

## IN BRIEF

 GPCRS**Glucagon receptor antagonist binding site identified**

Small-molecule antagonists of glucagon receptor (GCGR), a class B G protein-coupled receptor, reduce plasma glucose levels in patients with type 2 diabetes. Jazayeri *et al.* now report the 2.5 Å structure of human GCGR in complex with the antagonist MK-0893, providing an opportunity for structure-based drug design. MK-0893 binds to a novel allosteric site located outside the seven transmembrane (7TM) helical bundle in a position between TM6 and TM7, which prevents glucagon receptor activation by restricting the outward helical movement of TM6 required for G protein signalling.

**ORIGINAL ARTICLE** Jazayeri, A. *et al.* Extra-helical binding site of a glucagon receptor antagonist. *Nature* <http://dx.doi.org/10.1038/nature17414> (2016)

 CACHEXIA**Inhibiting FAO rescues muscle-wasting**

Cachexia is a devastating form of muscle wasting that is commonly associated with cancer. To understand the molecular basis of cachexia-associated muscle atrophy, Fukawa *et al.* carried out transcriptomic- and metabolomic-profiling analysis of human muscle stem cell-based models and human cancer-induced cachexia models in mice. This analysis revealed that cachectic cancer cells secrete inflammatory factors that induce muscle fatty acid oxidation (FAO), leading to oxidative stress, p38 mitogen-activated protein kinase (MAPK) activation and progressive muscle wasting. Inhibition of fatty acid-induced oxidative stress using etomoxir rescued weight loss and improved muscle mass in cachectic mouse models.

**ORIGINAL ARTICLE** Fukawa, T. *et al.* Excessive fatty acid oxidation induces muscle atrophy in cancer cachexia. *Nat. Med.* <http://dx.doi.org/10.1038/nm.4093> (2016)

 PAIN**Blocking pain in inherited erythromelalgia**

Gain-of-function mutations in *SCN9A*, which encodes the sodium channel Na<sub>v</sub>1.7 (expressed in the peripheral nervous system), has a crucial role in a chronic pain disorder, inherited erythromelalgia (IEM). Here, Cao *et al.* demonstrate that iPSC-derived sensory neurons (iPSC-SNs), generated from four patients with IEM carrying different *SCN9A* mutations, exhibit elevated excitability and increased sensitivity to heat compared with iPSC-SNs from non-IEM donors. The increased excitability and sensitivity of these neurons were reduced by the novel selective Na<sub>v</sub>1.7 blocker PF-05089771. A single oral dose of PF-05089771 decreased heat-induced pain in 4 out of 5 patients with IEM.

**ORIGINAL ARTICLE** Cao, L. *et al.* Pharmacological reversal of a pain phenotype in iPSC-derived sensory neurons and patients with inherited erythromelalgia. *Sci. Trans. Med.* **8**, 335ra56 (2016)

 CANCER**Peptibodies rescue mice from lymphoma**

The variable region of the B cell receptor (BCR), known as the idiotype, is a patient-specific tumour surface marker on lymphoma cells. To therapeutically target idiotypes, Torchia *et al.* created antibody-like molecules termed peptibodies comprised of a short synthetic patient-specific idiotype-binding peptide covalently linked to the amino-terminus of a recombinant immunoglobulin G crystallizable fragment (IgG Fc). The peptibodies crosslink idiotypes on human lymphoma cells, triggering BCR signalling and inducing apoptosis, resulting in complete clearance of human lymphoma in mouse xenograft models.

**ORIGINAL ARTICLE** Torchia, J. *et al.* Targeting lymphoma with precision using semisynthetic anti-idiotypic peptibodies. *PNAS* **113**, 5376–5381 (2016)