“Biological Bases of Age-Related Hearing Loss”

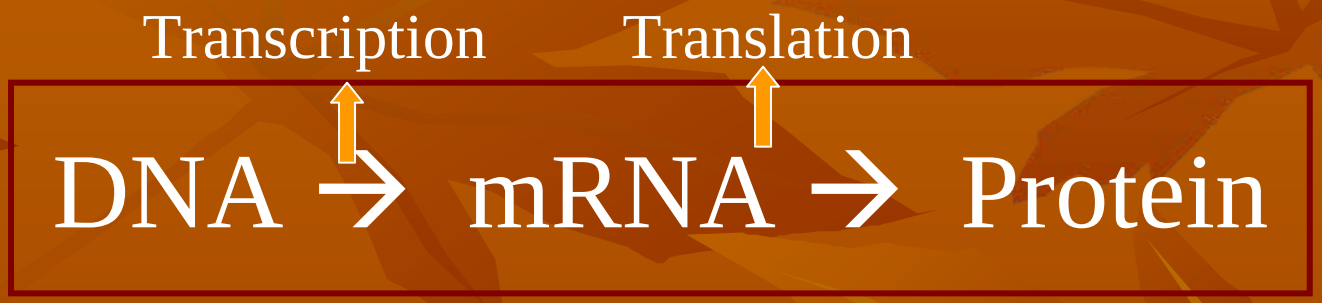
Robert D. Frisina, PhD
Professor and Assoc. Chair

Otolaryngology Department
University of Rochester Medical School,
International Center for Hearing & Speech Research
National Technical Institute for the Deaf

Morning Session: Presbycusis – What Goes Wrong in the Ear and Brain?

- Why don’t hearing aids work with many aged listeners?
- Is it all about hair cell loss? – No, but…
- 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).

