stages of the development process and may allow more precise reprogramming.

Identifying the right combinations of transcription factors, however, and the correct order in which they work together to generate cells of interest remains a work in progress. Reh and colleagues achieved a scientific milestone some years ago by converting Müller glia – specialized retinal glial cells – in adult mice into functioning inner nuclear layer retinal neurons by overexpressing the transcription factor Ascl1 and administering a histone deacetylase inhibitor at the same time. The main cell type to emerge from this experiment was the bipolar cell, an interconnecting neuron that links light-sensing photoreceptors to ganglion cells, which then transmit the visual information to the brain. The potential applications of this finding are limited, as it's not a cell type that is prone to injury – but it represents an important proof of the principle that cellular reprogramming is feasible. "The fact of the matter is when we make glia into neurons in the adult retina, they connect with the existing neurons. They make synapses. They respond to light. They have neuronal electrical properties," says Reh. "It's crazy really when you think about it. We had no reason to expect that was going to happen," Reh adds.

His group subsequently reported that they could dispense with the histone deacetylase inhibitor by adding a second transcription factor, Atoh1. This combination efficiently generated several types of retinal neurons, even in the absence of retinal injury. The most common cells generated by this protocol resembled retinal ganglion cells, although the differentiation process was incomplete and their axons did not extend to the brain. Another avenue of exploration involves knocking down expression of the transcription factors NRL and NR2e3, which are necessary for rod development and maintenance. In the absence of NRL and NR2e3, the cells become more cone-like, and they no longer die from disease-causing mutations that affect rods. What's more, the neighboring cones no longer die either, which offers a potential mechanism for prolonging cone survival in RP. This work has been conducted in mice, and Reh's group now aims to replicate it in larger animals. He is working with a startup, which is still in stealth mode, on translating this work into a therapy.

Mogrify also remains in early stage development, with its predictive cellular reprogramming system of the same name. It is based on an extensive computational effort to map the regulatory networks associated with large numbers of transcription factors active in various cell types. This enables it to identify possible transcription factor combinations that will drive 'transdifferentation', or the conversion of one cell type to another without the need to revert to a pluripotent state. The approach is broadly applicable – the company has programs in metabolic disease, hearing loss and fibrosis, as well as ophthalmology. "Any source cell can become any destination cell," Modis says. The system is not limited to transcription factors, either: it can also evaluate non-coding RNA species that modulate gene expression, such as microRNAs. The company has not disclosed details of its programs as yet, but in ophthalmology the focus is on regenerating photoreceptors and retinal ganglion cells. Optogenetics – the delivery of genes expressing photosensitive 'opsin' proteins to cells in the retina – and cell transplant represent two other regenerative approaches that are in active development, although the results from initial trials have been modest.

Restoring or at least preserving vision remains a distant goal. But the initial batch of trials now underway will generate valuable data that will inform future research.

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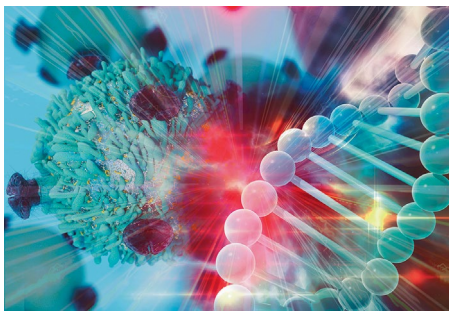
**News in brief**

# CAR-Ts made entirely within the body



Capstan Therapeutics, a start-up founded by a group of influential scientists from the University of Pennsylvania, has launched with $165 million to develop transient engineered chimeric antigen receptor (CAR)-T cells in vivo. The startup aims to develop modified mRNA contained in T cell-targeting lipid nanoparticles to generate disease-specific CAR-Ts in vivo. Its founders include CAR-T pioneers Carl June and Bruce Levine, as well as Drew Weissman, whose seminal work with Katalin Karikó on RNA nucleoside modification paved the way for mRNA-based vaccine development. Capstan aims to develop CAR-Ts without the unwieldy production routines and the toxic lymphodepletion protocols associated with current methods. As well as cancer, the company aims to tackle autoimmune disease, fibrosis and blood disorders by directing a programmed T cell response against defined pathological cell populations. Earlier this year, the founding scientists reported that its approach reduced fibrosis in a mouse model of cardiac injury. They engineered T cells to express a CAR directed against fibroblast activation protein, which is expressed in fibrosis. The mRNA payload was delivered in lipid nanoparticles decorated with antibodies that bind CD5, a receptor expressed by T cells and a subset of B cells but not required for cell function. The approach is transient as the mRNA is rapidly degraded, which eliminates safety concerns about engineered T cells persisting indefinitely; it also opens up the possibility of repeat dosing. The manufacturing is more akin to that of mRNA-based vaccines than current CAR-T therapies, which are notoriously difficult to scale. "It's unlikely that we will need our own manufacturing," says CEO Laura Shawver.