# Auditory/Vestibular Cell Lineage and Development Workshop

http://scientificprograms.nidcd.nih.gov/development/developmenthome.html

***August 22, 2002***
***Bethesda Marriott***
***Pooks Hill Road***
***Bethesda, Maryland***

The NIDCD held a workshop to discuss the present and future state of cell lineage and development research in the auditory and vestibular systems. The purpose of the workshop was to discuss and identify research opportunities to advance the molecular exploration in auditory and vestibular research. The workshop, organized by Nancy Freeman, Ph.D., Division of Extramural Research, NIH-NIDCD and chaired by Donna Fekete, Ph.D., Purdue University, consisted of an outstanding group of auditory and vestibular investigators (http://scientificprograms.nidcd.nih.gov/development/agenda.html).

The meeting began with opening remarks from NIDCD director James Battey, Jr., M.D., Ph.D., who welcomed the panelists and attending guests. Dr. Freeman provided the purpose and intent to the workshop panel. Dr. Fekete then proceeded with moderating the day's agenda and discussion period. Each speaker was given a 45-minute time slot that included ~5-10 minutes for discussion.

## Discussion Overview and Research Opportunities

Molecular and cellular research in the auditory and vestibular systems has made significant advances in recent years. Numerous model systems including, zebrafish, mouse, frog and chicken, are currently being used to dissect the complex developmental pathways leading to hearing and balance function. While significant advances have been made, there is still the need to broaden the auditory and vestibular developmental information. Improved, enhanced, or novel methodologies for gene expression, mutagenesis screens, and tissue/organ culture systems are needed to acquire information and physiological validation in an expedited manner.

At the fundamental core of the developing auditory/vestibular systems is the specification of cell fates. Elucidation of the complex cell development course taken for terminal formation of auditory and vestibular organs will be important for future reparative therapies. Some important factors that impact the forward progression of this field are the completion of detailed cell lineage and fate mapping analyses, the identification of key cellular markers, targeting and isolation of homogenous cell populations, and physiological assays for the acquisition of cell fate and cell differentiation.

Gene expression patterns continue to suggest that the early ear is rapidly subdivided into domains that may give rise to the different structural parts of the ear. However, at present it is not known how a specific region of the early ear corresponds to its eventual fate. High-resolution cell lineage and fate mapping studies are needed to interpret the expanding number of gene expression patterns described for both the developing auditory and vestibular systems. Globally, the molecular dissection of these areas of study will require new and improved reagent development in the form of gene manipulation and delivery systems, elucidation of signal transduction relationships and their involved components, and the manipulation of specific cell populations.

Fate mapping and lineage analysis:

- Determination of developmental origin of morphogenic maturation of finalized auditory structures. Determination if cell movements or early cell positions are general predictors of final cellular residence. Determination of possible differences that may result from species variability.

- Identification of regulatory mechanisms for genes associated with important structural-functional properties of cell types unique to the inner ear (such as hair cells, Deiters, Hensen, Claudius', interdental, and marginal/dark cells), and the spatio-temporal establishment from early to adult development.

- Elucidation of cellular origins and the true identification of auditory/vestibular progenitor cells. Establishment of subsequent cell lineage pathways. Identification of specific cellular progenitor markers.

- Correlative analyses of auditory/vestibular developmental pathways with functional integration to the CNS. Determination of peripheral and CNS structural relationship. Determination of synaptogenesis between hair cells and eighth nerve terminals.

- Expanded developmental work with invertebrates, such as *Drosophila*, in a context beyond the important gene homology, to specifically address hearing and balance function. Data acquisition of lineage pathways and centralized information dissemination from the various multiple model systems.

- Advancement of fate mapping and lineage analysis done at single cell resolution and real-time assessment.

- Completed comprehensive catalog of genes involved in auditory/vestibular developmental regulation. Increased isolation and identification of novel

auditory/vestibular genes. Expanded use of microarrays and generated tissue/stage state specific libraries.

- Expression analysis and mutational analysis using high throughput technologies such as array profiling.

- Investigations into the structural and functional relationship between vestibular organ neuronal interactions and inputs from other sensory systems, such as visual and other non-labyrinthine input.

The last few years, advances in genetics and molecular biology have begun to push forward knowledge of the molecular basis of cell fate acquisition in the inner auditory and vestibular systems. However, in view of the remarkable complexity of these systems, the small population of sensory cells contained within it, and the relatively modest numbers of labs devoted to the field, progress has lagged behind that of other sensory systems. Determination of lineage pathways, cell fate determinations and comparative system analysis will be crucial to moving the field forward. To that means, molecular reagents are key in providing the fundamental tools to study complex gene and protein function. The auditory and vestibular systems present unique challenges of inaccessibility, small sample size and improved *in vitro/in vivo* manipulation systems.

Molecular reagent development and enhancement:

- The identification of cellular markers specific to auditory/vestibular developmental stages and cellular pathways.

- Identification of auditory/vestibular gene specific promoters and associated transcriptional and enhancer regulatory factors.

- Mutational analysis, utilizing both knock in and knock out technologies. Use of gain and loss functional mutants.

- Complementation of functional assays and screens wherever possible for gene/protein function validation.

- Pursuit of potentially involved and existing hearing/balance genes in established mutant lines of zebrafish. Development of new directed screening strategies for ear specific markers.

- Gene transfer and delivery technologies into specific targeted auditory and vestibular areas, as well as organ/cell culture environment.

- Cre/Flox expression systems using auditory/vestibular specific promoters. Use of BAC and/or other transgenes.

- Enhanced or improved reporter systems specific to the auditory and vestibular systems to facilitate isolation of pure cell populations.

- Uniformity and universal mechanism to deposit, organize and share information between auditory/vestibular key molecular pathways.