of RNA that binds to both the enzyme and the target DNA[9]. This approach is also known as CRISPR–Cas gene editing. The guide RNA matches the mutant but not the wild-type gene, enabling Gao and colleagues to solve the problem of ensuring that the mutant form of the gene is cut whereas the wild-type version is left untouched.

Another challenge was to get Cas9 into the inner ear. *In vivo* gene-editing approaches often rely on viruses to introduce nuclease-encoding sequences into the organism being edited[10,11]. However, Gao and colleagues reasoned that, when the nuclease has done its job in the cell, it will no longer be required, so introducing the protein itself should suffice. They turned to a technique they had used previously[12], in which they packaged Cas9 protein bound to its guide RNA in a type of lipid droplet that can fuse with cells, enabling the editing machinery to enter. The authors injected these droplets into the inner ear of newborn Beethoven mice.

The inner ears of unedited adult Beethoven mice were barren of hair cells; however, their gene-edited adult siblings had inner-ear hair cells that were almost indistinguishable in shape and number from those in wild-type mice. The edited animals could be startled by a sudden loud noise, whereas their unedited siblings could not. More-sophisticated measurements also confirmed that hearing improved as a result of gene editing. Encouragingly, the engineered nuclease seems to have stayed true to its design and did not create undesired genetic changes of concern in the DNA of the hair cells.

A modest fraction of cells were edited. The authors propose that this low proportion of edited cells resulted in a beneficial 'halo'-like effect on neighbouring unedited cells that still contained the mutant form of the gene, preventing the death and degeneration of these neighbouring cells. Although the mechanism underlying this proposed halo effect is unclear, the finding offers encouragement for the clinical adoption of this approach, because it suggests that the genetic repair of all hair cells is perhaps not needed to achieve a beneficial effect on hearing.

Gao and colleagues' work provides an essential first step towards moving this type of approach nearer to the clinic by providing evidence that it is safe and effective in an animal that has a similar genetic mutation and comparable hearing loss to those in humans. How long could it be before individuals with this *TMC1* mutation might be treated using gene editing? One reason for optimism comes from the pace at which other gene-editing approaches have reached the clinic.

To give just a few examples from clinical trials, the gene *CCR5* has been inactivated in immune-system cells using a type of enzyme called a zinc-finger nuclease to try to reduce the viral load in people infected with HIV[13]. Immune cells have also been edited to generate cancer-targeting cells[14]. However, these techniques required cells to be removed from the patient's body for gene editing and then replaced. Ear cells cannot be removed, so a direct *in vivo* approach is needed, which is even more challenging to achieve than *ex vivo* gene editing.

Encouragingly, such *in vivo* gene editing (for a different condition) has been performed in a clinical trial using zinc-finger nucleases[15], and the work leading up to that[16] makes clear the next steps for Gao and colleagues' approach. A nuclease must be found that has clinical-grade potency and specificity in human cells. Lipids must be identified that can be safely injected along with the nuclease into the human inner ear. Next, this nuclease must be tested for safety in larger animals, such as primates. An *in vivo* virus-based gene therapy for direct injection into the eye[17] has been recommended for approval in the United States, and that work provides a road map for the scientific, medical and commercial considerations that need to be taken into account when moving to the clinic.

In 1902, the physician Archibald Garrod initiated the first study that demonstrated a link between a gene and a disease. Since then, more than 5,000 diseases have been linked to single-gene changes. However, without the tools to modify disease-causing forms of genes, geneticists have often been unable to see their knowledge put to use for clinical benefit. The progress being made with genome editing is changing this. Although Beethoven never heard his famous *Ode to Joy*, it could be that — thanks in no small part to his murine namesake's fateful encounter with Cas9 — we are getting closer to the day when individuals with deafness-causing mutations can be treated by gene editing to prevent hearing loss. ■

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MATERIALS SCIENCE

Rule-breaking perovskites

A material from the perovskite family of semiconductors emits light much more efficiently than expected. The explanation for this anomalous behaviour could lead to improvements in light-emitting technology. SEE LETTER P.189

MICHELE SABA

When a semiconductor absorbs light, a particle-like entity called an exciton can be produced. Excitons comprise an electron and a hole (the absence of an electron), and have two possible states: singlet and triplet. Triplet states were thought to be poor emitters of light, but, on page 189, Becker *et al.*[1] report that semiconductors known as lead halide perovskites have bright triplet excitons. The results could signify a breakthrough in optoelectronics because triplet states are three times more abundant than singlet states[2] and currently limit the efficiency of organic light-emitting diodes[3].

Conventional wisdom holds that triplet states are dark because of the spin selection rule[4], which forbids electrons from changing their intrinsic angular momentum (spin) during an optical transition — the process in which an atom or molecule switches from one energy state to another by emitting or absorbing light. The rule is taught in quantum-mechanics classes when atomic transitions are first introduced, and is so general that one might think that it is written in stone. Fortunately, there are loopholes that can be exploited.

The search for emissive triplet states has focused on a certain principle of quantum mechanics: if an electron's spin is coupled