PRIZE ESSAY

FINALIST

Will McLean

As an undergraduate, Will McLean studied biology at Tufts University before going on to attain a Ph.D. at the Massachusetts Institute of Technology within the Harvard-MIT Division of Health Sciences and Technology. While at MIT, his doctoral research elucidated the distinct progenitor cell types that exist within the inner ear and their capacity to form sensory cells and neural cell types. As a postdoctoral researcher at Harvard Medical School, he investigated maniuplation of signaling pathways to enable otherwise senescent progenitor cells of the cochlea to divide and form new sensory cells. He is currently vice president of biology and regenerative medicine at Frequency Therapeutics. Frequency is currently using McLean's insights to develop a drug to treat hearing loss by regenerating lost sensory cells. **www.sciencemag.org/content/359/6380/1113.3**

REGENERATIVE MEDICINE

Toward a true cure for hearing impairment

The regenerative power of progenitor cells holds promise for reversing hearing loss

By **Will McLean**

Five percent of the human population (360 million people) experience some form of hearing impairment. Patients with hearing loss often describe the experience as socially isolating, and recent research has shown a significant correlation with hearing loss and later onset of dementia.

Each of us is born with 15,000 sound-sensing cells per ear. Hearing loss occurs when these cells (called hair cells) die from noise exposure, certain medications, and other environmental factors. Unlike birds, fish, and amphibians, mammals lack the ability to regenerate these cells.

Currently, the only way to treat hearing loss is with palliative devices such as hearing aids. Although these technologies improve hearing performance for many patients, the benefit is limited because only the residual hair cells can be stimulated. Thus, a large unmet need exists for a therapeutic solution to restore hair cells.

Because other species regenerate hair cells, and other mammalian tissues regenerate, my colleagues and I reasoned that there must be a way to induce hair cell regeneration in mammals. We just needed to find the key to unlock this ability.

DEFINING THE LIMITATIONS OF INNER EAR PROGENITOR CELLS

The inner ear contains the hearing organ (cochlea) and balance organs (vestibular system), and both contain their own specialized hair cell types. Hearing and balance dysfunction can arise from hair cell loss or damage to the neurons that connect to these hair cells (or a combination of the two).

Although the hair cells of the inner ear cannot regenerate, it has been suggested that the inner ear contains stem cells that can form hair cells and neurons in cell culture (*1*). However, it was thought that this capability was all due to a single universal stem cell that was pluripotent. This was particularly surprising given the inner ear's limited ability to repair itself.

My research showed that instead of having a universal stem cell, the inner ear contains distinct populations of progenitor cells (*2*). One such population expresses the leucine-rich repeat–containing G protein–coupled receptor (Lgr5), a stem cell marker originally identified in the intestine (*3*). Later, it was found that Lgr5 cells also serve as hair cell precursors during cochlear development (*4*, *5*). We found that even after development, these cells could form new hair cells that had protein and gene expression profiles like native hair cells. When tested physiologically, these newly formed hair cells resembled those found in the mature organ.

I also showed that the balance organs have progenitor cells that could form fully functioning hair cells. Interestingly, the cochlea and vestibular system could only form hair cells from their native organ, suggesting that these two populations of progenitor cells are distinct.

Whereas previous work showed that neurons could be obtained from inner ear stem cells (*1*), presumably from the universal stem cell, my research showed that neural cell types specifically arise from glial cells within the inner ear that express myelination proteolipid protein 1 (Plp1) (*2*).

In addition to identifying a new population of progenitors, we also showed that the Plp1 cells have greater plasticity than cochlear or vestibular progenitor cells because they could form cell types outside of their native environment. In fact, the Plp1 progenitors formed neurons and glial cells from both the peripheral and central nervous system.

Together, this work demonstrated that different progenitor types exist within the ear that have defined capacities to form

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specific cell types. Thus, tailoring a treatment for hearing loss, balance ailments, or neural damage may require targeting mechanisms that are unique to each progenitor cell type.

UNLOCKING THE REGENERATIVE POTENTIAL OF PROGENITORS

Although it was shown that progenitor cells are present in the inner ear after organ development is complete, it was evident that such cells fail to divide and differentiate to repair the surrounding tissue. In addition to preventing hearing repair, this has also impeded drug discovery because it is difficult to obtain adequate numbers of primary cochlear cells for therapeutic screening.

To overcome this lack of regenerative behavior in the ear, studies of how intestinal Lgr5 cells regenerate served as inspiration (*6*). This particular stem cell is responsible for completely renewing your gut epithelium every 5 to 7 days. Using insights from pathways and signals that drive this process, a drug combination was identified that stimulates inner ear Lgr5 progenitor cells to divide by reprogramming them to a more plastic state (*7*). These drugs produced over 2000-fold more Lgr5 cells compared with methods used before, and the cells could be subsequently converted into nearly pure populations of hair cells. Further, these drugs proved to be effective with cells from adult mouse, nonhuman primate, and human. This breakthrough effectively relieved a bottleneck in the field and created the first large-scale drug-discovery platform for hearing loss.

From this initial discovery with single cells, it was further shown that treating damaged mouse cochleae with molecules that proliferate Lgr5 cells in cell culture could effectively induce progenitor cells to divide and regenerate lost hair cells in situ. This technology, referred to as Progenitor Cell Activation (PCA), was the catalyst for forming Frequency Therapeutics, a start-up that I cofounded with Bob Langer and Jeff Karp, that seeks to treat hearing loss and other ailments by using drugs to activate the body's progenitor cells to initiate repair. To date, PCA has been successfully used to identify drug combinations that elicit similar effects in multiple tissues throughout the body.

TRANSLATING DISCOVERIES INTO POTENTIAL TREATMENTS

Since publishing proof-of-concept results to regenerate hair cells in damaged tissue (*7*), recent experiments have shown that local treatment to the ear can elicit a functional hearing improvement in animals with hearing loss. Based on these results, Frequency Therapeutics has expanded development for therapeutic application in humans and recently completed a first-in-human phase I safety study that met all end points. Therefore, this work could one day provide patients with a regenerative therapy to restore their hearing.

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