IN BRIEF

CANCER

Targeting TREM2 to enhance immunotherapy

Immune checkpoint blockade is ineffective in some tumours, in part owing to the presence of immunosuppressive myeloid cells in the microenvironment. Here, Molgora et al. report that deficiency of the myeloid receptor TREM2 or treatment with an anti-TREM2 mAb reduces tumour growth in mouse cancer models and enhances the efficacy of anti-PD1 immunotherapy, while triggering changes in the tumour-infiltrating macrophage populations. TREM2 was expressed in infiltrating macrophages in more than 200 human tumours, and expression correlated with worse survival in colorectal and breast cancer.

ORIGINAL ARTICLE Molgora, M. et al. TREM2 modulation remodels the tumor myeloid landscape enhancing anti-PD-1 immunotherapy. *Cell* **182**, 886–900 (2020)

EPILEPSY

Treating Dravet syndrome with TANGO

No disease-modifying therapies exist for Dravet syndrome (DS), a severe form of epilepsy mostly caused by de novo mutations in *SCN1A* that result in NaV1.1 haploinsufficiency. Applying their targeted augmentation of nuclear gene output (TANGO) technology, Han et al. identify an ASO targeting a naturally occurring nonproductive alternative splicing event in *SCN1A* that results in nonsense-mediated decay of the wild-type transcript. The ASO increased expression of productive *SCN1A* mRNA and NaV1.1 protein in human cells and mouse brain. A single intracerebroventricular dose reduced seizure incidence and sudden unexpected death in epilepsy in DS mice.

ORIGINAL ARTICLE Han, Z. et al. Antisense oligonucleotides increase Scn1a expression and reduce seizures and SUDEP incidence in a mouse model of Dravet syndrome. *Sci. Transl Med.* **12**, eaaz6100 (2020)

IMMUNOTHERAPY

Degrading sialoglycans delays tumour growth

Cell surface sialoglycans suppress immune activation and are upregulated in malignancy, representing a potential target for cancer immune therapy. Building on previous work, Gray et al. optimize a targeted degradation strategy, in which a sialic acid-cleaving enzyme (sialidase) is fused to a HER2-targeting antibody, trastuzumab, to catalytically degrade sialoglycans in a tumour-specific manner. In mouse breast cancer models, the antibody–sialidase conjugate delayed tumour growth and enhanced immune cell infiltration, prolonging survival. These effects were dependent on Siglec-E checkpoint receptor expression on tumour-infiltrating myeloid cells.

ORIGINAL ARTICLE Gray, M. A. et al. Targeted glycan degradation potentiates the anticancer immune response in vivo. *Nat. Chem. Biol.* https://doi.org/10.1038/s41589-020-0622-x (2020)

METABOLIC SYNDROME

CRISPR-engineered fat cells prevent obesity

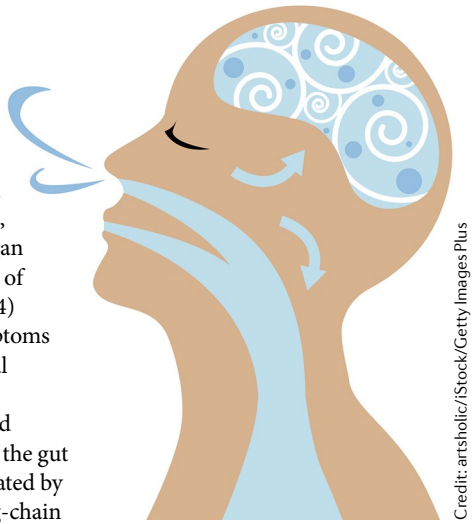
Activation of brown adipose tissue (BAT) to increase energy expenditure is an attractive anti-obesity strategy, but attempts so far have been limited by side-effects. Here, Wang et al. engineer human white pre-adipocytes using CRISPR–Cas9 to activate expression of uncoupling protein 1, thereby creating human brown-like (HUMBLE) cells. Transplantation of HUMBLE cells into diet-induced obese mouse models improved glucose tolerance and insulin sensitivity, increased energy expenditure and reduced weight gain, without side-effects. The HUMBLE cells activated endogenous BAT, through increased production and red blood cell-mediated delivery of nitric oxide.

ORIGINAL ARTICLE Wang, C.-H. et al. CRISPR-engineered human brown-like adipocytes prevent diet-induced obesity and ameliorate metabolic syndrome in mice. *Sci. Transl Med.* **12**, eaaz8664 (2020)

RESPIRATORY DISEASES

Fatty acid receptor gives lungs a breather

There is a continuing need for alternative treatment options for a substantial proportion of patients with respiratory disorders such as asthma and chronic obstructive pulmonary disease. Writing in *Science Translational Medicine*, teams led by Brightling, Milligan and Tobin report that agonists of free fatty acid receptor 4 (FFA4) can dampen asthma-like symptoms in mice, indicating its potential as a novel therapeutic target.



Credit: artsholic/iStock/Getty Images Plus

FFA4 is a G protein-coupled receptor (GPCR) expressed in the gut and pancreas, where it is activated by a range of free circulating long-chain fatty acids. Its involvement in regulating glucose homeostasis has previously been a focus of drug discovery efforts. However, recent studies have reported abundant expression of FFA4 in lung epithelial cells, suggesting that it might also be a target for respiratory diseases.

To confirm the activity of FFA4 in the airway epithelium, the authors used two well-characterized agonists, TUG-891 and the more specific TUG-1197. Treatment of lung slices from wild-type mice with the two ligands resulted in activation of the Gq11/phospholipase C/inositol phosphate signal transduction pathway downstream of FFA4, and in a rapid increase in intracellular calcium. This led to airway smooth muscle (ASM) relaxation in airways that had been precontracted with carbachol or serotonin, an effect that was surprising because elevation of calcium in ASM generally causes contraction rather than relaxation. This effect was indeed mediated by FFA4, since lung slices derived from *Ffa4*-knock-out mice showed no calcium response to TUG-1197.

Next, the authors evaluated the ability of FFA4 agonists to restore normal lung function in mouse models of acute and chronic ozone pollution, and in mouse models of inflammatory airway disease induced by cigarette smoke or house dust mites. In these models activation of FFA4 reduced airway resistance, returning lung function to near normal.

Activation of FFA4 with TUG-891 and TUG-1197 resulted in ASM relaxation even in the presence of an already established inflammatory lung disease. Milligan had hoped to see anti-inflammatory activity, and indeed, the compounds had an anti-inflammatory effect, with a reduction in the number of infiltrated neutrophils and macrophages. Finally, TUG-891 also relaxed lung tissue taken from healthy humans and precontracted with acetylcholine, supporting the relevance of the findings for potential progression of FFA4 modulators into clinical trials for respiratory diseases.

"Better and certainly more potent ligands will be needed. It will be interesting to see if companies that worked extensively on FFA4 in the context of glucose homeostasis and diabetes — but were never able to bring a compound targeting this receptor to clinical trials — might re-examine their chemistry programmes with this different indication in mind," concludes Milligan.

M. Teresa Villanueva

ORIGINAL ARTICLE Prihandoko, R. et al. Pathophysiological regulation of lung function by the free fatty acid receptor FFA4. *Sci. Transl Med.* **12**, eaaw9009 (2020)