First state-approved embryonic stem cell trials in China

Surgeons in Zhengzhou, China, are preparing to test the efficacy of neurons derived from embryonic stem cells (ESCs) as a treatment for Parkinson's disease—the first ESC-based clinical trial in China and the first anywhere in Parkinson's disease to use ESCs obtained from fertilized embryos. A second study, also to be conducted at the First Affiliated Hospital of Zhengzhou University, will use ESC-derived cells to reverse vision loss caused by age-related macular degeneration. Both efforts are being led by Qi Zhou of the Chinese Academy of Sciences Institute of Zoology in Beijing. For the trial in Parkinson's disease, a neurodegenerative condition that affects dopamine-producing cells, Zhou's team has selected ten patients who best match the HLA (human leukocyte antigen) types of ESCs in their cell bank. In a previous study in non-human primates, the researchers observed that ESCs injected into the brain turned into dopamine-releasing cells, according to *Nature*, which reported the trial go-ahead (*Nature* **546**, 15–16, 2017). Last year, a group at the Royal Melbourne Hospital in Australia initiated the first trial in Parkinson's disease using parthenogenetic neural stem cells from unfertilized eggs. The studies at Zhengzhou will follow regulations issued by China's National Health and Family Planning Commission in August 2015 aimed at preventing clinics from offering unauthorized and dubious treatments under the cloak of stem cell research. Such questionable practices had prompted China to place a moratorium on new clinical trials of stem cell therapies in 2012.

"Americans elected a president whose administration has openly disavowed the scientific method, data-based evidence, and basic research, and a Congress with just one PhD scientist. Now our current government leaders are running away from the future, rather than planning ahead for it." Amy Webb, CEO of the Future Today Institute, argues that without a national biology strategy, powerful technologies can wind up in the hands of a single entity, as might happen with the granting of the CRISPR–Cas9 patent to the Broad Institute. (*Wired*, 11 May 2017)

"We'll run through a cinderblock wall to get to a patient. We're proud of this, so I'm bragging about it a little bit." Joshua Bilenker, CEO of Loxo Oncology in Stamford, Connecticut, talks about the company's decision to accept very sick patients into a phase 2 trial of their lead small molecule for rare cancers driven by TRK-ALK fusions, an uncommon practice in most commercial trials. (*Forbes*, 3 June 2017)

of the CAR is the same [as other companies' constructs]. The outside part? We have no idea." Another explanation for Legend Biotech's "impressive" data, says Maus, could be patient selection. The Chinese trial participants were not as heavily pretreated as those enrolled in US studies of other anti-BCMA CAR-Ts—and it's known that patients with fewer prior treatment failures generally tend to fare better.

BCMA may be the lead target now for anti-myeloma CAR-T strategies, but it's hardly the only one. For example, doctors at the Chinese PLA General Hospital in Beijing have developed a CAR-T therapy directed against CD138, a protein also known as syndecan-1 that mediates myeloma cell adhesion; and a group from Baylor College of Medicine in Houston have created one directed against the kappa-light chain of antibodies produced by malignant plasma cells.

Elsewhere, Carl June and his colleagues at the University of Pennsylvania Perelman School of Medicine in Philadelphia are working with the Swiss drug giant Novartis on a BCMA-specific CAR-T therapy; in the meantime, they have also given myeloma patients a version of Novartis' anti-CD19 tisagenlecleucel-T, which is currently under regulatory review for the treatment of acute lymphoblastic leukemia. Although CD19 is rarely expressed on malignant myeloma plasma cells, as it is with leukemic B cells, the antigen is found on the surface of cancer stem cells associated with the disease, and early clinical reports suggest that combining tisagenlecleucel-T with traditional therapies can help myeloma patients achieve long-term remission (*N. Engl. J. Med.* **373**, 1040–1047, 2015).

How does CAR-T cell therapy compare to what is now front-line therapy, which is a stem-cell transplant?

Other CAR-T targets also in development include CS1 (also called SLAMF7) and CD38. But according to Maus, "It's hard to imagine they're going to be better than BCMA on their own, because they have expression on other cells, and so that therapeutic window gets a bit smaller in terms of targeting non-tumor cells." Their clinical value, says Maus, will likely be in CAR-T combinations or for those who relapse on anti-BCMA therapy after their myeloma cells evolve to evade the onslaught of engineered T-cells. Or they could find a therapeutic niche in other disease settings.

Michael Rosenzweig and his colleagues from City of Hope in Duarte, California, recently measured the expression levels of BCMA and CS1 in bone marrow samples taken from ten patients with multiple myeloma and another ten with a related plasma cell disorder called amyloid light-chain (AL) amyloidosis. As they reported in the July issue of *Cytotherapy* (**19**, 861–866, 2017), all the samples contained plasma cells expressing CS1, but only the myeloma samples had appreciable levels of BCMA as well. Rosenzweig's conclusion: "It doesn't look like a BCMA-directed therapy would be effective for AL amyloidosis," he says. So, he and his team are now advancing a CS1-targeted CAR-T product, with a first-in-human study expected to launch within the year for myeloma patients; amyloidosis trials would follow soon thereafter.

With CAR-Ts now entering the myeloma milieu and yielding at least partial responses in most patients when given at higher doses, "the question that is on everybody's mind is: 'How does CAR-T cell therapy compare to what is now front-line therapy, which is a stem-cell transplant?'" says Rafael Fonseca, a myeloma specialist at the Mayo Clinic in Phoenix, Arizona. "My prediction is that [CAR-T] is going to be easier, it's going to be better and it's not going to be associated with some of the longer toxicities we have with stem-cell transplants, so I don't think it takes a lot of imagination to start envisioning a future where myeloma patients will maybe have their disease controlled with some form of an induction regimen potentially to be followed by a CAR-T cell therapy approach."

And because the conditioning regimen for a CAR-T infusion involves much lower doses of chemotherapy than those needed to wipe out the bone marrow ahead of an autologous stem-cell transplant, "potentially this could become therapy that is available to older individuals as well," Fonseca adds, noting that, because of the risk of toxic complications, autologous stem cell transplantation is currently often reserved for those patients younger than 65 years of age.

Such a future of bespoke CAR-T treatments for all myeloma patients could present manufacturing and logistics challenges, though, and so many companies are also focusing on ways to target BCMA with off-the-shelf antibody-based therapies. GlaxoSmithKline, for example, has a phase 1 trial ongoing to evaluate an antibody–drug conjugate that targets BCMA and releases a payload of the microtubule-disrupting agent monomethyl auristatin-F, while Amgen, Janssen, Celgene and others