loss and how to counter it. "Until recently the dogma was that hearing loss was all about hair cells," says Holtzman. "But Charles Liberman at Massachusetts Eye and Ear, who cofounded Decibel in 2015, has shown that even before you get hair cell damage you can see synaptic damage, which can affect hearing fidelity and the ability to discriminate sounds." Decibel has two preclinical programs focused on synaptic damage, known as synaptopathy: one based on a macromolecule and the other using an antibody approach. Decibel declined to disclose any further details.

Decibel is not alone in drawing on this new understanding. Otonomy is currently developing OTO-413 for restoring synaptic function in speech-in-noise hearing loss, in which patients struggle to hear speech against any kind of background noise despite hearing the pure tones in standard audiometry tests. "In speech-in-noise hearing loss, sensory hair cells and spiral ganglion neurons are still there, they're just not connected," says Kathie Bishop, CSO at Otonomy, based in San Diego, California.

Otonomy's OTO-413 is brain-derived neurotrophic factor (BDNF) delivered in a sustained-release formulation. "BDNF can reconnect these synapses, and with our formulation we get several weeks' exposure following a single injection. We've tested this in animal models, and right now we're going through the required toxicology studies and the Investigational New Drug enabling work to start a clinical trial planned in the first half of 2019."

Neurons are also being targeted in other approaches. Auris Medical, a biopharma based in Basel, Switzerland, has AM-101 (Keyzilen; esketamine hydrochloride)—an NMDA (*N*-methyl-D-aspartate) antagonist in a biodegradable otic gel intended to target aberrant excitation of the auditory nerve—in phase 3 trials for the treatment of certain types of tinnitus. Despite not meeting efficacy endpoints in early trials, AM-101 has a Fast Track designation from the US FDA, and revised trials are ongoing. Another Auris candidate, AM-111—a peptide inhibitor of the JNK stress kinase—has also reached phase 3 and gained Fast Track status from the FDA, as well as Orphan Drug status from both the European Medicines Agency and the FDA. AM-111, also delivered in an otic gel, blocks apoptosis in stress-injured sensory cells.

Cochlear hair cell regeneration is another active area of research. Although many non-mammalian species can regenerate lost hair cells, humans and other mammals cannot. "In recent years there have been significant advances in understanding cochlear progenitor cells and how they're controlled that has opened up some significant therapeutic opportunities," says Chris Loose, cofounder and CSO of Frequency Therapeutics.

Frequency is developing combination therapies to awaken dormant progenitor cells by simultaneously targeting two pathways to activate and push them into a developmentally malleable state that could potentially allow them to differentiate into functional hair cells.

The company's lead candidate combination, FX-322, combines a small-molecule activator of the Wnt signaling pathway and the FDA-approved agent valproic acid, an inhibitor of histone deacetylases. *In vitro* studies using cochlear tissue from rodent, nonhuman primate and human samples support such an activity for this combination, says Frequency's LeBel. In August 2018, the company launched a phase 1/2 trial of FX-322, delivered by intratympanic injection, in stable sensorineural hearing loss.

Sound Pharmaceuticals also aims to regenerate cochlear cells, but taking a small interfering RNA approach. The therapeutic agent is SPI-5557, which inhibits $p27^{Kip1}$, an inhibitor of cyclin-dependent kinase whose deletion in mice leads to proliferation of supporting cells and the regeneration of hair cells. Sound anticipates launching a phase 1/2 trial of SPI-5557 at the end of 2019.

Although most otological therapies are delivered locally to the ear by injection, Sound's SPI-1005 and SPI-3005 are oral formulations of a small molecule, whose size (~300 daltons) allows them to cross that blood–labyrinth barrier that prevents other molecules leaving systemic circulation and entering the ear. The active agent, ebselen, mimics a catalytic antioxidant enzyme in the cochlea that protects and repairs hair cells from oxidative damage. Sound is running early-stage clinical trials for SPI-1005 to protect against acoustic trauma and for treating Meniere's disease and tinnitus, and for SP-3005 against ototoxicity induced by aminoglycoside antibiotics, platinum-containing chemotherapy or loop diuretics.

In September 2018, Decibel announced that it had obtained an exclusive, worldwide license to develop and commercialize ORC-13661, an early stage drug for treating aminoglycoside-induced hearing loss and balance disorders originally developed by Oricula Therapeutics, which entered phase 1 trials in May 2018.

With all this activity, hearing-loss researchers such as Avraham see a bright future. "There's been a lot of progress made in the past ten years, and I predict the next ten will be much greater", she says. "There has been a lag in our field, and we're relieved that companies are now busy in this space, as we need them take the basic research into the clinic."

Dan Jones *Brighton, UK*

Roche's cell squeeze provokes killers

SQZ Biotechnologies and Roche have expanded their three-year cell therapy partnership to develop antigen-presenting cells (APCs) for immuno-oncology. The biotech gains $125 million up front and in near-term milestones, and up to $250 million in total milestones per product. The partners aim to generate APCs powered up to directly provoke killer ($CD8^+$) T cells into action.

The CellSqueeze technology consists of a microchip that gently forces APCs to pass through a narrow channel in a microfluidic device. The pressure temporarily disrupts the cell membrane and creates pores that allow external substances—including whole proteins and potentially tumor lysates—to penetrate the cells. This type of mechanoporation is gentler to cell integrity and causes fewer gene expression changes than electroporation. In this collaboration, the APCs will be derived from the patient's own peripheral blood mononuclear cells and loaded with tumor antigens using SQZ's platform.

As the approach does not require genetic modification or cellular expansion, it could be cheaper, quicker and safer than other cell-based immunotherapy platforms such as CAR-T cell therapies. The partnership will focus on developing cancer therapies, particularly for those cancers difficult to treat with other cell-based immunotherapy approaches—including head, neck and cervical cancers and other solid tumors.

Joana Osorio

"**Kendall Square is to science what New York is to finance, what Paris is to culture, what Washington is to government."** Jay Bradner, president of the Novartis Institutes for Biomedical Research, comments on the rise of Kendall Square and Cambridge, Massachusetts, as a fulcrum for biotech. (*Bloomberg*, 5 October 2018)

"By adopting foreign price controls on the very small number of innovative medicines that make it to market, this proposal will severely chill investment in new cures and therapies for America's seniors." Biotechnology Innovation Organization CEO Jim Greenwood comments on the Trump administration's proposed drug pricing policy. (*GEN*, 26 October 2018)

"As a result of Merck's decision, more than a half-million children in West Africa may not receive the vaccine in 2018 and 2019." GAVI, the vaccine alliance, reacts to Merck ending a long-standing agreement to supply rotavirus vaccine to West Africa while pivoting to the Chinese market. (*National Public Radio*, 1 November 2018)"