

“Aging, Genetics and Central Auditory Neurobiology”

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Presbycusis – What Goes Wrong in the Ear and Brain?

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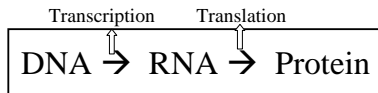
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- Timing is everything! –
- Feedback loop from the brain to the ear declines, starting in middle age
- Promising bioengineering avenues for prevention and therapeutics!

Gene Expression Experiment: The Central Theme



- The arrows represent the transfer or flow of information.
- DNA and RNA store information in a base-4 code (the four nucleotides).
- Proteins store information in a base-20 code (the 20 amino acids).

Experimental Design For GeneChip Study

- **Hypothesis:** Gene expression changes in the ear and the brain occur in presbycusis – Key Neurotransmitters, Cell Cycle Pathways and Membrane Channels

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RNA samples from individual mice on *individual microarrays*

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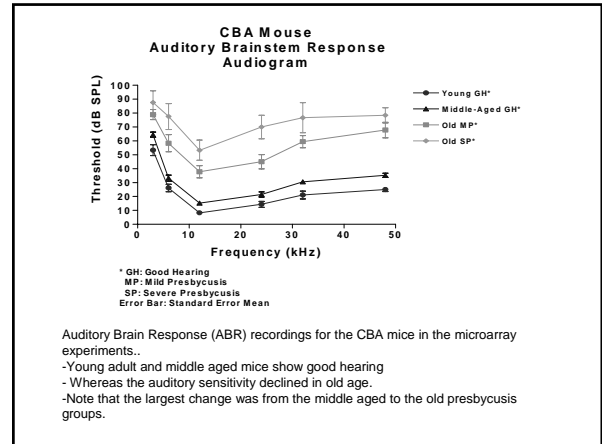
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- **Project Strengths:** Number of replicates, N=80, strengthened the statistical analysis. One chip-one mouse allows exploration of the biological phenotype variance from mouse to mouse.

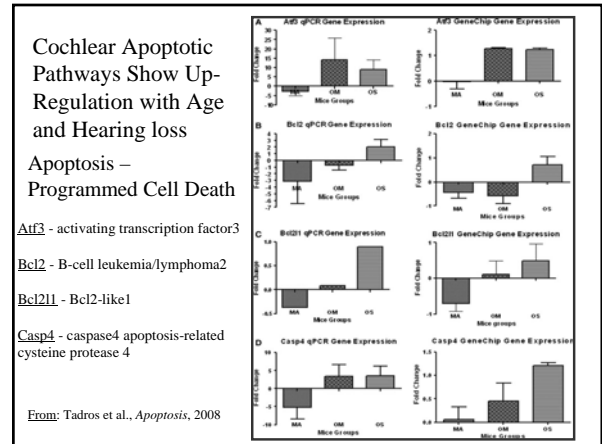
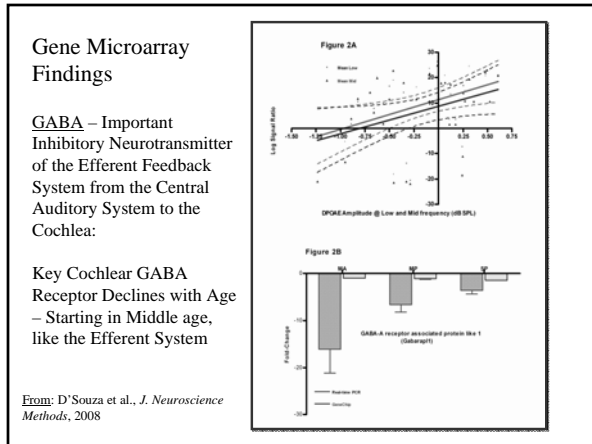
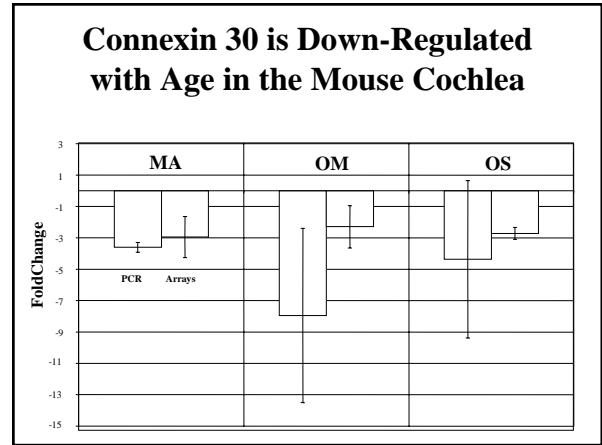
Presbycusis Microarray -Animal Subject Group Details

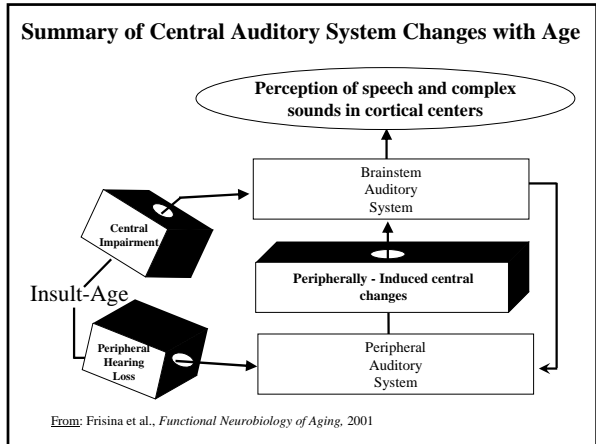
Groups of Mice	No. of Mice	No. of Chips, 1 chip/mouse	Age - Months	Gender
Young Control	9	9	3.5 ± 0.4	Male=5 Female=4
Middle aged Good Hearing	17	17	12.3 ± 1.5	Male=8 Female=9
Old - Mild Presbycusis	9	9	27.7 ± 3.4	Male=4 Female=5
Old - Severe Presbycusis	6	6	30.6 ± 1.9	Male=2 Female=4