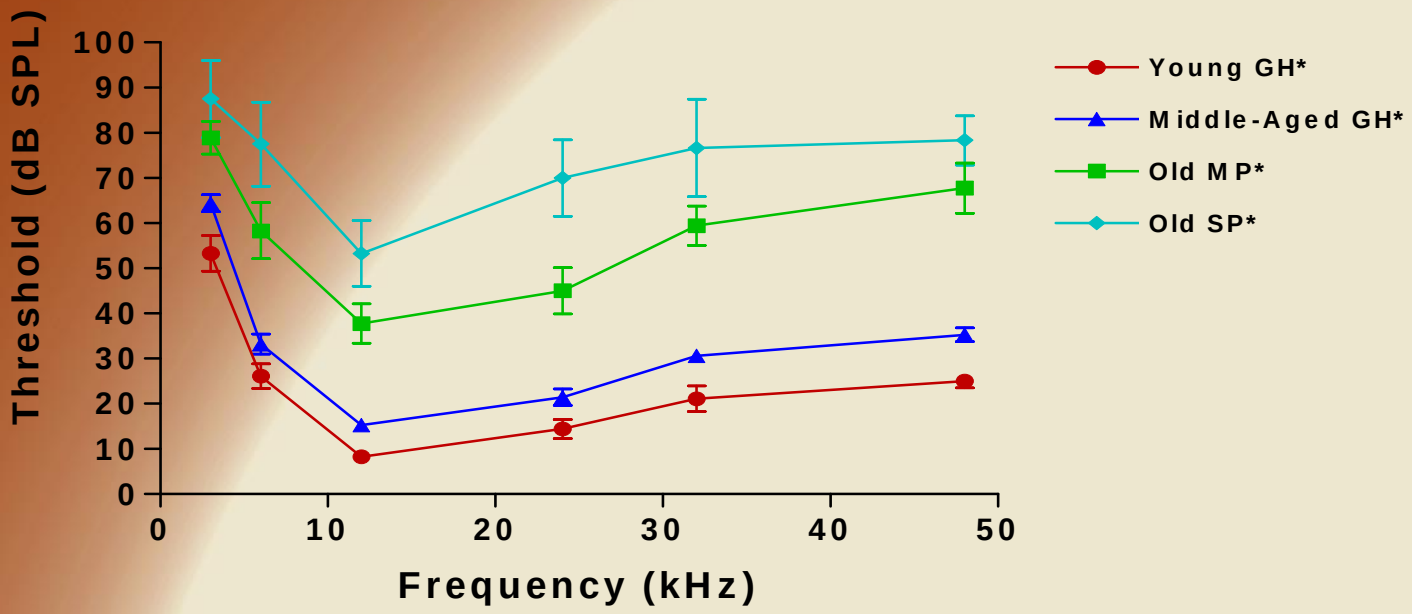
Experimental Design For GeneChip Study

- **Hypothesis:** Gene expression changes in the ear and the brain occur in presbycusis
- **Animal Model:** CBA Mice – slow progressive hearing loss
- **Tissue :** Cochlear and inferior colliculus (auditory midbrain) RNA samples from individual mice on *individual microarrays*
- **Investigative Tool:** Affymetrix GeneChip, one chip analyzes 22,600 gene probes for each sample, from each mouse
- **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

