IN BRIEF

⇨ TARGET IDENTIFICATION

A new player in Hedgehog signalling

Bassilana et al. identified new small-molecule modulators of the Hedgehog signalling pathway, which is known to drive tumorigenesis. The series of cyclohexyl-methyl aminopyrimidine compounds acted downstream of the Smoothened protein, and target identification studies revealed that they stimulated the orphan G protein-coupled receptor GPR39, which then signals to GLI transcription factors to block signalling. So GPR39 is a new component in Hedgehog signalling, and the inhibitors will be useful to study this receptor.

ORIGINAL RESEARCH PAPER Bassilana, F. et al. Target identification for a Hedgehog pathway inhibitor reveals the receptor GPR39. Nature Chem. Biol. http://dx.doi.org/10.1038/nchembio.1481 (2014)

⇨ BIOTECHNOLOGY

The full repertoire of humanized antibodies

Transgenic mice that are currently used to generate fully human antibodies cannot capture the complete human antibody repertoire, thus limiting the diversity of antibodies that can be produced. This study engineered the full complement of variable region genes from human immunoglobulin loci into precise locations in the mouse genome. Antigen immunization of these mice produced high-affinity mouse–human chimeric antibodies with broad epitope coverage and long human-like complementarity-determining region 3 (which binds antigens). The authors note that these mice could be used as models of the human antibody response, to discover therapeutic human monoclonal antibodies and to aid vaccine design.

ORIGINAL RESEARCH PAPER Lee, E-. C. et al. Complete humanization of the mouse immunoglobulin loci enables efficient therapeutic antibody discovery. Nature Biotech. 32, 356–363 (2014)

⇨ NEURODEGENERATIVE DISORDERS

Blood-based biomarkers for Alzheimer's disease?

Biomarkers of presymptomatic Alzheimer's disease are urgently needed to aid early drug intervention. This paper studied elderly individuals for 5 years with the aim of finding biomarkers that could predict who would develop mild cognitive impairment or Alzheimer's disease. They identified a panel of ten lipids — which were associated with cell membrane integrity — from peripheral blood that predicted conversion to a disease state within 2–3 years with a high degree of accuracy. Further validation studies, such as those in diverse demographic groups of individuals, will help to verify this finding.

ORIGINAL RESEARCH PAPER Mapstone, M. et al. Plasma phospholipids identify antecedent memory impairment in older adults. Nature Med. 20, 415–418 (2014)

⇨ ANTICANCER DRUGS

Drug–virus combination destroys tumours

Tumours that are infiltrated by lymphocytes are more sensitive to the effects of immune checkpoint inhibitors. This paper showed that the inflammatory responses generated by oncolytic viruses increased the infiltration of lymphocytes to distant (that is, non-injected) tumours. When an oncolytic virus was combined with a CTLA4 (cytotoxic T lymphocyte antigen 4) inhibitor, mice rejected pre-established tumours and had improved survival, which suggests that the combination of oncolytic viruses and immune checkpoint inhibitors has clinical potential.

ORIGINAL RESEARCH PAPER Zamarin, D. et al. Localized oncolytic virotherapy overcomes systemic tumor resistance to immune checkpoint blockade immunotherapy. Sci. Transl. Med. 6, 226ra32 (2014)