Functional Anatomy and Ion Channel Exchange in the Mammalian Inner Ear – Cochlear Tissue

For Gene Arrays
 -Organ of Corti
 -Lateral Wall





Glutamate – The Primary Excitatory Neurotransmitter of the Auditory System

Pycs plays a role in converting glutamate to proline

- Its deficiency in old age may lead to:
 - Glutamate increases and proline deficiencies in the auditory midbrain
 - Playing a role in the subsequent inducement of glutamate toxicity and loss of proline neuroprotective effects

From: Tadros et al., *Brain Research*, 2007

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Slc1a3 is a glutamate transporter

- Gene expression changes with age and hearing loss may reflect a cellular compensatory mechanism to protect against age-related glutamate or calcium excitotoxicity

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Upregulation of Serotonin Receptors with Age and Hearing Loss in the Inferior Colliculus – Auditory Midbrain

Gene Expression

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Protein Expression

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Upregulation of Serotonin Receptors with Age and Hearing Loss in the Inferior Colliculus – Auditory Midbrain

- Could help compensate for declines in Serotonin with age
- Could result in age-related Ca⁺⁺ toxicity by increasing the intracellular concentration of IP₃

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- Compensatory up-regulation of calretinin

Serotonin-induced Calcium-related Excitotoxicity

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Serotonin-induced Calcium-related Excitotoxicity

Group	IP3 levels (pmol/mg protein)
Old Hearing CBA	~0.8
Old Deafened CBA	~1.2
Young Hearing CBA	~0.8
Old Deaf C57	~1.5
Young Hearing C57	~0.8

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Novel Micro-Infusions and High Resolution Imaging of the Mouse Cochlea

Improved Imaging Accelerates Development of:

- Optimal Cochlear Infusion Micro-Systems
- Micro-Pumps using MEMs Technologies
- Evaluation of Surgical Alternatives

Note: The entire volume of the mouse cochlea is on the order of 600 nanoliters

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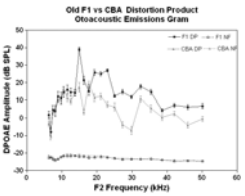
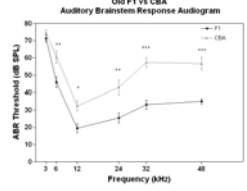

Genetically Cross the CBA and C57 Mouse Strains: Discovered a new mouse model for aged human listeners who have audiograms within the normal hearing range: mice with "Golden Ears"

From: Frisina et al., *Neurobiology of Aging*, In Press

Frequency (kHz)	Old F1 (dB SPL)	CBA (dB SPL)
3	~75	~75
6	~45	~45
12	~25	~25
24	~35	~35
32	~45	~45
48	~55	~55

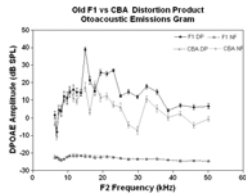
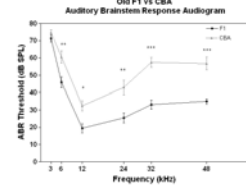
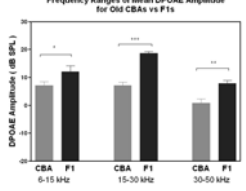

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Rochester Hearing/Deafness Research Group

Otolaryngology - U. Rochester

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- Dr. Owen Brimijoin - Physiology
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- Susan Frisina, RN – Med. Genetics
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- Dr. U-Cheng Leong - Physiology
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- Dr. David Eddins - Psychoacoustics
- Fray Mapes, MA – Res. Audiology
- Dr. Dina Newman – Genetics

Additional Media Clips

We discovered a new mouse model for aged persons (about 5%) with exceptionally good hearing sensitivity:
Scientific American: <http://www.scientificamerican.com/article.cfm?id=say-what-mice-that-resist>
Popular Science: <http://www.popsci.com/science/article/2009-11/new-breed-mice-retains-great-hearing-and-see-lives-old-age>
Science Daily: <http://www.sciencedaily.com/releases/2009/11/091109121213.htm>

In a clinical research study we discovered that low levels of the hormone aldosterone are linked to age-related hearing loss:
The Medical News: <http://www.medical.net/news/2006/02/16/15986.aspx>
American Speech, Hearing & Language Association: <http://www.asha.org/and/articles/oldhearingloss.htm>
University of Rochester: <http://www.umc.rochester.edu/news/story/index.cfm?id=1022>

In the largest clinical research study to date, we found that HRT can hurt hearing in older women:
Proceedings of the National Academy of Sciences: <http://www.pnas.org/content/103/38/14246.full?maxoshow=&HTS=10&hits=10&RESULTSFORMAT=&fulltext=Frisinga&searchid=16&FIRSTINDEX=0&docresourcetype=FWCIT>
Science Daily: <http://www.sciencedaily.com/releases/2006/09/060905225618.htm>
Deafness Research UK: <http://www.deafnessresearch.org.uk/HRT%20linked%20to%20hearing%20loss-3182.tcl>
Bottom Line: http://www.bottomlinesecrets.com/article.html?article_id=42805

Breakthrough evidence implicating the role of brain declines in age-related hearing loss:
University of Rochester: <http://www.umc.rochester.edu/news/story/index.cfm?id=735>