IN BRIEF

DIABETES

Protecting β-cells in type 1 diabetes

Cell replacement therapy is an attractive approach to treat type 1 diabetes (T1D), but without immune suppression, autoimmunity would destroy transplanted β-cells. Using a genome-scale CRISPR screen in a mouse model of T1D, Link et al. discover that deletion of *Rnls* protects β-cells from immune destruction and confers endoplasmic reticulum stress resistance. RNLS is a flavoprotein oxidase to which the FDA-approved monoamine oxidase B inhibitor pargyline binds, as indicated by structure-based modelling. Oral pargyline treatment protected transplanted β-cells in diabetic mice and prevented or delayed diabetes onset in mouse models of T1D.

ORIGINAL ARTICLE Link, J. et al. Genome-scale in vivo CRISPR screen identifies *RNLS* as a target for beta cell protection in type 1 diabetes. *Nat. Metab.* https://doi.org/10.1038/s42255-020-0254-1 (2020)

LYSOSOMAL STORAGE DISORDERS

Exon skipping combats Batten disease

The lysosomal storage disease CNL3 Batten disease is caused by mutations in *CLN3*, often resulting in deletion of exons 7 and 8, leading to a premature termination codon in exon 9. Here, Centa et al. develop antisense oligonucleotides (ASOs) that induce exon skipping of exon 5 and restore the open reading frame. Exon 5-targeted ASOs exerted robust exon skipping in cell lines derived from patients with CLN3 Batten disease. ICV injection of an exon 5-targeted ASO induced stable exon skipping for up to 14 months, lowered brain accumulation of subunit c of mitochondrial ATP synthase, rescued motor deficits and increased survival in mouse disease models.

ORIGINAL ARTICLE Centa, J. et al. Therapeutic efficacy of antisense oligonucleotides in mouse models of CLN3 Batten disease. *Nat. Med.* https://doi.org/10.1038/s41591-020-0986-1 (2020)

CARDIOMYOPATHY

Statin therapy improves endothelial dysfunction

The molecular mechanisms underlying LMNA-related dilated cardiomyopathy (DCM) remain poorly understood. Sayed et al. now report that iPSC–derived endothelial cells (ECs) generated from a family with LMNA-related DCM exhibit decreased functionality. Transcriptional profiling of the LMNA mutant iPSC-ECs implicated the transcription factor KLF2 as an important regulator of EC dysfunction. Lovastatin induced *KLF2* and improved endothelial dysfunction in LMNA iPSC-ECs and in patients with LMNA-related DCM. Furthermore, lovastatin improved the functional phenotype of LMNA iPSC-cardiomyocytes when cocultured with LMNA iPSC-ECs.

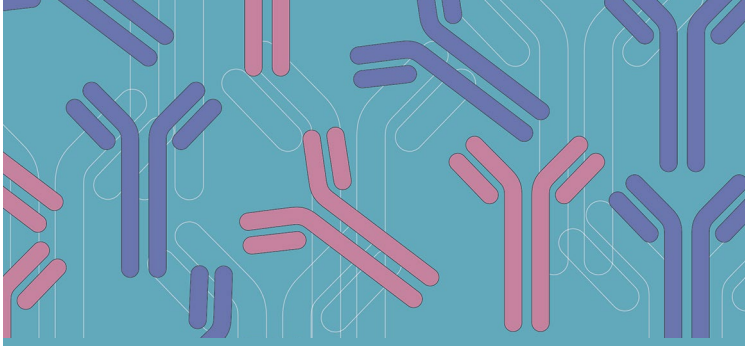
ORIGINAL ARTICLE Sayed, N. et al. Clinical trial in a dish using iPSCs shows lovastatin improves endothelial dysfunction and cellular cross-talk in LMNA cardiomyopathy. *Sci. Transl Med.* **12**, eaax9276 (2020)

CANCER

Multi-antigen-specific T cell therapy for multiple myeloma

Most patients with multiple myeloma (MM) eventually relapse or become refractory to treatment. Here, Lulla et al. develop an immunotherapeutic approach, comprised of ex vivo expanded autologous T cell lines from 23 patients with MM, that simultaneously targets five MM-expressed tumour-associated antigens: PRAME, SSX2, MAGEA4, NY-ESO-1 and survivin. In a study of 21 patients with MM, infusion of these multi-tumour-associated antigen T cells was safe and well tolerated. In addition, clinical responses, associated with T cell expansion and persistence, were observed in three patients.

