IN BRIEF

HIV

Inhibiting the HIV capsid protein

New approaches to treating HIV infection are needed, given the development of multidrug resistance and current daily antiretroviral regimens. Here, Link et al. present the small molecule GS-6207, which targets the HIV-1 capsid protein to disrupt viral replication. In vitro, GS-6207 exhibited picomolar antiviral activity against all subtypes of HIV-1 tested and displayed synergy when combined with other antiretroviral agents, without cross-resistance or cytotoxicity. In 40 healthy participants, a single subcutaneous injection of GS-6207 was safe and well tolerated, remaining active for more than 24 weeks. In 32 patients with untreated HIV-1 infection, a single dose of GS-6207 reduced viral load by the ninth day.

ORIGINAL ARTICLE Link, J. et al. Clinical targeting of HIV capsid protein with a long-acting small molecule. *Nature* https://doi.org/10.1038/s41586-020-2443-1 (2020)

AUTOIMMUNE DISEASE

Selectively targeting pathogenic T_H17 cells

Targeting inflammatory T_H17 cells can effectively treat autoimmune diseases, but existing approaches also inhibit homeostatic T_H17 cells, thereby increasing the risk of infection. Here, Wu et al. report that inflammatory T_H17 cells in the spinal cord of EAE mice express higher levels of glycolysis pathway genes than commensal bacteria-induced homeostatic T_H17 cells. Specific knockout of glucose phosphate isomerase selectively eliminated inflammatory T_H17 cells. Unlike homeostatic T_H17 cells, inflammatory T_H17 cells could not compensate by pentose phosphate pathway flux and increased mitochondrial respiration, owing to their hypoxic environment.

ORIGINAL ARTICLE Wu, L. et al. Niche-selective inhibition of pathogenic T_H17 cells by targeting metabolic redundancy. *Cell* https://doi.org/10.1016/j.cell.2020.06.014 (2020)

CANCER

Targeting CD70 in acute myeloid leukaemia

Hypomethylating agents (HMAs) are the mainstay of therapy for older or unfit patients with AML, but responses are limited and relapse occurs. Riether et al. show that HMA treatment increases the expression of CD70 on cultured leukaemic stem cells (LSCs, the major cause of relapse) from patients with AML, leading to increased CD70/CD27 signalling. The αCD70 mAb cusatuzumab eradicated LSCs in vitro and in a patient-derived xenograft model. In a phase I/II trial in untreated older patients with AML, one dose of cusatuzumab followed by combination therapy with the HMA azacitidine reduced LSCs and led to complete remission in 66% of patients.

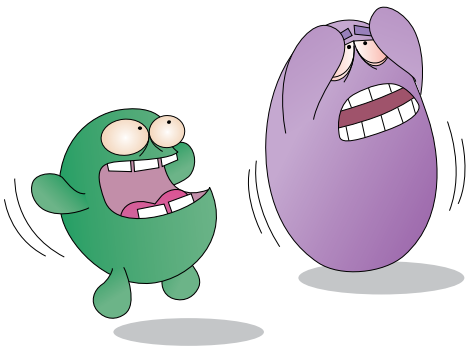
ORIGINAL ARTICLE Riether, C. et al. Targeting CD70 with cusatuzumab eliminates acute myeloid leukemia stem cells in patients treated with hypomethylating agents. *Nat. Med.* https://doi.org/10.1038/s41591-020-0910-8 (2020)

GENETIC DISORDERS

ASO rescues Pelizaeus-Merzbacher disease

No effective therapies exist for the X-linked leukodystrophy Pelizaeus-Merzbacher disease (PMD), caused by mutations in the proteolipid protein 1 gene *Plp1*, and characterized by loss of myelinating oligodendrocytes. Elitt et al. show that CRISPR–Cas9-mediated germline suppression of *Plp1* in a mouse model of severe PMD restored oligodendrocytes, functional myelin and lifespan. Postnatal injection of a *Plp1*-targeting antisense oligonucleotide decreased Plp1 protein, partially restored myelination and rescued oligodendrocyte numbers, improved motor and respiratory function, and extended lifespan.

ORIGINAL ARTICLE Elitt, M. et al. Suppression of proteolipid protein rescues Pelizaeus-Merzbacher disease. *Nature* https://doi.org/10.1038/s41586-020-2494-3 (2020)



Credit: Philip Patenall/ Springer Nature Limited

ANTIBACTERIAL DRUGS

Two birds with one stone

Since the 1960s, there has been a decline in the discovery of new antibiotics, particularly against Gram-negative bacteria. Increases in antibiotic resistance call for an urgent need to identify suitable candidates for broad-spectrum antibiotics with novel mechanisms of action (MoA).

In a recent study, Martin, Sheehan, Bratton et al. used a small-molecule screen to identify a compound (SCH-79797) that shows promising bactericidal activity against both Gram-positive and Gram-negative bacteria. After confirming antibiotic activity against a variety of pathogens in vitro, the authors showed that SCH-79797 is effective against a lethal dose of *Acinetobacter baumannii* in the wax worm *Galleria mellonella*, prolonging survival without any noticeable toxicity. The authors found that SCH-79797 has a low frequency of resistance in methicillin-resistant *Staphylococcus aureus* and *A. baumannii* in vitro. Remarkably, no resistant clones emerged, despite using sub-lethal concentrations over 5–30 passages, indicating sustained action that is not species specific.

To investigate the MoA, the authors turned to image-based bacterial cytological profiling and compared cell death phenotypes between SCH-79797 and established antibiotics with known MoAs. Their analysis showed that the MoA of SCH-79797 was distinct from any other tested antibiotic. Using high-throughput thermal proteome profiling followed by a screen with a *Bacillus subtilis* CRISPRi knockdown library, the authors identified a dihydrofolate reductase (DHFR; an *Escherichia coli* FolA homologue) as the target of SCH-79797. In vitro enzyme assays showed that SCH-79797 directly inhibits DHFR activity. SCH-79797 was also found to be distinct from other FolA inhibitors like trimethoprim, in that it also affects bacterial cell membrane integrity, conferring a dual MoA. The authors also observed that a single treatment with SCH-79797 was more potent than a combination of two antibiotics — trimethoprim and nisin, or polymyxin B and daptomycin.

Delving into the chemistry behind the dual MoA, the authors found that the pyrroloquinazolinediamine core of SCH-79797 contributes to DHFR inhibition while the hydrophobic isopropylbenzene targets membrane integrity. To further demonstrate this, they synthesized a derivative, Irresistin-16 (IRS-16), that is more hydrophobic than SCH-79797. IRS-16 recapitulated the dual MoA on bacteria both in culture and in vivo, reducing the vaginal burden of *Neisseria gonorrhoeae* in a mouse infection model for gonorrhoea.

In sum, this study presents a promising candidate for a novel broad-spectrum antibiotic and highlights the potential in combining multiple MoAs into a single chemical for the treatment of diverse bacterial pathogens.

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ORIGINAL ARTICLE Martin, J. K. II, et al. A dual-mechanism antibiotic kills Gram-negative bacteria and avoids drug resistance. *Cell* https://doi.org/10.1016/j.cell.2020.05.005 (2020)