CBA Mouse
Auditory Brainstem Response
Audiogram



* GH: Good Hearing
MP: Mild Presbycusis
SP: Severe Presbycusis
Error Bar: Standard Error Mean

Auditory Brainstem Response (ABR) recordings for the CBA mice in the microarray experiments..

-Young adult and middle aged mice show good hearing

- Whereas the auditory sensitivity declined in old age.

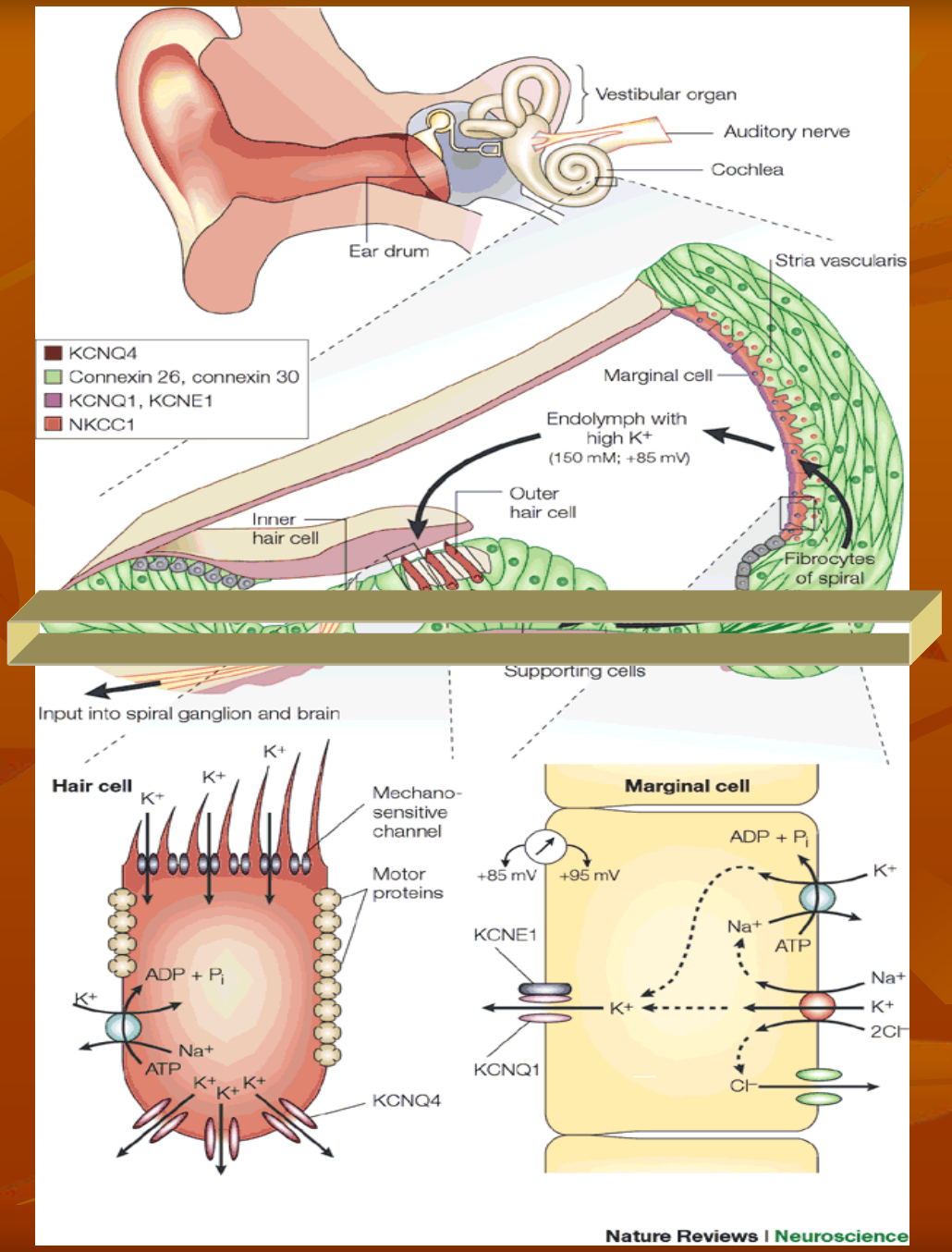
-Note that the largest change was from the middle aged to the old presbycusis groups.

