SPEECH AND HEARING BIOSCIENCE AND TECHNOLOGY

END OF SUMMER TALKS

DAY 1

TUESDAY SEPTEMBER 15, 2009

ABSTRACTS

Lineage tracing of mouse hair cells using Sox2

Naomi Bramhall
Advisor: Albert Edge

The organ of Corti consists of two main cell types, the hair cells necessary for mechanotransduction of the acoustic stimulus and the supporting cells surrounding them. Supporting cells in the inner ear have been shown to give rise to hair cells in animals demonstrating hair cell regeneration. Manipulation of particular molecular pathways has led to the development of new hair cells in mammals, although mammals do not typically show evidence of hair cell regeneration. However, it is difficult to definitively determine the mechanism of regeneration of these hair cells and whether they are derived from supporting cells. Genes that can serve as supporting cell specific markers will be useful for following any changes in supporting cell fate in response to hair cell regeneration treatment. The transcription factor Sox2 is a possible candidate marker gene due to its supporting cell specific expression in the inner ears of adult mice. By using transgenic mice with inducible expression of this marker gene, lineage tracing can be performed to determine whether supporting cells are hair cell progenitors.

This summer's project involves treatment of neonatal mouse organ of Corti explant cultures with a gamma secretase inhibitor previously shown to induce the formation of new hair cells. Additional hair cells were observed in treated cultures. Generation of supernumary hair cells in vitro is necessary to perform future lineage tracing experiments with the transgenic mice.

Toward Hair cell regeneration: β-CATENIN UPREGULATES ATOH1 EXPRESSION

Yen-Fu Cheng
Advisor: Albert Edge

Atoh1, a basic helix-loop-helix transcription factor, plays a critical role in the differentiation of several epithelial and neural cell types, including hair cells of inner ear. We found that β-catenin, the key mediator of the canonical Wnt pathway, increased expression of Atoh1 in human bone marrow stem cells and neural progenitor cells, and baseline Atoh1 expression was decreased by siRNA directed at β-catenin. The upregulation of Atoh1 was caused by an interaction ofβ-catenin with the Atoh1 enhancer that could be demonstrated by chromatin immunoprecipitation. Inhibition of Notch signaling, which has previously been shown to induce bHLH transcription factor expression, was found to increase β-catenin expression in progenitor cells of the nervous system. Since this could be a mechanism for upregulation of Atoh1 after inhibition of Notch, we tested whether siRNA toβ-catenin prevented the increase in Atoh1 and found that β-catenin expression was required for increased expression of Atoh1 after Notch inhibition.

Examining gap detection ability in mouse following temporary threshold shifts using prepulse inhibition of the acoustic startle response

Ann E. Hickox
Advisor: M. Charles Liberman

A mouse model has been developed demonstrating primary neural degeneration of cochlear afferent nerve fibers following an acoustic trauma (Kujawa & Liberman, 2006). This neuronal loss is seen despite complete recovery of thresholds and no loss of cochlear sensory cells. However, the amplitude of the first wave of the ABR waveform is decreased by 50%, and histological study reveals a 50% loss of cochlear nerve terminals and a comparable delayed loss of nerve cell bodies and central axons. Although thresholds assessed in quiet are normal, it is possible that the observed neural dysfunction could compromise encoding of complex stimuli or of stimuli presented in background noise. Numerous studies reveal that certain human listeners demonstrate increased difficulty of speech perception in noise, as well as other perceptual deficits, in the presence of otherwise normal hearing thresholds in quiet. This suggests that this particular mouse model could be useful in revealing connections between physiological and perceptual dysfunction using supra-threshold tests of auditory perception. In this study, mouse auditory perception is assessed using prepulse inhibition (PPI) of the acoustic startle response (ASR), a graded response arising from a reflex-elicited whole-body series of muscle contractions following an intense, unexpected sound. ASR amplitude can be attenuated by the detection of a preceding acoustic stimulus (or prepulse), and the strength of this inhibition is thought to reflect the perceptual salience of the prepulse. In this initial study, 17 week-old CBA/CaJ mice were exposed to an 8-16 kHz octave band of noise at 100 dB SPL for 2 hours. Exposed mice (n = 2) and age- and strain-matched unexposed mice (n = 3) were assessed at 7 weeks post-exposure using a PPI paradigm in which a gap of varying duration serves as the prepulse stimulus in an otherwise continuous background noise.

White Matters: Investigating the Effects of Musical Training on Temporo-Frontal Fiber Tracts in Children

Gus F. Halwani
Advisor: Gottfried Schlaug, M.D., Ph.D.

Previous studies in functional neuroimaging have suggested a functional distinction between right and left temporo-frontal activation (left or right fronto-temporal activation is correlated with semantic or prosodic tasks respectively, for review: Glasser & Rilling, Cortex 2008). The following work represents an effort to corroborate these functional findings with structural observations of the arcuate fasciculus (AF), a prominent white-matter fiber tract connecting each hemisphere's posterior temporal gyrus to the inferior frontal regions.

