Infectious diseases

Monoclonal antibody treats yellow fever

Most people infected with the mosquito-borne yellow fever virus (YFV) exhibit only mild symptoms, but the mortality rate of hospitalized patients is up to 50%. There is currently no approved treatment for YFV infection and although a live-attenuated prophylactic vaccine (YFV-17D) exists, immunization coverage remains low in some vulnerable populations, and it can cause uncommon severe side effects. Here, Ricciardi et al. screened 37 YFV-reactive monoclonal antibodies (mAbs) isolated from memory B cells of YFV-17D-immunized volunteers, and identified two that potently neutralized pathogenic laboratory-adapted and primary isolates of YFV in vitro. A single injection of either of the mAb candidates to hamsters three days post-infection prevented virus replication, protected from liver disease and significantly increased survival, without affecting weight gain. The mAbs were similarly effective in rhesus macaques, with a single intravenous dose administered two days after YFV infection protecting all 8 animals from death, whereas the 2 control animals required euthanasia 5 days post-infection. YFV RNA was undetectable in the serum and liver of treated macaques, and there were no signs of liver dysfunction.

Sarah Crunkhorn

Original article: Ricciardi, M. J. et al. Therapeutic neutralizing monoclonal antibody administration protects against lethal yellow fever virus infection. *Sci. Transl Med.* **15**, eade5795 (2023)

Proteomics

Decrypting drug action at the level of PTMs

Although most cancer drugs modulate the activity of enzymes that regulate post-translational modifications (PTMs), little systematic information is available about drug action at the level of PTMs. To address this, Zecha et al. have developed a quantitative proteomic approach termed decryptM, which is able to assess target and pathway engagement and decrypt the mechanism of action of diverse cancer drugs by systematically measuring their dose- and time-resolved modulation of PTMs in cells. DecryptM was applied to 12 human cancer cell lines and 31 cancer drugs, comprising chemotherapeutic agents, protein interaction inhibitors, proteasome inhibitors, epigenetic drugs, kinase inhibitors and antibodies. Key findings from the decryptM analysis included the identification of novel phosphorylation sites linking chemotherapeutics to DNA damage response, new insight into how cells mount a stress response to covalent proteasome inhibitors, the characterization of drug-specific signatures for kinase inhibitors, and the discovery of a new model for the mode of action of the anti-CD20 antibody rituximab. The resulting 1.8 million drug dose–response curves are available as an interactive molecular resource in ProteomicsDB. The method should be applicable to any molecule that modulates cellular activity by affecting PTMs or protein expression.

Sarah Crunkhorn

Original article: Zecha, J. et al. Decrypting drug actions and protein modifications by dose- and time-resolved proteomics. *Science.* **380**, 93–101 (2023)

Antivirals

DENV inhibitor effective in non-human primates

Dengue — which can be caused by any of the four Dengue virus (DENV) serotypes (DENV-1–4) — represents the most rapidly spreading mosquito-borne viral disease worldwide, and there are currently no antiviral drugs available for treatment or prophylaxis. Building on findings from a previous anti-DENV-2 screen, Goethals et al. characterize the small-molecule DENV inhibitor JNJ-1802. In vitro, the compound exerted picomolar-to-nanomolar antiviral potency against a panel of 20 DENV strains that represent the diversity of genotypes within the four serotypes. JNJ-1802 was found to act by blocking the NS3–NS4B interaction within the viral replication complex and exhibited a high barrier to resistance. In mice, JNJ-1802 demonstrated prophylactic activity against DENV-1–4 and was also effective in a therapeutic setting: when treatment was initiated after infection at the time of peak viraemia, DENV RNA was efficiently reduced. Oral JNJ-1802 treatment starting 3 days before infection also showed excellent prophylactic efficacy against DENV-1 and DENV-2 infection in rhesus macaques, with viral RNA remaining undetectable in animals receiving the highest dose. JNJ-1802 has successfully completed a phase I clinical study in healthy volunteers.

Sarah Crunkhorn

Original article: Goethals, O. et al. Blocking NS3–NS4B interaction inhibits dengue virus in non-human primates. *Nature* **615**, 678–686 (2023)

Covid-19

Host-directed antiviral blocks SARS-CoV-2 entry

Currently authorized direct-acting antivirals for the treatment of SARS-CoV-2 infection, which target the viral polymerase and viral protease, have been associated with viral resistance and variable efficacy. Given the potentially higher barrier to drug resistance, as well as increased breadth of activity across coronavirus variants and species, host-directed therapeutics represent an attractive alternative approach. Here, Wei et al. demonstrate in vitro that a mammalian SWItch/Sucrose Non-Fermentable (mSWI/SNF) chromatin remodelling complex, canonical BRG1/BRM-associated factor (cBAF), is essential for SARS-CoV-2 entry into cells, and entry requires the catalytic activity of the ATPase subunit SMARCA4. Mechanistically, mSWI/SNF complex catalytic activity was shown to be essential for DNA accessibility at the angiotensin-converting enzyme 2 (ACE2) locus. Furthermore, the transcription factors HNF1A/B were demonstrated to bind to and direct cBAF complexes to sites of high HNF1A/B motif density at the ACE2 locus, to regulate ACE2 expression. In cell lines and primary human cell types — including human bronchial epithelial cells — inhibiting mSWI/SNF ATP-dependent chromatin remodelling activity using three different orally bioavailable SMARCA4/2-specific small-molecule inhibitors and degraders attenuated ACE2 expression, preventing infection with diverse SARS-CoV-2 variants and a remdesivir-resistant mutant virus.

Sarah Crunkhorn

Original article: Wei, J. et al. Pharmacological disruption of mSWI/SNF complex activity restricts SARS-CoV-2 infection. *Nat. Genet.* **55**, 471–483 (2023)