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

<u>For Gene Arrays</u>

-Organ of Corti

-Lateral Wall

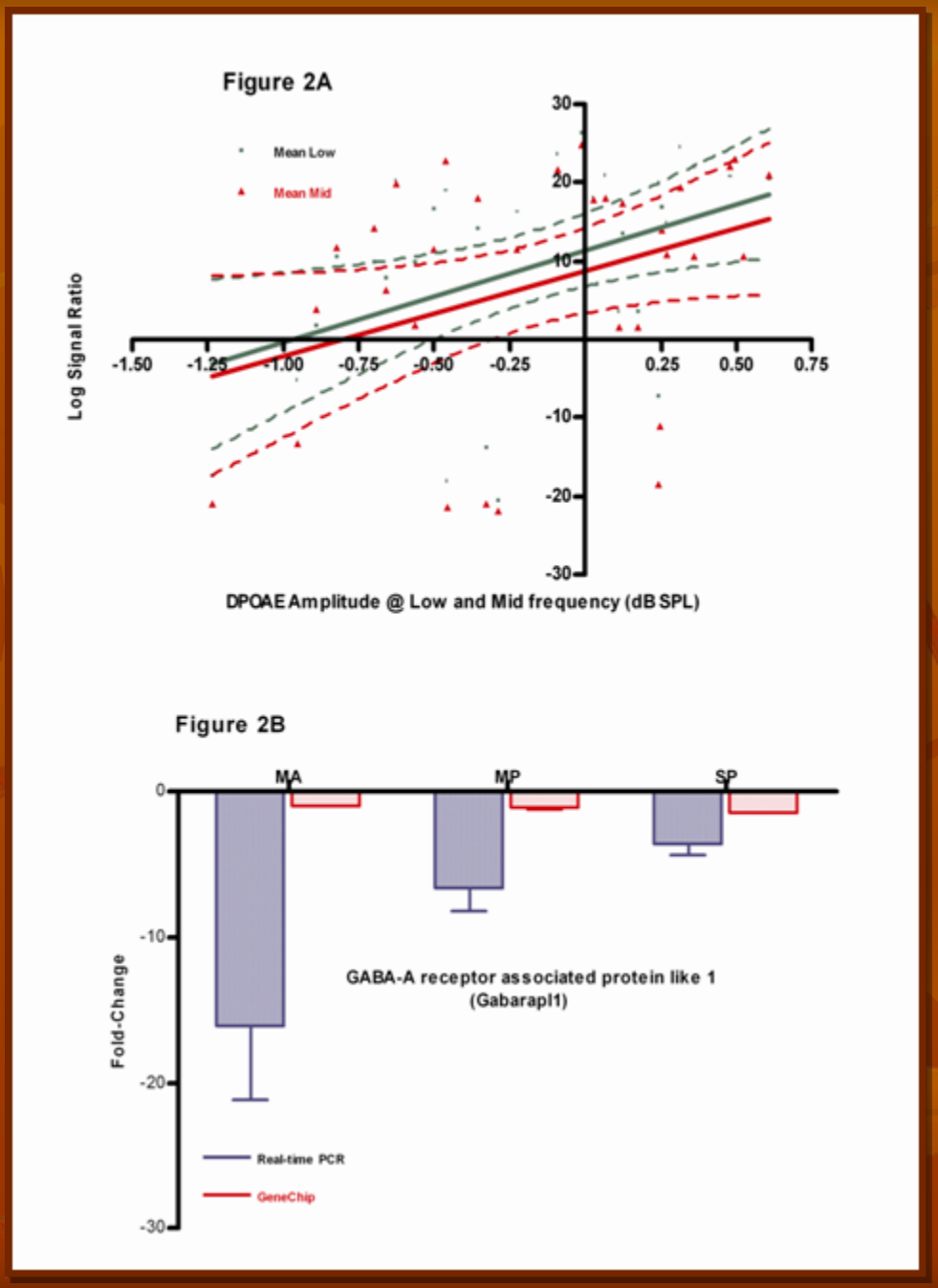


Gene Microarray Findings

GABA – Important Inhibitory Neurotransmitter of the Efferent Feedback System from the Central Auditory System to the Cochlea:

Key Cochlear GABA Receptor Declines with Age – Starting in Middle age, like the Efferent System

