood levels above the *E. coli* minimum inhibitory concentration for 8 h. When evaluated in mouse septicaemia models, infected with both wild-type and multidrug-resistant Gram-negative strains, darobactin completely protected animals. It also significantly decreased pathogen burden in neutropenic mice infected with *E. coli mcr-1*.

Excitingly, *dar*-type operons are present in other animal-associated bacterial species, and such species could be a much-needed source of novel antimicrobials.

Stacey-Lynn Paiva

ORIGINAL ARTICLE Imai, Y. et al. A new antibiotic selectively kills Gram-negative pathogens. *Nature* https://doi.org/10.1038/s41586-019-1791-1 (2019)
RELATED ARTICLES Lewis, K. Platforms for antibiotic discovery. *Nat. Rev. Drug Discov.* **12**, 371–387 (2013) | Lepore, C. et al. The small-molecule antibiotics pipeline: 2014–2018. *Nat. Rev. Drug Discov.* **18**, 739 (2019)