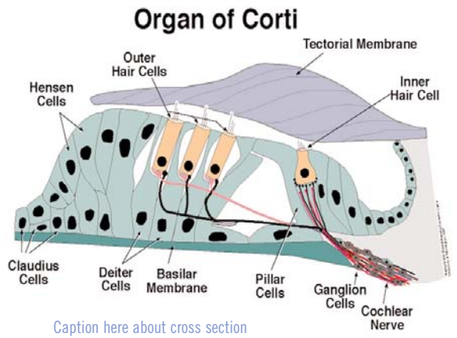
research areas crucial to completing the effort. Given the increasing competition for scarce research dollars, a comprehensive and integrated research plan with fair sharing of effort is highly likely to attract outstanding scientists to this effort. Collaboration will be enhanced by 1) providing joint interest in the intellectual properties created by this research, 2) active involvement in research design and priorities, 3) the realization that the goal of the project is larger than any one lab can reasonably tackle, and 4) the opportunity to participate in such a unique venture, which is compelling from a personal and a professional view.

Once this group of scientists from both inside and outside the auditory neuroscience community is brought together, collaborative decisions about new approaches can be made, and implementation can begin.

The Budget

Implementing the Hearing Regeneration Initiative will require approximately $1 million to $1.5 million per year for five to seven years, or approximately $10 million overall, to support a multifaceted, large-scale effort. This level of stable long-term funding would enable five or more senior investigators to devote 50 percent of their laboratory efforts and resources exclusively to this effort. Each of the investigators would need between $200,000 and $300,000 per year to commit half their time and staff to the project. These funds would provide salary support for investigators and technical staff, research supplies, and equipment upgrades. No funds would be used for construction or renovation. The number of participating labs would ultimately be determined by the size of the HRI fund.



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We have received from a private foundation a major leadership gift of $1.5 million spread over 2004 – 2005. This gift also includes the promise of an additional $1.25 million in matching funds contingent on securing dollar-for-dollar matching donations in 2005 through 2007. We have already escalated our research effort based on the initial gift and have begun planning for the remainder. We are seeking donors to help meet the challenge of raising $1.25 million over the next three years to assure that this important matching-fund opportunity is not lost, while continuing our campaign to raise the remaining $6 million to complete the Hearing Regeneration Initiative.

A significant gift would accelerate progress and help us to unleash the exciting potential of hair cell regeneration research. The Office of Development at the University of Washington's School of Medicine is empowered to discuss possibilities with interested donors on behalf of the Bloedel Hearing Research Center.

For more information on the Hearing Regneration Initiative, please contact Andrea King, UW Medicine Associate Director of Development, at (206) 221-4769 or aking@u.washington.edu.

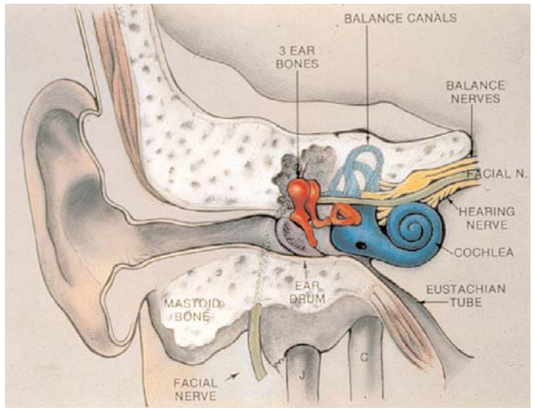
UW Medicine

THE HEARING REGENERATION INITIATIVE

A Potential Cure for Inner Ear Hearing Loss

The Problem

Hearing loss is the most common human disability: one person in 10 is directly affected, and 40 percent of the population has a hearing-impaired friend or family member. All of these people have experienced first hand the difficulties that occur when people cannot communicate normally. Although hearing aids and cochlear implants have helped many children and adults with hearing disabilities, we believe the potential to cure deafness is at hand and should be pursued. We are committed to assuring that all children have the tools to develop spoken language to communicate and that no person should be deprived of the vital company of friends and family because of hearing loss.



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Most cases of severe hearing loss result from damage to the cells in the inner ear. Without these cells, which collectively transform sound energy into nerve discharges, hearing is not possible. The primary sound receptors in the inner ear (called hair cells) are very sensitive, but they are also very fragile and susceptible to damage from many causes including noise, aging, toxic medications, infection, trauma, and genetic conditions. Other cells support and power the hair cells. All the cells of the inner ear are completely formed before birth; when they are lost in humans or any other mammal, they are not replaced, and permanent hearing loss results. Birds, on the other hand, regrow their inner ear cells spontaneously after damage, and hearing is restored.

Regeneration

Over the past decade, regrowth of certain human cells has become a clinical reality. For example, new skin can be grown in the laboratory and used to resurface burns. We now know that new hair cells can be formed under certain laboratory conditions. The search to identify these conditions and the factors that regulate cell regrowth is the heart of the research initiative planned by University of Washington scientists. While the primary focus of the initiative is on hair cell regeneration, all the cell types in the inner ear will be examined.

Researchers at the Virginia Merrill Bloedel Hearing Research Center at the University of Washington were the first to discover hair cell regeneration in birds, and they continue to be the leaders in the field of hair cell regeneration research. They have confirmed that regenera-

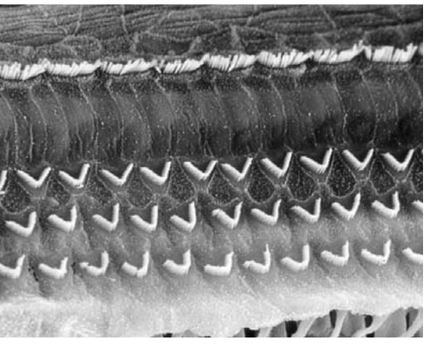
tion of inner ear structures in mammals (as well as birds) is possible. UW researchers are now poised to take the next step in bringing this possibility closer to a practical treatment for the hundreds of millions of hearing-impaired people worldwide.