From: D'Souza et al., *J. Neuroscience Methods*, 2008



Cochlear Apoptotic Pathways Show Up-Regulation with Age and Hearing loss

Apoptosis – Programmed Cell Death

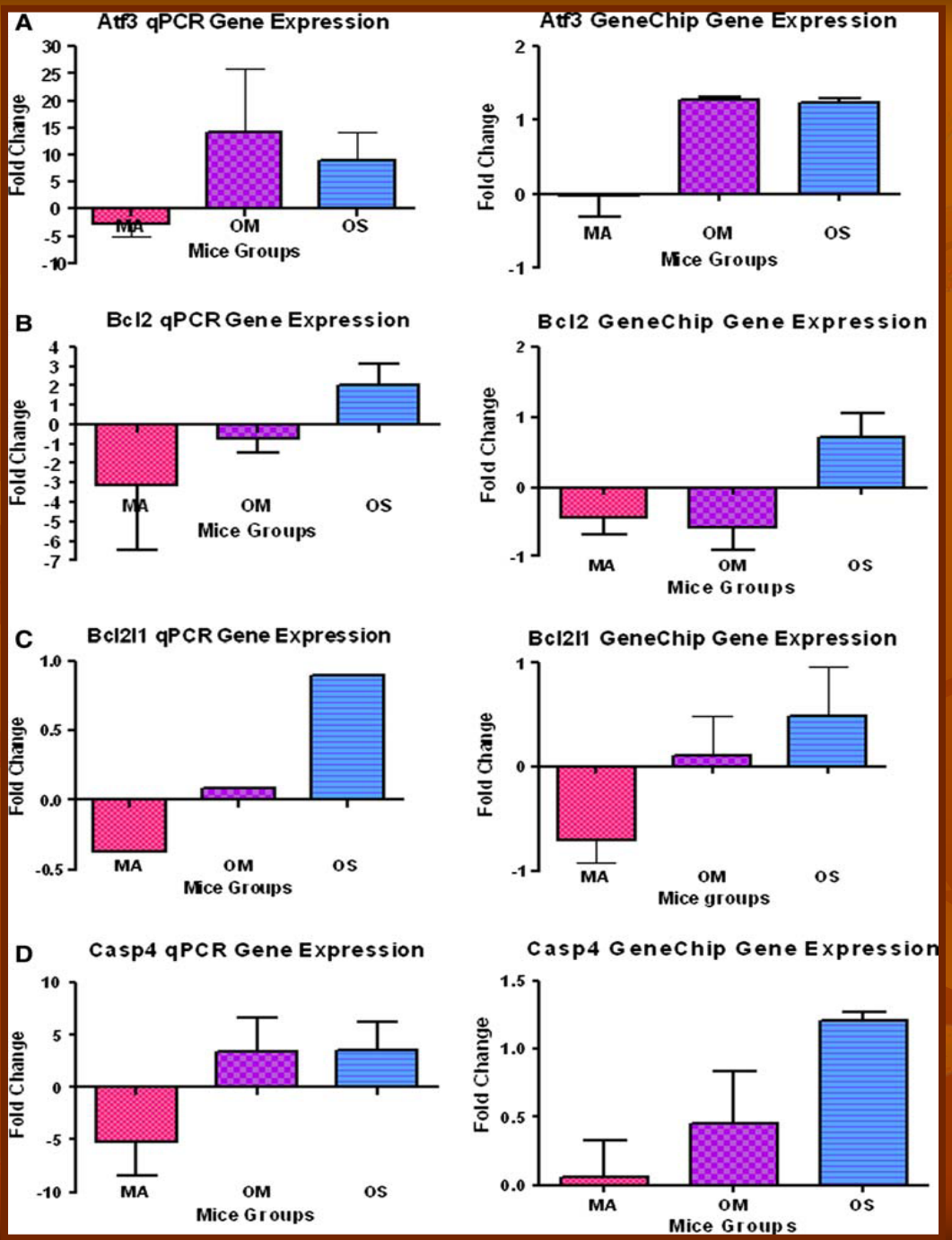
Atf3 - activating transcription factor3

Bcl2 - B-cell leukemia/lymphoma2

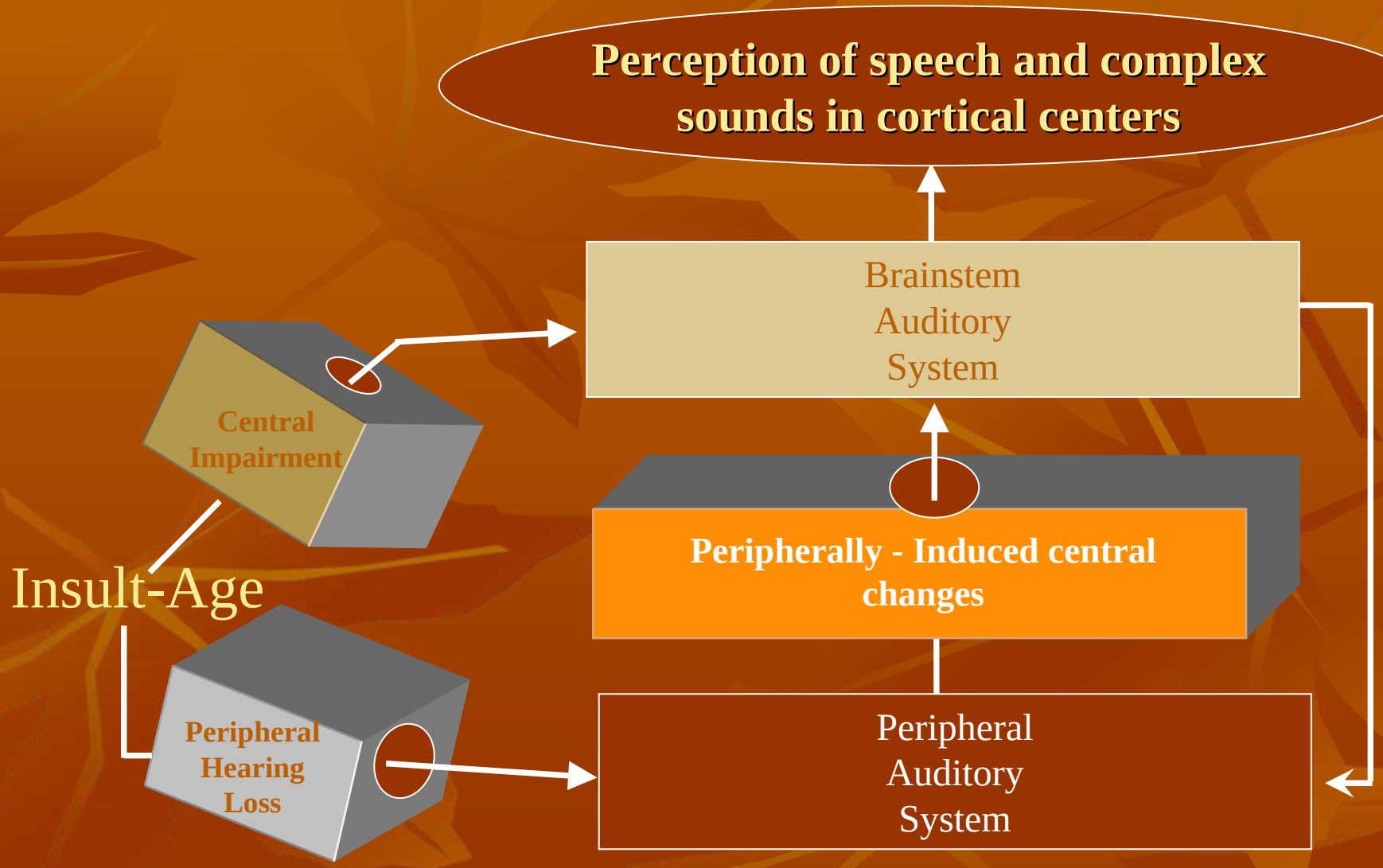
Bcl2l1 - Bcl2-like1