ORIGINAL ARTICLE Lulla, P. et al The safety and clinical effects of administering a multiantigen-targeted T cell therapy to patients with multiple myeloma. *Sci. Transl Med.* **12**, eaaz3339 (2020)



Credit: Susanne Harris/Springer Nature Limited

CANCER

Blocking GDF15 signalling reverses cachexia

Many patients with cancer develop cachexia, characterized by anorexia and progressive loss of adipose tissue and skeletal muscle. However, the molecular mechanisms mediating cachexia remain poorly understood and no approved therapies exist. Writing in *Nature Medicine*, Allan and colleagues demonstrate that antibody-mediated antagonism of the receptor for growth differentiation factor 15 (GDF15) reverses cancer cachexia in mice.

GDF15 is a circulating protein that has been implicated in energy homeostasis and body weight regulation. Notably, circulating levels of GDF15 correlate with cachexia and reduced survival in patients with cancer. Studies in mice have indicated that GDF15-induced weight loss is mediated by a GDNF family receptor-α-like (GFRAL)-Ret proto-oncogene (RET) signalling complex in brainstem neurons, so Allan and colleagues set out to investigate GDF15–GFRAL–RET signalling inhibition as an approach to treating cancer cachexia.

The authors first generated a library of 100,000 hybridoma clones from mice immunized with the GFRAL extracellular domain. This enabled identification of the monoclonal antibody 3P10, which inhibited GDF15-induced signalling in cells co-expressing RET and GFRAL. Further analysis showed that 3P10 specifically interacted with GFRAL via the D3 domain, preventing RET recruitment to the GDF15–GFRAL complex.

In wild-type mice, subcutaneous injection of 3P10 blocked recombinant GDF15 (rGDF15)-induced signalling and brainstem neuronal activation, which altered body weight: a single dose of 3P10 prevented rGDF15-induced weight loss, and weekly administration of 3P10 accelerated the cumulative weight gain in mice on a high-fat diet.

Next, the authors investigated potential anticachectic effects of GFRAL inhibition. In multiple mouse cancer models (each exhibiting high levels of serum GDF15), subcutaneous injection of 3P10 prevented tumour-induced body-weight loss, preserving both adipose tissue and skeletal muscle. Furthermore, when 3P10 was administered to a human xenograft model after significant body weight loss, the mice gained back almost all of the lost weight.

The mechanism mediating GDF15-induced cachexia and its reversal by 3P10 in tumour-bearing mice was independent of food intake, and effects on lipolysis played a key role. Lipid oxidation was increased and glucose oxidation was reduced in tumour-bearing mice during their active weight loss phase: effects that were reversed by 3P10. In addition, rGDF15 induced expression of genes involved in lipid metabolism in adipose tissues in wild-type mice, and GDF15-mediated weight loss was prevented in adipose triglyceride lipase-knockout mice. Furthermore, degeneration of adrenergic neurons in the peripheral sympathetic nervous system prior to GDF15 administration in mice prevented weight loss, indicating that the effect is dependent on the peripheral sympathetic nervous system.

Based on the promise of GFRAL inhibition as a novel strategy for the treatment of cancer cachexia, this approach is currently being investigated in phase I trials.

Sarah Crunkhorn

ORIGINAL ARTICLE Suriben, R. et al. Antibody-mediated inhibition of GDF15–GFRAL activity reverses cancer cachexia in mice *Nat. Med.* https://doi.org/10.1038/s41591-020-0945-x (2020)