NEWS IN BRIEF

Alzheimer prevention failure rattles field, anew

Failed trials of amyloid-modulating Alzheimer disease candidates don't come as much of a surprise any more. But with Amgen and Novartis's recent decision to halt two phase III trials of the BACE1 inhibitor umibecestat for secondary prevention of the neurodegenerative disease in high-risk patients, a longer shadow has now fallen on the prospects for these agents in earlier lines of treatment as well.

In the Generation S1 trial, the sponsors were testing umibecestat and the amyloid vaccine CAD106 in cognitively unimpaired individuals aged 60 to 75 years with two *APOE4* genes, a risk factor for developing Alzheimer disease. In Generation S2, they were testing umibecestat in cognitively unimpaired participants aged 60 to 75 years with at least one *APOE4* allele. But in July the companies announced that the drug was associated with worsening in some measures of cognitive function, and discontinued development of the BACE inhibitor.

After past failures of amyloid-modulating drugs, researchers have posited that these agents need to be used earlier in the course of disease — potentially years before symptoms are detectable — to prevent neuronal death. The Generation S1 and S2 trials were testing this hypothesis, and in both cases the BACE inhibitor came out lacking.

Umibecestat, also known as CNP520, now follows the same fate as Merck & Co.'s verubecestat, Janssen's atabecestat and AstraZeneca and Eli Lilly's lanabecestat, BACE inhibitors that were discontinued after failing in later stages of disease.

Researchers are still holding out hope for a few prevention trials of anti-amyloid antibodies. The Alzheimer's Prevention Initiative is testing Roche's crenezumab in asymptomatic patients with presenilin 1 mutations, which predispose carriers to early-onset disease. The DIAN-TU trial is testing Roche's gantenerumab and Lilly's solanezumab in patients with Alzheimer disease-causing mutations who are within 15 years of the predicted age of cognitive symptom onset. And the A4 trial is testing solanezumab in older individuals who do not yet show symptoms of Alzheimer disease cognitive impairment or dementia.

Asher Mullard

First in vivo CRISPR candidate enters the clinic

Editas Medicine and its partner Allergan have advanced AGN-151587 into a phase I/II trial for patients with Leber congenital amaurosis type 10, a rare and inherited form of blindness.

AGN-151587, previously called Edit-101, is the first CRISPR–Cas9 genome-editing medicine that is administered directly to patients. Doctors inject the adeno-associated virus-based candidate subretinally, so that it can cut out a mutation in the *CEP290* gene in photoreceptor cells in the eye. Spark Therapeutics and Novartis's voretigene neparvovec, the first gene therapy to gain approval in the US, corrects a different form of the inherited eye disease, by introducing a normal copy of the *RPE65* gene to patients with Leber congenital amaurosis type 2.

Several other CRISPR-focused companies have prioritized ex vivo applications of their technologies.

With CRISPR Therapeutics and partner Vertex Pharmaceuticals' CTX001, for example, patient's haematopoietic stem cells are harvested and then engineered ex vivo with CRISPR to boost the production of fetal haemoglobin, before being re-infused into patients. CRISPR is used in this case to cut the DNA that encodes BCL11A, a transcription factor that otherwise represses fetal haemoglobin expression. The partners launched phase I/II development of CTX001 in patients with β-thalassaemia and with sickle cell disease last year, making it the first ex vivo CRISPR-based candidate into the clinic in Europe and the US.

CRISPR Therapeutics and Tmunity Therapeutics have also independently started testing cancer-killing cellular therapies that are engineered using CRISPR. CRISPR Therapeutics' phase I candidate CTX110 is an off-the-shelf CD19-targeting chimeric antigen receptor-T cell, and the company credits its use of CRISPR as a means of achieving enhanced precision and efficiency during the manufacturing of this therapeutic. Tmunity's phase I NY-ESO-1-redirected T cells are autologous T cell receptor (TCR)-engineered therapeutics. The company uses CRISPR during the production of these cells to disrupt expression of endogenous TCRα, TCRβ and PD-1.

Intellia Therapeutics and partner Regeneron are working towards a 2020 investigational new drug application for their in vivo NTLA-2001, a systemically delivered CRISPR treatment for transthyretin amyloidosis.

Asher Mullard

Longer-lasting HIV drugs

Antiretroviral therapies have revolutionized AIDS care, changing what was once a death sentence into a chronic and controllable condition. But antiretroviral therapy (ART) cocktails still have to be taken on a daily basis, and treatment interruptions can result in relapse as well as the emergence of drug resistance. Longer-lasting options could soon make these interruptions less common.

ViiV Healthcare recently submitted its once-monthly combination of cabotegravir and rilpivirine for regulatory approval in the European Union, months after it submitted it for approval in the US.

Cabotegravir is ViiV's integrase inhibitor, and it has never been approved before.

Rilpivirine is Janssen's non-nucleoside reverse transcriptase inhibitor, which has been approved before as a once-daily agent in combination with other antiretrovirals.

If approved, this new combination will be the first monthly, injectable treatment for HIV. In two pivotal trials this combination worked just as well as daily three-drug pills, and most people preferred the once-monthly option, ViiV reported earlier this year.

Merck & Co., meanwhile, has presented early data on a candidate that could provide an even longer-acting option. On the basis of a small 12-patient trial, an islatravir-eluting subdermal implant is likely to provide antiviral activity for 8–16 months, they reported at the International AIDS Society Conference on HIV Science in July.

Islatravir, formerly called MK-8591, is a nucleoside reverse transcriptase translocation inhibitor. Merck licensed the small molecule from Yamasa, a manufacturer of soy sauce.

A long-lasting version of this drug — delivered either as an eluting implant or as a once-monthly pill — could be particularly useful for pre-exposure prophylaxis, Daria Hazuda, vice president of infectious diseases and vaccine discovery at Merck, recently told *Nature Reviews Drug Discovery*. The company is looking for agents that it can combine with islatravir into a longer-lasting ART cocktail option.

Asher Mullard