Casp4 - caspase4 apoptosis-related cysteine protease 4

From: Tadros et al., *Apoptosis*, 2008



Summary of Central Auditory System Changes with Age



From: Frisina et al., *Functional Neurobiology of Aging*, 2001

Glutamate – The Primary Excitatory Neurotransmitter of the Auditory System

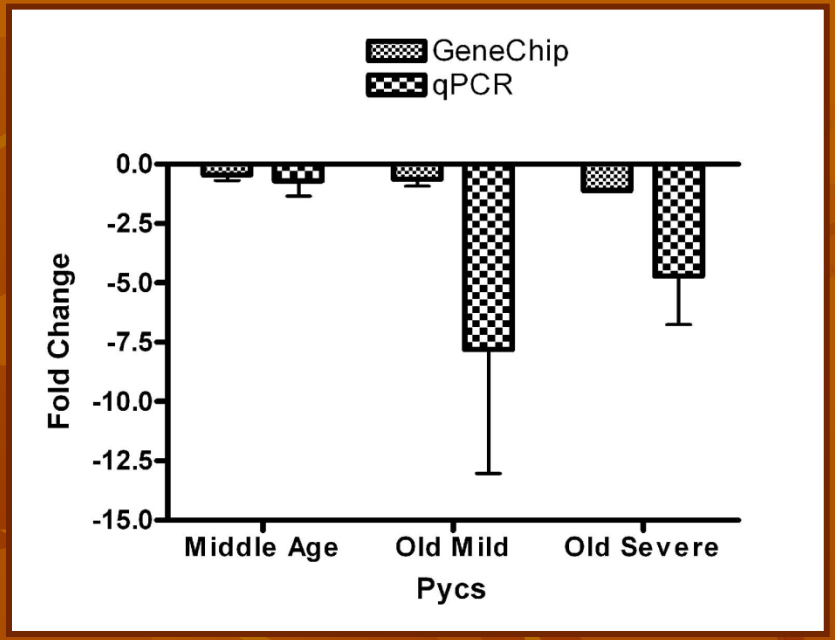
Pycs plays a role in converting glutamate to proline

