NEWS IN BRIEF

FDA approves first CAR T therapy

The FDA gave the green light to Novartis's tisagenlecleucel for the treatment of acute lymphoblastic leukaemia (ALL), marking a historic approval for a first-in-modality chimeric antigen receptor (CAR) T cell therapy.

CAR Ts are an *ex vivo* form of gene therapy, in which T cells are removed from cancer patients, genetically modified to express cancer-cell seeking receptors, and re-infused into patients. Tisagenlecleucel, like many of the first-generation CAR Ts, is modified to target the B cell antigen CD19, depleting these cells for the treatment of various blood cancers. The drug was approved on the basis of a clinical trial in 63 patients with relapsed or refractory B cell precursor ALL, in which the overall remission rate within 3 months of treatment was 83%.

"We're entering a new frontier in medical innovation with the ability to reprogramme a patient's own cells to attack a deadly cancer," said FDA commissioner Scott Gottlieb.

Several other CAR Ts are on their way to patients, including Kite Pharma's CD19-targeting axicabtagene ciloleucel for refractory aggressive non-Hodgkin lymphoma. The FDA is expected to rule on this application by the end of November. In August, Gilead Sciences agreed to buy Kite for nearly US$12 billion.

Safety issues, however, continue to loom over the field. Tisagenlecleucel carries a black box warning that notes the risk of cytokine release syndrome and neurological events. Other companies have fared worse, and have had to put clinical trials of CAR Ts on hold owing to fatalities. Cellectis — a company that is using gene-editing tools called TALENs to engineer T cells from healthy donors into allogeneic 'off-the-shelf' CAR Ts — suffered such a setback in September, after a patient with a blastic plasmacytoid dendritic cell neoplasm died in a trial of CD123-targeting UCART123. Juno Therapeutics halted a study of its lead CD19-targeting CAR T in 2016 after two patients died from cerebral oedema.

The field is also still struggling to figure out how to use CAR Ts in solid tumours and how to overcome manufacturing issues (*Nat. Rev. Drug Discov.* **16**, 301–304; 2017).

Novartis has priced tisagenlecleucel at $475,000 per treatment, renewing concerns about the high cost of new cancer drugs.

Asher Mullard

CETP inhibitors stumble on

Merck & Co's anacetrapib hit its primary end point in a large phase III cardiovascular outcomes trial, defying industry expectations for a drug class that many experts had dismissed. But questions remain about whether the cholesteryl ester transfer protein (CETP) inhibitor will meet the regulatory or commercial cut.

CETP inhibitors are lipid-modulating drugs that increase high-density lipoprotein (good) cholesterol and reduce low-density lipoprotein (bad) cholesterol. Despite high hopes for these drugs as a means of reducing cardiovascular risk, several candidates have bombed out in clinical trials. Pfizer pulled the plug on its phase III candidate torcetrapib in 2006 after the drug increased the risk of death. Roche stopped phase III development of its dalcetrapib owing to futility in 2012, and Eli Lilly halted phase III development of evacetrapib in 2015 for the same reason.

Merck is one of just a few companies that has persevered. In August, the company reported detailed results from a 30,500-patient phase III trial that showed that the rate of major coronary events with anacetrapib was 10.8% versus 11.8% with placebo, a relative risk reduction of 9%. The data were presented at the European Society of Cardiology Congress in Barcelona in August and published in the *New England Journal of Medicine*.

Cardiologists called this treatment effect modest, and were disappointed that the treatment did not appear to confer a mortality benefit. In light of the past failures of CETP inhibitors, some specialists said further clinical trials would be needed to validate the new findings. Merck is evaluating the data and deciding on its next steps.

At least two other companies are also still holding out hope for CETP inhibitors. DalCor Pharmaceuticals licensed Roche's dalcetrapib in 2015, and is running a phase III trial of the drug in a genetically defined population of patients with *ADCY9* polymorphisms. Amgen still lists its CETP inhibitor AMG899 in its phase II pipeline.

Asher Mullard

Parkinson disease repurposing promise

The asthma drug salbutamol, a β2-adrenoceptor agonist, may reduce the risk of Parkinson disease (PD), suggests epidemiological and basic research published in *Science*.

PD is a neurodegenerative condition that is characterized by the accumulation of α-synuclein in the brain. When researchers at Harvard Medical School in Boston set out to find drugs that could lower α-synuclein expression, they discovered that salbutamol offered promise in both *in vivo* and *in vitro* models. Collaborating with researchers in Norway, they performed a large-scale epidemiological study of 4 million Norwegians to show that people who used this drug for the treatment of asthma were approximately one-third less likely to develop PD than people who did not use the drug. Conversely, Norwegians who used the β2-adrenoceptor antagonist propranolol to control high blood pressure were twice as likely to develop the neurodegenerative disease.

These results do not prove causation, but the real-world and mechanistic evidence suggest that salbutamol or another β2-adrenoceptor agonist could provide a path forward for PD treatment. "Evaluation in additional populations and in clinical trials will be required to determine whether the insights gained in this work can be translated to patients with PD," the authors write.

"Our study presents a path to drug development that is distinct from traditional approaches. Targeting the endogenous expression of a human disease gene may be a useful strategy for other diseases attributed to copy number variation or regulatory variants. The drug development pipeline tested in this study could be more generally applicable to rapid discovery and translation of therapeutics for other brain diseases," they add.

Earlier this year Roche advanced the first anti-α-synuclein antibody into phase II trials (*Nat. Rev. Drug Discov.* **16**, 371–373; 2017).

Asher Mullard