Restoration of Hearing and Vision with Gene Therapy

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The Corey Laboratory has made fundamental advances in our understanding of the process of auditory transduction, including the recent identification of a pivotal sensor protein. This groundbreaking work has transformed our understanding of hearing and hearing loss and lays the groundwork for precision-targeted therapies to treat genetic deafness and blindness.

"Hair cells" of the inner ear are the receptor cells that convert a physical stimulus such as sound into neural signals that the brain can understand. Many different proteins are involved; when one or another of these has a mutation, hair cells cannot convert the sound and the person is deaf. Protocadherin-15 (PCDH15) is one such protein. PCDH15 is also used in the photoreceptor cells of the eye, so patients with PCDH15 mutations become blind over a period of about 30 years. Their combined deafness and blindness is known as Usher syndrome type 1F.

To develop a therapy for Usher 1F, we and collaborators have explored different methods to deliver a functional copy of the PCDH15 gene to hair cells of the inner ear and photoreceptor cells of the retina. We engineered a "mini-PCDH15" gene that would fit in an AAV vector. We also developed a line of PCDH15 conditional knockout mice that are deaf like Usher 1F patients. We injected AAV9-PHP.B vectors carrying the mini-PCDH15 gene into the inner ears of newborn deaf mice and tested hearing after four weeks. The mice receiving the mini-PCDH15 gene retained most of their hearing. With light and scanning electron microscopy, we found that the hair cells in untreated Usher 1F mice degenerated, but hair cells in treated mice had normal morphology.

If gene therapy with mini-PCDH15 works in the demanding environment of the inner ear, it is likely to also work to prevent the progressive blindness. We are testing efficacy of mini-PCDH15 in retinas of a zebrafish model of Usher 1F, and will test mini-PCDH15 delivery in nonhuman primate retinas to assess proper localization in photoreceptor cells and to evaluate toxicity.

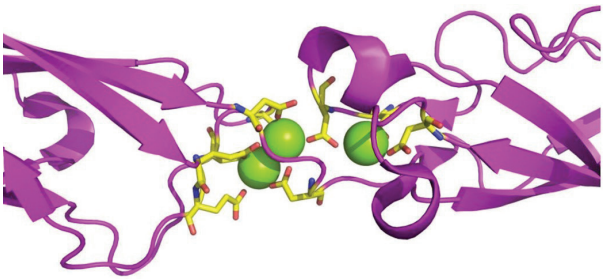

Figure 1. Engineering mini-PCDH15 based on atomic structure. PCDH15 has 11 EC repeats in its extracellular domain; to make a mini version we removed 5 of them. Adjacent EC repeats are each linked by three calcium ions (green) coordinated by side chains of aspartate and glutamate residues (yellow). Design of mini-PCDH15 required careful replication of this architecture in a synthetic EC-EC junction. Image: Sotomayor et al., 2012

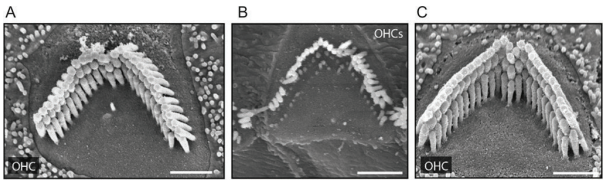

Figure 2. Rescue of hair cells with mini-PCDH15. A. Top of a normal hair cell showing the cilia bundle. B, Bundle of a PCDH15 knockout mouse at P30. The bundle is degenerating and the cell will die. C. Bundle in a mouse treated at P0 with an AAV encoding mini-PCDH15. Morphology is normal. scale bar = 1 μm Image: Maryna Ivanchenko