MR and diffusion tensor images (DTI) were acquired in two groups of children: one group participated in regular instrumental music instruction and practice, while the other group did not. Various parameters of the AF (volume, number of fibers, diffusivity) were analyzed, and the differences between groups were compared in hopes of elucidating the contributions of musical training to the volume and composition of these particular white-matter tracts.

The musically trained group of children exhibited a more robust arcuate fasciculus in general, with the lateralization of this effect varying depending on the instrument in which the subject received training. In

particular, keyboard players showed increased volume in the left-inferior AF relative to non-musician controls, while the string players showed a tendency towards relatively increased tract volume in the right-inferior AF.

These results support the notion of training-induced white matter plasticity, providing important information about auditory-motor connectivity in the brain and how it might be remodeled in individuals that formally learn and regularly practice musical instruments. Studies to follow will conduct similar analyses on other age groups in order to ascertain the persistence of the trends observed in children. Subsequently, a longitudinal comparison across these samples may illuminate musical training's possible contributions to white matter plasticity in general and particularly the connectivity and functional coordination between the temporal and frontal lobes over time

Single molecule mRNA detection of key genes during murine otocyst development through fluorescence in situ hybridization

Annalisa Powlowski
Advisors: Alexander van Oudenaarden, PhD, MIT and Konstantina Stankovic, MD, PhD, HMS, MEEI

Recently, I proposed to study development of the mammalian inner ear using a novel technique, fluorescent in situ hybridization[1], which allows simultaneous localization and quantification of multiple mRNA species on a single molecule level within individual cells. Detailed understanding of dynamic changes in gene expression in the developing cells of the inner ear has a potential to influence future regenerative therapies, since the mammalian cochlea does not spontaneously regenerate. This summer, I studied genes that are known to play key roles in cochlear development[2], including Notch1, Delta-like1 and Hes1, and whose expression may be altered in adult tissue after acoustic injury[3]. These experiments aimed at understanding the relationships between Delta-like1, Notch1 and Hes1 during development. Future experiments will focus at understanding the interactions between these genes before and after acoustic injury, in order to see if the same relationships from development hold.

[1]Raj A, van den Bogaard A, Rifkin S A, van Oudenaarden A, and Tyagi S, Imaging individual mRNA molecules using multiple singly labeled probe, Nature Methods 5, 877 (2008).
[2] Lanford PJ, Lan Y, Jiang R, Lindsell C, Weinmaster G, Gridley T, Kelley MW, Notch signaling pathway mediates hair cell development in mammalian cochlea, Nat Genet. 1999 Mar; 21(3):253-4.
[3] Stone JS, Rubel EW, Delta1 expression during avian hair cell regeneration, Development. 1999 Feb; 126(5):961-73.

Autoregressive Modeling of Voiced Speech
Maria Andrey Berezina
Advisors: D. Rudoy and P. J. Wolfe

As is well known, the classical linear predictive model for speech fails to take into account the quasi-periodic nature of the glottal flow typical during voicing. In this talk we describe how to incorporate an estimate of the glottal flow directly into the the traditional linear prediction framework, through the use of flexible basis function expansions that we show lead to efficient algorithmic procedures. As we demonstrate with a variety of examples of real and synthesized speech waveforms, this not only allows for improved estimation of vocal tract transfer function parameters in a manner that is also more robust to pitch variation, but also precludes the need for nonlinear optimization procedures typically required in glottal waveform estimation. We conclude by outlining potential clinical applications of this technique, including direct estimation of the degree of aspiration noise present in a given utterance.

The Proteome of Perilymph
Andrew Lysaght
Advisor: Konstantina Stankovic

Current diagnostic tools limit a clinician's ability to discriminate between many causes of sensorineural hearing loss. This leads to the frequent diagnosis of the idiopathic condition, leaving patients with poor prognostic vision and only general treatment options. As a first step toward developing new diagnostic tools and improving patient care, we are using mass-spectroscopy to map the proteome of perilymph in pathologic and non-pathologic conditions. Differences in protein expression are being used to generate lists of candidate biomarkers and pathway analysis is being applied to identify novel applications for known pharmaceuticals.

Transcriptome Sequencing and Stapes Prosthesis Sensing
Bo Zhu
Advisor: Konstantina Stankovic

This summer we began developing a stapes prosthesis outfitted with sensors to allow continuous, in vivo monitoring of cochlear perilymph. A first-order engineering design of the device was drafted, which laid out the necessary electronic components and preliminary sizing parameters of the prosthesis outer shell. A comprehensive literature search was performed to determine the particular ion of interest for the first prototype to sense (Magnesium) in the cochlear fluid. Another literature search was done to determine the animal species to test the prototype on, based on dimensional similarity to the human auditory system. We have also begun to investigate possible alternative energy sources to power this device.