IN BRIEF

GENOME EDITING

Controlling CRISPR–Cas9 activity

The activity of CRISPR–Cas9 must be precisely controlled for safe application in genome-engineering technologies. To address this, Maji et al. develop a series of high-throughput assays to screen small-molecule libraries, derived from diversity-oriented synthesis, for *Streptococcus pyogenes* Cas9 (spCas9)–DNA binding and spCas9 DNA-cutting activity. The screen identified BRD0539 as a potent inhibitor of spCas9, which was validated in cell-based assays. The small molecule disrupted spCas9–DNA binding and exerted dose and temporal control of spCas9 in human cell lines. Importantly, BRD0539 was stable in human plasma.

ORIGINAL ARTICLE Maji, M. et al. A high-throughput platform to identify small-molecule inhibitors of CRISPR–Cas9. *Cell* **177**, 1067–1079 (2019)

INFECTIOUS DISEASES

Towards a vaccine for equine encephalitis viruses

There are no approved treatments or vaccines for the mosquito-borne alphaviruses, Western, Eastern and Venezuelan equine encephalitis viruses (WEEV, EEEV and VEEV). Here, Ko et al. develop a trivalent virus-like particle-based vaccine comprising a plasmid encoding structural proteins for WEEV, EEEV and VEEV. In non-human primates (NHPs), vaccine immunization stimulated neutralizing antibody responses against each EEV and resulted in full protection against aerosol challenges of all three EEVs. Passive transfer of IgG from immunized NHPs into mice conferred protective immunity.

ORIGINAL ARTICLE Ko, S.-Y. et al. A virus-like particle vaccine prevents equine encephalitis virus infection in nonhuman primates. *Sci. Transl Med.* **11**, eaav3113 (2019)

TYPE 2 DIABETES

Inhibiting insulin degradation

Insulin-degrading enzyme (IDE) — a metalloprotease that can modulate blood glucose levels by degrading insulin or glucagon — represents an attractive target for the treatment of type 2 diabetes. To identify substrate-selective IDE inhibitors (SSIs) that block insulin degradation, but not glucagon degradation, Maianti et al. carried out a high-throughput small-molecule screen for exo-site ligands (which do not interact with the catalytic site but occupy part of the substrate-binding cavity). X-ray crystallography revealed that the optimized SSIs potently blocked insulin binding to the exo-site, but allowed the formation of a catalytically competent IDE–inhibitor–glucagon ternary complex.

ORIGINAL ARTICLE Maianti, J. P. et al. Substrate-selective inhibitors that reprogram the activity of insulin-degrading enzyme. *Nat. Chem. Biol.* **15**, 565–574 (2019)

CYSTIC FIBROSIS

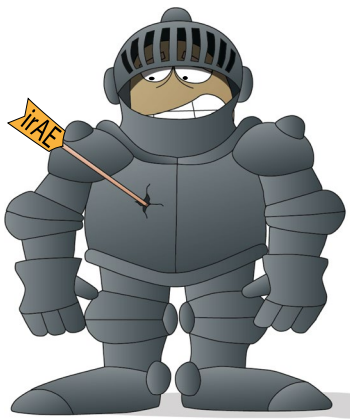
Phage therapy for *Mycobacterium abscessus*

Patients with cystic fibrosis (CF) frequently develop drug-resistant non-tuberculosis mycobacteria infections. Here, Dedrick et al. exploit a collection of over 10,000 bacteriophages to identify phages that can infect GD01, a strain of *Mycobacterium abscessus* responsible for the chronic and disseminated infection of a 15-year-old patient with CF who had undergone bilateral lung transplantation. In vitro, a cocktail of 3 phages infected and killed GD01. In the patient with CF, intravenous administration of the 3-phage cocktail every 12 hours over 32 weeks gradually healed the surgical wound and skin lesions and improved lung and liver function.

ORIGINAL ARTICLE Dedrick, R. M. et al. Engineered bacteriophages for treatment of a patient with a disseminated drug-resistant *Mycobacterium abscessus*. *Nat. Med.* **25**, 730–733 (2019)

CANCER IMMUNOTHERAPY

Prophylactic TNF blockade reduces autoimmune toxicity



Credit: P. Patenall/ Springer Nature Limited

Despite the synergistic efficacy of nivolumab and ipilimumab in some advanced-stage solid tumours, serious immune-related adverse events (irAEs) are common. A new study now demonstrates that prophylactic tumour necrosis factor (TNF) blockade reduces gastrointestinal irAEs in mice treated with dual immune-checkpoint inhibition (DCI).

The group of Ignacio Melero (University of Navarra, Spain) first demonstrated that DCI exacerbated dextran sulfate sodium (DSS)-induced autoimmune colitis in mice, which was ameliorated with prophylactic administration of an anti-TNF antibody or the TNF inhibitor etanercept. Importantly, TNF blockade before DCI did not impair antitumour efficacy in syngeneic mouse models of colon cancer and melanoma, and even improved the survival and xenograft-rejection rate in DSS-treated syngeneic mouse models.

> “prophylactic TNF inhibition could improve the safety of DCI regimens while preserving — or even enhancing — efficacy”

TNF blockade was found to enhance DCI-induced $CD8^+$ T cell infiltration (in the tumour and lymph nodes) and decrease activation-induced cell death in DCI-treated $CD8^+$ T cells in vitro and in vivo, providing a mechanistic rationale for these observations.

The expression of *TNF*-related transcripts and genes was found to be upregulated in normal colonic mucosal tissues from a group of four patients treated with DCI who developed colitis compared with those from four healthy individuals without bowel inflammation or cancer. In a graft-versus-host disease mouse model, prophylactic etanercept treatment reduced DCI-induced exacerbation of colitis. Similarly, in a colon cancer xenograft-induced humanized mouse model of colitis, concomitant etanercept treatment did not weaken the antitumour effects of nivolumab–ipilimumab, and, importantly, it diminished xenograft-induced colitis.

The findings have clear translational relevance, whereby prophylactic TNF inhibition could improve the safety of DCI regimens while preserving — or even enhancing — efficacy, and perhaps enabling ipilimumab doses to be safely increased.

“An ongoing pilot trial in France (NCT03293784) is testing safety of the combined strategy, and a larger randomized phase II trial should soon test efficacy,” adds Melero.

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ORIGINAL ARTICLE Perez-Ruiz, E. et al. Prophylactic TNF blockade uncouples efficacy and toxicity in dual CTLA-4 and PD-1 immunotherapy. *Nature* **569**, 428–432 (2019)