News in brief

Big mRNA players focus on flu vaccines

Pfizer and BioNTech's mRNA vaccine for influenza and COVID-19 began phase 1 trials in November, joining the growing number of jabs aiming to capitalize on mRNA technology. The trials will administer Pfizer's quadrivalent influenza vaccine (qIRV (22/23)), encoding the hemagglutinin glycoproteins of four influenza strains, and the companies' Omicron-tailored bivalent COVID-19 vaccine that targets the original SARS-CoV-2 strain and BA.4 and BA.5 variants. Moderna is also in phase 1/2 trials with a vaccine (mRNA-1073) combining its quadrivalent influenza and original-strain COVID vaccines (mRNA-1273). Other mRNA-made jab combinations in phase 1 trials include Moderna's influenza, COVID-19 and respiratory syncytial virus vaccine (mRNA-1230).

Pfizer and Moderna, as well as heavyweights Sanofi Pasteur, partnered with Translate Bio, and GlaxoSmithKline, working with CureVac, are also pursuing single mRNA flu vaccines. Yet mRNA-made flu shots have yet to match the efficacy of COVID-19 mRNA vaccines. The upside of mRNA technology is, however, that it is substantially faster than traditional methods, such as the decades-old egg-based production, newer cell-based systems or recombinant protein vaccine production — all of which require onerous purifications. Shorter production times mean that vaccines can be made closer to the start of flu seasons than current vaccines, allowing better matching to the year's circulating strain. mRNA technology also allows large numbers of antigens to be incorporated — Moderna announced it is investigating one-time universal flu vaccines that would also allow cheap, local manufacture.

to progress over time" says Azad Bonni, senior vice president and global head of neuroscience and rare diseases at Roche Pharma Research and Early Development.

Others are targeting more than one neurotoxic protein at once. Annovis Bio aims to simultaneously reduce high levels of amyloid-β, tau, α-synuclein and TDP-43 proteins because, although they have different molecular functions, they share some common molecular pathway. "All four [proteins] impair axonal transport," says Maria Maccecchini, CEO and founder of Annovis. "To use an antibody or an antisense oligonucleotide against one toxic protein is going to fail," she says. The company's small molecule buntanetap, an enantiomer of phenserine, is a translation inhibitor that targets an iron-response element in the 5′ untranslated region of several mRNAs whose proteins are found in Lewy bodies. In an exploratory phase 2a trial with buntanetap (previously known as ABVS401), Annovis reported lowering α-synuclein aggregates and improving cognition, in both PD and Alzheimer's disease. A phase 3 trial in 450 patients with early PD has started, with interim results expected early next year.

Recent results implicate mitochondrial membranes in the initial seeding of α-synuclein aggregates. A team led by Sonia Gandhi at the Francis Crick Institute in London observed the elusive initial events that lead to intracellular seeding taking place in cortical neurons from patients with PD using a 3D single-molecule Förster resonance energy transfer (FRET) biosensor. They observed intermediate α-synuclein oligomer deposits on mitochondrial membranes.

Initial evidence for mitochondrial dysfunction in PD emerged in the 1980s when drug abusers were exposed to MPTP, an environmental toxin, resulted in an immediate and irreversible parkinsonian syndrome. MPTP inhibited the mitochondrial electron transport chain, leading to a toxic accumulation of α-synuclein and free radical production leading to oxidative cellular damage.

For Pretzel Therapeutics, the goal is to modulate mitochondrial biology. "Parkinson's patients seem not to be able to create enough copies of mitochondrial DNA," says Gabriel Martinez, CSO and co-founder of Pretzel. Pretzel is not yet disclosing its targets, but Baruch Harris, chief operating officer, says: "There are almost 200 genes linked to mitochondrial disease."

Gene-based understanding of PD is paving the way to a plethora of new drugs. "α-synuclein, *LRRK2* and *GBA1* are the priority targets," says Hirst. One of the most frequent mutations is in the leucine-rich repeat kinase 2 (*LRRK2*) gene. The increased kinase activity is involved in regulating vesicular trafficking via phosphorylation of Rab small GTPases. Biogen has a collaboration with Ionis Pharmaceuticals to investigate an antisense oligonucleotide against *LRRK2* mRNA in phase 1 clinical trials. Curiously, LRRK2 kinase activity is elevated in the dopamine neurons of patients with Parkinson's disease whether or not they have mutations in the gene, widening the market for any successful therapeutic.

Pathogenic LRRK2 activity is also thought to disrupt the balance between lysosomal membrane repair and lysophagy. Oncodesign has developed a macrocyclic inhibitor of LRRK2 kinase in collaboration with the French pharma company Servier. Macrocycle drugs are molecules with a cyclic framework, most of them derived from natural products. Because they can cross the blood–brain barrier, an important requirement for a PD agents, they are being investigated by other companies, including Neuraly, to counter pathologic α-synuclein.

The blood–brain barrier certainly poses an obstacle for monoclonal antibody entry into the brain, one that gene therapy and antisense approaches can potentially overcome. Ionis's antisense oligonucleotide ION464, also developed in partnership with Biogen, targets α-synuclein and is in phase 1 trials for another synucleinopathy, and a PD trial is expected to follow any positive results, says Hirst. Biogen is also partnering with Sangamo to apply a zinc finger gene-editing technique to reduce α-synuclein gene expression. Sangamo's ST-502, delivered using an adeno-associated virus, is in preclinical testing.

Another common mutation in PD that has piqued drug hunters' interest is the β-glucocerebrosidase (*GBA1*) gene, involved in sphingosine metabolism. It results in a deficiency of the lysosomal glucocerebrosidase enzyme, which leads to glycolipid accumulation and α-synuclein deposition, a process that increases during normal aging. Several studies have suggested that ramping up GBA activity with GBA activators could increase glycosphingolipid clearance and attenuate α-synuclein levels.

Prevail Therapeutics, which Eli Lilly announced in 2020 it would acquire for $880 million, is testing an adeno-associated virus-based gene therapy to replace mutated *GBA1*. The viral vector is injected into the cisterna magna, above the spinal canal, to deliver the gene therapy to the brain, where it will