IN BRIEF

GENETIC DISORDERS

Antifungal agent fights cystic fibrosis

Cystic fibrosis (CF) is caused by loss-of-function mutations in the CF transmembrane conductance regulator, which result in compromised epithelial HCO_3^- and Cl^- secretion, reduced airway surface liquid (ASL) pH and impaired respiratory host defences. Now, Muraglia et al. report that amphotericin B — a small-molecule natural product that forms unselective ion channels and is currently used as an antifungal agent — restored HCO_3^- secretion, ASL pH, viscosity and antibacterial activity in cultured airway epithelia from patients with CF and increased ASL pH in a pig model of CF.

ORIGINAL ARTICLE Muraglia, K. A. et al. Small-molecule ion channels increase host defences in cystic fibrosis airway epithelia. *Nature* **567**, 405–408 (2019)

CANCER

Targeting EBV-associated malignancies

Epstein–Barr virus (EBV) establishes lifelong latent infection in most adults and is the cause of a wide range of cancers. Here, Messick et al. combined a fragment-based approach and X-ray crystallography to identify small-molecule inhibitors of Epstein–Barr nuclear antigen 1 (EBNA1), which is consistently expressed in all EBV-positive tumours. A 2,3-disubstituted benzoic acid compound series was identified that potently and selectively inhibited EBNA1 DNA binding activity in vitro, and blocked tumour growth and increased survival in EBV-dependent mouse xenograft models.

ORIGINAL ARTICLE Messick, T. E. et al. Structure-based design of small-molecule inhibitors of EBNA1 DNA binding blocks Epstein-Barr virus latent infection and tumor growth. *Sci. Transl Med.* **11**, eaau5612 (2019)

INFECTIOUS DISEASES

Inhibiting *Wolbachia* to treat parasitic diseases

There is an urgent need for novel treatments for the neglected tropical diseases onchocerciasis and lymphatic filariasis, caused by filarial parasites. By screening a library of anti-infective compounds, Taylor et al. found the macrolide veterinary antibiotic, tylosin A, to potently inhibit the bacterial endosymbiont *Wolbachia* — necessary for the viability and fertility of filarial worms. The orally available tylosin A analogue, A-1574083, depleted *Wolbachia* and microfilarial worm loads in mouse and gerbil infection models of lymphatic filariasis, with superior efficacy to tetracycline antibiotics. No adverse effects were observed in dog and rat toxicology studies.

ORIGINAL ARTICLE Taylor, M. J. et al. Preclinical development of an oral anti-*Wolbachia* macrolide drug for the treatment of lymphatic filariasis and onchocerciasis. *Sci. Transl Med.* **11**, eaau2086 (2019)

CANCER

Targeting macrophages enhances chemotherapy

Tumour-associated myeloid cells have been associated with limited chemotherapy efficacy and poor prognosis. In mouse models of breast cancer, Salvagno et al. show that the monoclonal antibody 2G2, which targets the colony-stimulating factor 1 receptor required for macrophage development and tumour infiltration, abates tumour-associated macrophage numbers and synergizes with cisplatin to inhibit tumour growth and extend survival, by triggering an intratumoural type I interferon response. Eliminating immunosuppressive neutrophils further increased tumour response to cisplatin.

ORIGINAL ARTICLE Salvagno, C. et al. Therapeutic targeting of macrophages enhances chemotherapy efficacy by unleashing type I interferon response. *Nat. Cell Biol.* https://doi.org/10.1038/s41556-019-0298-1 (2019)

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VIRAL INFECTION

Antibody-inspired small molecule for influenza A

Influenza infections can lead to severe illness and are responsible for up to an estimated 650,000 deaths worldwide annually. The existence of broadly neutralizing antibodies (bnAbs) that target the conserved stem of the viral envelope glycoprotein haemagglutinin (HA) suggests that strain-agnostic therapeutics could be developed. Now, an orally available small molecule that binds to the region of HA that is targeted by bnAbs has been developed. This molecule protected mice from a lethal challenge with influenza virus.

Influenza A can be classified into eighteen HA subtypes, each of which is in one of two phylogenetic groups. Most seasonal influenza vaccines contain attenuated or inactivated virus, and are only effective against a few subtypes. Furthermore, the relative abundance of different viral strains varies from year to year, and vaccine developers must alter their vaccine composition accordingly each year. A bnAb, CR6261, was identified that has activity against group 1 influenza A viruses, providing evidence that targeting the bnAb binding site could have cross-strain and cross-subtype efficacy, meaning that prophylactics would not have to change each year.

In the recently published article, a library of ~500,000 compounds was screened to identify molecules that could displace HB80.4, a computationally designed peptide that binds to the same region of the HA stem as CR6261. Numerous benzylpiperazines displaced HB80.4, and the top benzylpiperazine hit, JNJ6715, was used for further development.

Medicinal chemistry optimization of JNJ6715 to improve solubility and stability identified JNJ4796. JNJ4796 is bioavailable, has a half-life of 2.4 hours in mice after oral administration and does not substantially modulate relevant human proteins.

Both CR6261 and JNJ4796 inhibit a conformational change in HA, induced by low pH, that triggers viral fusion. The antibody and the small molecule bind components of two HA monomers that are present in the trimeric stem. In conformational change inhibition assays and protease-susceptibility assays, these two agents prevented HA from adopting the low-pH-induced conformation.

The authors tested JNJ4796 in a lethal influenza challenge mouse model. Oral administration of JNJ4796, commencing 1 day before lethal challenge, protected 100% of mice from 25 times the median lethal dose of a mouse-adapted strain of influenza A. Furthermore, in a 3D cell culture model of human bronchial epithelial cells that was infected with influenza A virus, treatment with JNJ4796 reduced viral titres 96 hours post-infection.

These data suggest that orally available small molecules that target the bnAb binding site could provide cross-strain protection from influenza infection.

Megan Cully

ORIGINAL ARTICLE van Dongen, M. J. P. et al. A small-molecule fusion inhibitor of influenza virus is orally active in mice. *Science* **363**, eaar6221 (2019)