IN BRIEF

CANCER

Converting cancer cells to fat

Cancer cell plasticity plays a major role in tumour progression and therapy resistance and is enhanced by de-differentiation processes, such an epithelial–mesenchymal transition (EMT). Ishay-Ronen et al. treat mouse EMT-derived breast cancer cells with the anti-diabetic drug rosiglitazone plus BMP2, which induces adipogenesis and generates functional postmitotic adipocytes, through inhibition of transforming growth factor-β-induced MEK–ERK signalling. In mouse breast cancer models, the FDA-approved MEK inhibitor trametinib plus rosiglitazone converted invasive and disseminating cancer cells into postmitotic adipocytes, suppressed the growth of tumours and prevented metastasis.

ORIGINAL ARTICLE Ishay-Ronen, D. et al. Gain fat–lose metastasis: converting invasive breast cancer cells into adipocytes inhibits cancer metastasis. *Cancer Cell* **35**, 17–32 (2019)

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Targeted therapy for chordoma

There are currently no approved therapies for the rare bone cancer, chordoma. Using CRISPR–Cas9 loss-of-function screens in chordoma cell lines, Sharifnia et al. identify the T gene (which encodes the T-box-family transcription factor brachyury) to be essential for cell viability. A small-molecule screen in chordoma cell lines identified CDK7/12/13 inhibitors to have potent antiproliferative effects, mediated by loss of super-enhancer-driven brachyury expression. In a mouse chordoma model, their CDK7/12/13 inhibitor THZ1 downregulated brachyury expression and reduced tumour proliferation.

ORIGINAL ARTICLE Sharifnia, T. et al. Small-molecule targeting of brachyury transcription factor addiction in chordoma. *Nat. Med.* https://doi.org/10.1038/s41591-018-0312-3 (2019)

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Eliminating disseminated tumour cells

Disseminated tumour cells (DTCs) are resistant to chemotherapy and are likely responsible for late distant recurrence of breast cancer. In mice, Carlson et al. show that chemotherapy selects for DTCs in the perivascular niche of bone marrow. These DTCs were protected from chemotherapy by the microvascular endothelium through integrin-mediated interactions, irrespective of their cell cycle status. In mouse breast cancer models, antibodies targeting β1 integrin sensitized DTCs to chemotherapy and prevented bone metastasis.

ORIGINAL ARTICLE Carlson, P. et al. Targeting the perivascular niche sensitizes disseminated tumour cells to chemotherapy. *Nat. Cell Biol.* **21**, 238–250 (2019)

COMPUTATIONAL CHEMISTRY

Patent-evading drug synthesis

Retrosynthesis software can generate efficient new synthetic routes to known compounds. Molga et al. applied such software to identify routes that bypass patent-protected aspects in the synthesis of marketed drugs. The method involves identifying the bonds in the target molecule whose formation is essential to patent-protected processes, and requiring the software to preserve them during retrosynthesis-based planning for new routes. The strength of this approach is demonstrated through the design of patent-evading syntheses for the marketed drugs linezolid, sitagliptin and panobinostat.

ORIGINAL ARTICLE Molga, K. et al. Navigating around patented routes by preserving specific motifs along computer-planned retrosynthetic pathways. *Chem* https://doi.org/10.1016/j.chempr.2018.12.004 (2019)

Credit: PASIEKA/SPL/Science Photo Library/Getty

GENE THERAPY

CRISPR restores expression in models of vision loss

Inherited retinal dystrophies can present as early as infancy and lead to severe or complete vision loss. They are also often monogenic and therefore amenable to gene therapy. Editas Medicine has now developed a CRISPR–Cas9-based approach that can restore gene expression in mouse and non-human primate (NHP) models of the retinal dystrophy Leber congenital amaurosis type 10 (LCA10), thereby potentially moving gene editing with CRISPR platforms one step closer to the clinic.

LCA is the most common cause of childhood blindness, affecting 2–3 per 100,000 neonates. 20–30% of affected individuals have LCA10, which is an autosomal recessive condition caused by mutations in *CEP290*. The most common mutation generates a novel splice site, which leads to a premature stop codon in the resulting mRNA. Although other retinal dystrophies, including LCA2, could potentially be treated with gene therapies delivered by adeno-associated viruses (AAVs), the *CEP290* gene is too large to be packaged in AAV vectors.

The authors developed a pair of *Staphylococcus aureus* guide RNAs to direct Cas9 to remove the alternative splice site and restore normal gene expression. In fibroblasts from patients with LCA10, transfection of the guide RNAs and *S. aureus* Cas9 increased expression of wild-type (WT) CEP290 mRNA and protein. They put these guide RNAs into an AAV vector containing *S. aureus* Cas9 under the control of the retina-specific promoter GRK1 and called the resulting vector EDIT-101.

EDIT-101 was first assessed using a retinal explant model. In 25 explants from a single donor, an average of 41.7% of the photoreceptor cells were edited, and an average of 16.6% of cells were edited in a manner that should lead to correct CEP290 expression. For near-normal vision, approximately 10% of foveal cone photoreceptors must be functional, so the level of editing observed in explants is consistent with the potential for restoration in patients. No off-target editing was observed in the cell lines or explants.

In a human mutant-CEP290 knock-in mouse model, subretinal delivery of 1 ul of 1×10^{13} or 1×10^{12} viral genomes (vg) per ml of EDIT-101 resulted in editing of ~21% of retinal cells by 6 weeks after treatment. These levels of editing were maintained throughout the studies, which were 6 or 9 months in duration. The highest level of productive editing was observed with intermediate doses: 60.8% with a dose of 3×10^{12} vg per ml.

The authors then moved to an NHP model in order to assess the efficacy of editing in an animal with a retina that is anatomically similar to that of humans. Because of sequence divergence between NHPs and human *CEP290*, NHP-specific guide RNAs were developed and packaged into AAVs along with *S. aureus* Cas9. At the highest and most effective dose (100 ul of 1×10^{12} vg per ml), 27.9% of the cells contained edited versions of *CEP290*.

This study provides the proof-of-concept for further development of EDIT-101. Clinical trials are expected to begin later this year.

Megan Cully

ORIGINAL ARTICLE Maeder, M. L. et al. Development of a gene-editing approach to restore vision loss in Leber congenital amaurosis type 10. *Nat. Med.* https://doi.org/10.1038/s41591-018-0327-9 (2019)

FURTHER READING Gordon, K. et al. Gene therapies in ophthalmic disease. *Nat. Rev. Drug Discov.* https://doi.org/10.1038/d41573-018-00016-1 (2019)