IN BRIEF

NEURODEGENERATIVE DISEASE

A PERK for the therapy of prion disease

The unfolded protein response (UPR), which triggers cellular toxicity, is characteristic of prion disease, Alzheimer's disease and Parkinson's disease. This paper showed that an inhibitor of PERK (PRKR-like endoplasmic reticulum kinase), which is a mediator of the UPR pathway, prevented the development of prion disease in mice. Importantly, the orally available compound GSK2606414 also abolished established prion disease and restored the synthesis of synaptic proteins, although weight loss and hyperglycaemic side effects occurred. This study suggests that PERK could be targeted in neurodegenerative disorders that involve the UPR.

ORIGINAL RESEARCH PAPER Moreno, J. A. *et al.* Oral treatment targeting the unfolded protein response prevents neurodegeneration and clinical disease in prion-infected mice. *Sci. Transl. Med.* **5**, 206ra138 (2013)

TARGET VALIDATION

Tinkering with heart disease

Reperfusion therapy following an acute myocardial infarction can detrimentally increase oxidative stress and cause myocyte death. This study showed that these side effects are mediated by troponin I-interacting kinase (TNNI3K); a myocyte-specific kinase. The authors developed two TNNI3K inhibitors that reduced mitochondria-derived superoxide generation and infarct size when given during reperfusion therapy in a mouse model. Moreover, the inhibitors preserved cardiac function and limited chronic adverse remodelling, which suggests that TNNI3K is a plausible target for heart disease therapy.

ORIGINAL RESEARCH PAPER Vagnozzi, R. J. *et al.* Inhibition of the cardiomyocyte-specific kinase TNNI3K limits oxidative stress, injury, and adverse remodeling in the ischemic heart. *Sci. Transl. Med.* **5**, 207ra141 (2013)

NEURODEGENERATIVE DISEASE

Patient stem cells give clues to ALS

A nucleotide GGGGCC-repeat expansion in the *C9ORF72* gene is found in amyotrophic lateral sclerosis (ALS), but how this triggers disease is unclear. This paper used induced pluripotent stem cells (iPSCs) derived from patients with ALS as a model. These cells had enhanced glutamate excitotoxicity and altered transcription — effects that were also seen in brain samples from patients with ALS. In addition, the RNA-binding protein ADARB2 (RNA-editing deaminase B2) interacted with the GGGGCC repeat in iPSCs, showing that toxicity is due to a gain-of-function mechanism. Antisense oligonucleotides to the *C9ORF72* gene reversed the phenotype of the iPSCs.

ORIGINAL RESEARCH PAPER Donnelly, C. J. *et al.* RNA toxicity from the ALS/FTD *C9ORF72* expansion is mitigated by antisense intervention. *Cell* **80**, 415–428 (2013)

COMPUTATIONAL BIOLOGY

Structural insights into allosteric GPCR drugs

Dror *et al.* used computational modelling to garner information on how ligands bind to the allosteric binding site on G protein-coupled receptors (GPCRs). The authors determined conformations of the M2 muscarinic acetylcholine receptor in combination with several structurally diverse allosteric ligands, which revealed they had similar binding interactions — some of which were contrary to previous predictions. This information was then used to make structural changes to ligands to alter their predicted allosteric effects in *in vitro* studies.

ORIGINAL RESEARCH PAPER Dror, R. O. *et al.* Structural basis for modulation of a G-protein-coupled receptor by allosteric drugs. *Nature* **503**, 295–299 (2013)