CENTER ON HUMAN DEVELOPMENT & DISABILITY
UNIVERSITY of WASHINGTON

CHDD Outlook 2012 Issue #4
News from the Center on Human Development and Disability at the University of Washington Health Sciences Center

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Hair Cell Regeneration Could Change Way World Sounds and Feels for Millions

by Joel Schwarz

Hair cells are tiny sensory receptors that are necessary for humans to hear and to maintain their balance. They are called hair cells because they have hair-like structures, or stereocilia, projecting from their surface. Stereocilia are critical for conversion of the energy in sound waves into signals that can be processed by the brain. They also help hair cells to encode changes in head position that allow us to maintain our orientation in space and to coordinate our movements.

Stone studies cellular and molecular mechanisms of hair cell production that may someday improve hearing and balance in humans with hearing loss.

Hair cells can be damaged in a variety of ways including loud sounds, medicine such as antibiotics and anti-tumor drugs, genetic conditions, infection, disease and age. Hair cell damage is very common, particularly in the elderly, and it leads to debilitating, irreversible deficits in hearing and/or balance because hair cells are not regenerated. While hearing aids and cochlear implants improve hearing for many people, they do not enable listeners to hear well in noisy environments. This problem can lead to social isolation and to compromises in education and employment. There are few treatments for balance problems, but vestibular implants are under development at the UW and elsewhere.

Researchers at the University of Washington's Bloedel Center, including a number also affiliated with the Center on Human Development and Disability (CHDD), are exploring ways to regenerate hair cells in order to enhance hearing and balance in millions of individuals with inner ear damage. One of these investigators is Jennifer Stone, Ph.D., an associate research professor of otolaryngology. Her work is focused on understanding how hair cells are produced during development and how they might be regenerated in humans after damage.

Regeneration of hair cells was considered to be impossible until the late 1980s, when researchers discovered that birds spontaneously produce new auditory and vestibular hair cells following severe hair cell loss and regain hearing and balance function. These findings provided researchers an important animal model to study, according to Stone. "This finding showed us that at least some warm-blooded vertebrates have an innate mechanism to produce new hair cells once they are lost during adulthood," she said.

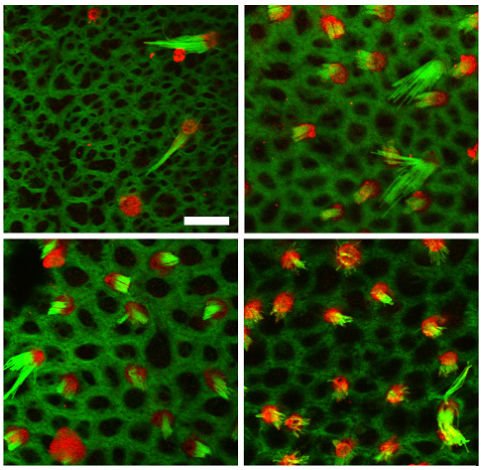
Stone's lab now looks at the cellular and molecular mechanisms of hair cell production in avian and small mammalian models, chickens and mice, respectively. Late last year her lab, working with

cultured mouse vestibular organs, published a paper in the Journal of Neuroscience that showed mature mice have a natural capacity to initiate vestibular hair cell regeneration and this capacity is enhanced when an inhibitory signaling pathway is blocked. “The study showed that adult mice have a very robust pro-regenerative response to damage, but the process doesn’t go on to completion,” explained Stone. Many progenitor cells (cells with capacity to convert into another cell type, with or without cell division) begin to phenotypically convert into hair cells, but they are diverted along the way. However, when researchers in her lab blocked signaling through the notch pathway, which mediates lateral inhibition between immature precursor cells, there was a thirty-fold increase in the number of progenitor cells that fully converted into hair cells. “This work showed that the notch pathway severely inhibits the number of vestibular hair cells that are normally regenerated in adult mice,” Stone said.

Discoveries such as this are small stepping stones along a long path that could lead to new methods to treat hearing and balance deficits for millions of people. Stone estimates that treatment using hair cell regeneration for humans is 10 to 20 years away. “It is a difficult challenge to form new hair cells that survive and connect appropriately with the brain. While it is clear that hair cells are the best cells to do the job, we don’t know if one needs 100 or 3,000 of them to produce improvements in hearing and balance function that are superior to current treatments,” she said. “That said, it is our belief that hair cell regeneration will ultimately be the most effective cure for sensorineural hearing and balance deficits.”

To develop treatments through regeneration, Stone said researchers need to take the following four steps:

- Identify additional therapeutic agents that enhance regeneration in mice and other mammals.
- Develop safe methods of manipulating those factors in live mammals.
- Show that these manipulations will lead to lasting improvement in hearing or balance function.
- Find ways to deliver therapeutic agents to humans in a safe and beneficial manner.



This series of images shows hair cells (labeled for myosin VIIa in red) at different times after hair cell ablation. Hair cells with small bundles are replaced in specific regions of the utricle. Notice the increase from upper left to lower right.

A number of other CHDD research affiliates are conducting lines of work that touch on other aspects of hair cell regeneration. Edwin Rubel, Ph.D., a professor of otolaryngology/head and neck surgery, physiology and biophysics, has been exploring hearing in birds and rodents for decades and is currently using a zebrafish model to study hair cell regeneration. Elizabeth Oesterle, Ph.D., a research associate professor of otolaryngology/head and neck surgery, is working on stimulating new cell division in mature birds and mammals after hair cell damage. Clifford Hume, M.D., Ph.D., an associate professor of otolaryngology/head and neck surgery, is exploring the transcription factors, or genetic switches, controlling hair cell regeneration. Olivia Bermingham-McDonogh, Ph.D., a research associate professor of biostructure, studies the genetics of the developing cochlea and factors that prevent the regeneration of hair cells in mammals.

CHDD is an interdisciplinary center dedicated to the prevention and amelioration of developmental disabilities through research, training, clinical service, and community outreach. CHDD includes the University Center of Excellence in Developmental Disabilities and the Eunice Kennedy Shriver Intellectual and Developmental Disabilities Research Center.

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