Nature Reviews Drug Discovery | Published online 1 Jun 2016

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 $Na_v1.7$ (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 $Na_v1.7$ 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-idiotype peptibodies. *PNAS* **113**, 5376–5381 (2016)