Hearing Health Foundation
Prevention | Research | Cure

HRP Hearing Restoration Project

Strategic Research Plan of the *Hearing Restoration Project* (HRP)

The ongoing promise of hair cell regeneration is closer to reality than ever. The HRP Consortium works collaboratively to provide a practical understanding of hair-cell regeneration, which will enable development of therapies for hearing restoration. Our consortium has identified major roadblocks that have stymied the field, and has designed rational approaches to overcome these barriers. We will then identify targets for drug-based restoration of hearing, and partner to screen for suitable drugs. Our approaches to the development of experimental strategies for hair-cell regeneration are highly integrated and involve the efforts of the majority of consortium members.

In the cochlea, the hearing organ, we know that the supporting cells are the progenitors of new hair cells after injury; in nonmammalian vertebrates, after noise or drug damage to hair cells, these supporting cells give rise to new hair cells through cell division and direct cellular conversion. By contrast, spontaneous regeneration in mammals—including mice and humans—does not occur, except for limited numbers of hair cells appearing after certain experimental manipulations. Moreover, we know relatively little about the cells that remain in the cochlea after damage; these are the cells we must target to form new hair cells.

With sufficient resources, we anticipate that our multifaceted approach to hearing restoration, drawing from the collective strength of the collaborative group, will lead to viable therapies for hearing loss within a decade.

PHASE 1—DISCOVER PATHWAYS AND DETERMINE CELL FATE

1a—Genomic Profiling: In Phase I of our project, we will determine how mammalian supporting cells are blocked from forming new hair cells. We will use genome-wide profiling experiments to compare supporting cell responses to injury in species that regenerate their hair cells (chicks, zebrafish) to those that do not (mouse). We expect to identify the molecular triggers for hair-cell regeneration, as well as the major chemical signaling pathways that underlie the subsequent cellular responses.

1b—Determine Supporting Cell Population After Damage: In the second component of Phase I, we will identify which supporting cell populations remain after damage. To achieve this goal, we use genetic tools to trace the fate of supporting cells after damage, identifying their origins and determining their gene expression profiles. This information will allow us to target these cell populations more effectively. Additional experiments will define the cellular identity of the damaged cochlear epithelium in humans, which might differ from mice. Experiments to achieve Phase I will be carried out during Years 1-5.

PHASE 2—VERIFY PATHWAYS AND DEVISE REGENERATION STRATEGIES

Once the research of Phase I reveals appropriate triggers, pathways, and target cells, we will initiate projects aimed directly at inducing new hair cells in the mature mammalian inner ear. In these projects, we will manipulate specific target genes and pathways in the mammalian cochlea *in vitro* and *in vivo*. We will also determine whether regeneration of hair cells with free-standing hair bundles in mammals is sufficient to restore significant auditory function and whether regeneration of the complete three-dimensional structure of the cochlea is required. Phase II will be carried out in earnest in Years 3-8.

PHASE 3—IDENTIFY DRUGS THAT TRIGGER HAIR-CELL REGENERATION

In Phase III of the HRP, we will partner with pharma or biotech to carry out drug screening on the pathways we identify in the first two phases. Useful drugs will stimulate hair-cell generation in damaged cochleas; drugs will be examined first in animal models, and then later in humans. Phase III will be initiated by Year 8 and may require several years; success will depend on the thoroughness of the characterization carried out in Phases I and II.

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