In both a practical and a theoretical way, the only path to restoring lost hearing is through regeneration. The details of the research strategies that we believe will lead to success are spelled out in the accompanying material. In these pages we provide a brief executive overview.

The Need: Accelerating the Progress

The search for the critical genes and cellular processes regulating hair cell regeneration in mammals has made substantial progress since hair cell regeneration in birds was discovered 15 years ago. This progress has been painstakingly slow, however, for several reasons. First and foremost, hair cell regeneration is a complex puzzle to solve. Second, only a small number of investigators are studying hair cell regeneration, and communication among these investigators is sporadic. Third, financial support has been a challenge. This research has depended largely on NIH funding, typically in the form of relatively small three-year grants. Thus, investigators have to apply and reapply for grants on a seemingly continual basis, which takes time away from creative thinking, communication with peers, and completing experiments. Moreover, investigators tend to submit grant proposals based on low-risk experiments, which are more likely to be funded. These issues have caused the majority of past studies on hair cell regeneration to be narrowly focused and non-exploratory. Clearly, a bold new vision is needed to accelerate progress, and adequate private funding is needed to support that vision.

Reaching Our Goal: A Collaborative Multidisciplinary Approach



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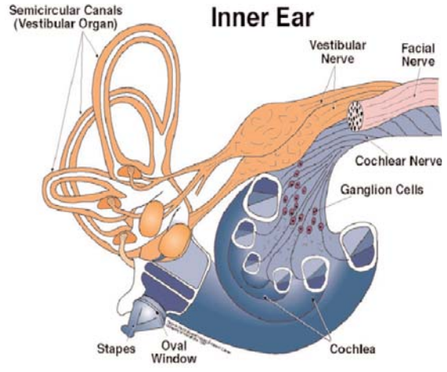
We believe that for hair cell regeneration to become a mainstream treatment for curing hearing loss, we must bring great minds together to initiate research approaches that are novel, high-risk, and high throughput. The best way to achieve this goa is to encourage researchers to look outside their own areas of interest. By creating a forum for the cross-pollination of ideas and engaging other scientists who think creatively about their own systems' issues every day, we can develop new strategies. Combining expertise in auditory system science with expertise in cellular regulation is the most likely approach to make significant progress in determining how to induce regrowth in human hair cells.

Collaborative research groups have been widely used in clinical research. For example, modern clinical trials for cancer therapy require large numbers of patients in order to determine treatment effectiveness. Collaborative research groups have been important in genetic research where expertise in a wide range of areas is vital.

In basic science, by contrast, collaborative research projects are not often used. The nature of fundamental research and the available funding mechanisms have made such collaborative work difficult. In the past, basic scientists have tended to work alone or in small groups under the senior scientist's direction. Because of competition for limited federal funding, sharing one's best ideas with a potential competitor might be risky. In the collaborative model, where funding is assured, sharing ideas is a natural and fruitful endeavor.

At the University of Washington's Virginia Merrill Bloedel Hearing Research Center, collaborative research has been the rule. A broad-based multidisciplinary team of researchers has been in place for many years, bringing a wide range of strategies and expertise to bear in unraveling some of the complex questions around the treatment of hearing loss. Indeed, the Bloedel team has dominated the world's literature on hair cell regeneration with more reports of fundamental research than any other lab.



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Already in place is the Bloedel team of Edwin Rubel, Elizabeth Oesterle, Jennifer Stone, Olivia Bermingham-McDonogh, Clifford Hume, and George Gates. Each is working on distinct but complementary and interrelated areas associated with hair cell regeneration. **Dr. Rubel** is focused on cell cycle control in model systems for studying hair cell regeneration. **Dr. Oesterle** is studying the role of leukocytes, growth factors, and transcription factors in promoting progenitor cell division and hair cell differentiation in the mammalian inner ear. **Dr. Stone** is characterizing hair cell progenitors and stem cells from the mature avian inner ear, the role of transcription factors on promoting cell cycle exit, and hair cell differentiation. **Dr. Bermingham-McDonogh** is delineating the role of growth factors in regulating cell proliferation and differentiation in inner-ear development and regeneration. **Dr. Hume** is examining in vitro control of neurite outgrowth and reinnervation of regenerated hair cells in the mammalian inner ear. **Dr. Gates** is the clinical collaborator and team coordinator.

While this will constitute the initial core group of investigators, a major part of this plan is to recruit the collaboration of senior investigators with active laboratories within the UW system. These lab groups will not have expertise in hearing or the inner ear, but will have great expertise and ongoing experience in areas of cellular and molecular biology essential to our goal of regenerating human inner-ear hair cells.

The Plan

Thanks to the recent major lead gift for this initiative, we are taking the next step. Assembling a scientific advisory group of internationally recognized scientists will begin this process. We will hold a scientific "think-tank" this fall in Seattle with these experts and notable auditory scientists to brainstorm about the most likely avenues for success. We will then implement the first round of scientific experiments to evaluate these ideas.

We will hold progress report meetings at least every six months in which the participating investigators will present the results of their work, discuss the next steps, and agree upon specific hypotheses to test and the experiments designed to test them. Each participating laboratory will volunteer to carry out the experiments best suited to their skills and experience. All labs will maintain close communication on a regular basis to address those technical issues that invariably arise in this type of research. Thanks to modern information technology, sharing images and data over the Internet allows rapid communication among the collaborators.

The scientists included in this consortium have established world-class laboratories with equipment, personnel, and research networks linking them to the other major laboratories in their area of research. Collectively they provide the necessary expertise and facilities in the