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IN BRIEF

ANTIBIOTICS

Reversing resistance

Acquired *Mycobacterium tuberculosis* resistance to the commonly used antibiotic ethionamide (ETH) is mediated by mutations in the bacterial enzymatic pathway that is required for biological activation of the drug. Here, Blondiaux *et al.* identify a series of spiroisoxazoline compounds — named small molecules aborting resistance (SMARt) — which trigger an alternative activation pathway for ETH. The combination of SMARt-420 plus ETH was active against a panel of drug-resistant clinical *M. tuberculosis* strains and in mice infected with an ETH-resistant strain of *M. tuberculosis*.

ORIGINAL ARTICLE Blondiaux, N. *et al.* Reversion of antibiotic resistance in *Mycobacterium tuberculosis* by spiroisoxazoline SMARt-420. *Science* **355**, 1206–1211 (2017)

VIRAL INFECTIONS

Targeting host kinases

Targeting host pathways that are exploited by viruses represents a promising antiviral strategy. Bekerman *et al.* show that the host cell kinases AP2-associated protein kinase 1 (AAK1) and cyclin G-associated kinase (GAK), which activate the host adapter proteins AP1 and AP2, are required by hepatitis C virus, dengue virus (DENV) and Ebola virus (EBOV) for host infection. In cells, the anticancer kinase inhibitors sunitinib and erlotinib (which inhibit AAK1 or GAK) exhibited antiviral activity against multiple viruses. In mouse models of DENV and EBOV infections, the combination of both drugs reduced viral load and increased survival.

ORIGINAL ARTICLE Bekerman, E. *et al.* Anticancer kinase inhibitors impair intracellular viral trafficking and exert broad-spectrum antiviral effects. *J. Clin. Invest.* http://dx.doi.org/10.1172/JCI89857 (2017)

CANCER

Identifying synergistic drug combinations

Drug combinations are commonly used to counter drug resistance in cancer therapy. To identify synergistic drug target combinations, Han *et al.* have developed a scalable CRISPR-based double-knockout system that enables parallel pairwise gene knockout. Application of this system in a chronic myeloid leukaemia (CML) cell line generated the largest mammalian genetic interaction map to date, which comprises 490,000 single guide RNAs against 21,321 drug target combinations. The predicted target pairs translated to potent synergistic drug combinations in CML cells, including imatinib-resistant cells.

ORIGINAL ARTICLE Han, K. *et al.* Synergistic drug combinations for cancer identified in a CRISPR screen for pairwise genetic interactions. *Nat. Biotech.* http://dx.doi.org/10.1038/nbt.3834 (2017)

G PROTEIN-COUPLED RECEPTORS

Novel probe for MRGPRX2

The orphan MAS-related G protein-coupled receptor member X2 (MRGPRX2) is expressed primarily in human dorsal root ganglia and mast cells, and has been suggested to modulate pain and itch. Using a high-throughput screen of 5,695 unique compounds, Lansu *et al.* discovered that many exogenous and endogenous opioids are agonists of MRGPRX2. Subsequent *in silico* structure-based modelling and docking identified the potent and highly selective MRGPRX2 probe ZINC-3573. The MRGPRX2-activating opioids and ZINC-3573 induced intracellular Ca^{2+} release and degranulation in a human mast cell line.

ORIGINAL ARTICLE Lansu, K. *et al. In silico* design of novel probes for the atypical opioid receptor MRGPRX2. *Nat. Chem. Bio.* http://dx.doi.org/10.1038/nchembio.2334 (2017)