IN BRIEF

NEURODEGENERATION

New strategy for SBMA therapy

Spinal bulbar muscular atrophy (SBMA) results from a polyglutamine expansion in the androgen receptor (AR). Recently, co-regulator binding through the activation function 2 (AF2) domain of the AR has been indicated as essential for pathogenesis. Here, Badders and colleagues screened a panel of small molecules that had previously been identified as modulating co-regulator binding to the AR AF2 domain, which revealed that 1-[2-(4-methylphenoxy)ethyl]-2-[(2-phenoxyethyl) sulfanyl]-1H-benzimidazole (MEPB) was able to rescue toxicity in a *Drosophila* SBMA model. In a preclinical trial in SBMA mice, intraperitoneal MEPB treatment augmented body weight, rotarod activity and grip strength, improved gait and hindlimb clasping and ameliorated neurogenic atrophy, neuronal loss and testicular atrophy.

ORIGINAL ARTICLE Badders, N. M. et al. Selective modulation of the androgen receptor AF2 domain rescues degeneration in spinal bulbar muscular atrophy. *Nat. Med.* https://doi.org/10.1038/nm.4500 (2018)

TYPE 2 DIABETES

Targeting glutamine metabolism

Reducing elevated glucagon signalling in diabetic patients is an attractive strategy for the treatment of hyperglycaemia. Using mouse primary hepatocytes, Miller and colleagues demonstrate a key contribution of glutamine to newly synthesized glucose in response to glucagon stimulation. Short hairpin RNA-mediated knockdown of hepatic glutaminase 2 (GLS2) — which catalyses the first step in glutamine metabolism — reduced glucagon-stimulated glutamine-to-glucose flux in mice. In *Gls2*-knockout mice challenged with a high-fat diet, fasting glucose levels were reduced compared with wild-type mice. Human primary hepatocytes exhibiting natural gain-of-function missense mutations in GLS2 displayed higher glutaminolysis and glucose production, further highlighting GLS2 as a promising antidiabetic target.

ORIGINAL ARTICLE Miller, R. A. et al. Targeting hepatic glutaminase activity to ameliorate hyperglycemia. *Nat. Med.* https://doi.org/10.1038/nm.4514 (2018)

MALARIA

Clues to vaccine design

Vaccination with attenuated *Plasmodium falciparum* sporozoites (PfSPZs) can induce robust immune responses. However, the specific mediators of this protective immune response remain undefined. To investigate this, Seder and colleagues first isolated monoclonal antibodies directed against the Pf circumsporozoite protein (PfCSP) — which covers the surface of the sporozoites and has a critical role in the invasion of hepatocytes — from several human subjects immunized with an attenuated PfSPZ vaccine. One of the antibodies, CIS43, conferred sterile protection in two different mouse models of malaria infection. The antibody limited cleavage of PfCSP on PfSPZ, a process required for sporozoite infection of hepatocytes. Similarly, Lanzavecchia and colleagues isolated immunoglobulin M (IgM) and IgG antibodies from malaria-exposed Tanzanian volunteers who had been repeatedly injected with irradiated PfSPZs. The isolated antibodies demonstrated potent neutralizing activity in mice with humanized livers. The most highly neutralizing IgG antibodies are encoded by *VH3-30*^{f} genes. Analysis of the crystal structure of one of the *VH3-30*^{f} antibodies in complex with the PfCSP N-terminal junctional peptide revealed the structural basis for recognition.

ORIGINAL ARTICLES Tan, J. et al. A public antibody lineage that potently inhibits malaria infection through dual binding to the circumsporozoite protein. *Nat. Med.* https://doi.org/10.1038/nm.4513 (2018) | Kisalu, N. et al. A human monoclonal antibody prevents malaria infection by targeting a new site of vulnerability on the parasite. *Nat. Med.* https://doi.org/10.1038/nm.4512 (2018)