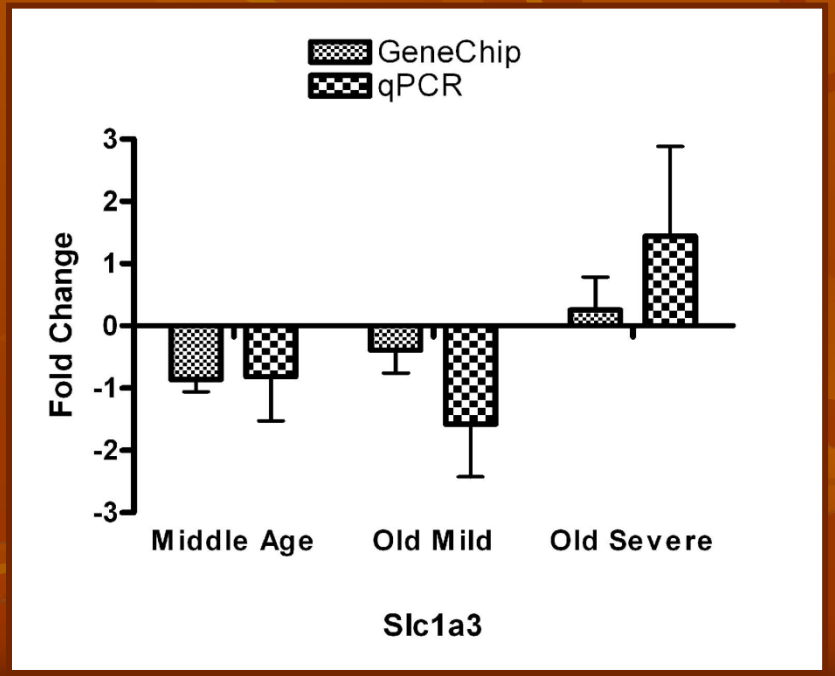
- Its deficiency in old age may lead to:
- Glutamate increases and proline deficiencies in the auditory midbrain
- Playing a role in the subsequent inducement of glutamate toxicity and loss of proline neuroprotective effects

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 excitoxicity

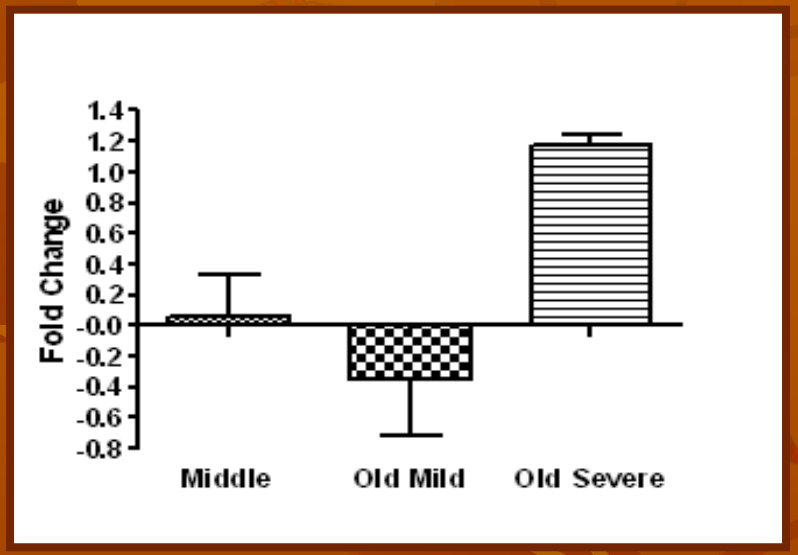
From: Tadros et al., *Brain Research*, 2007



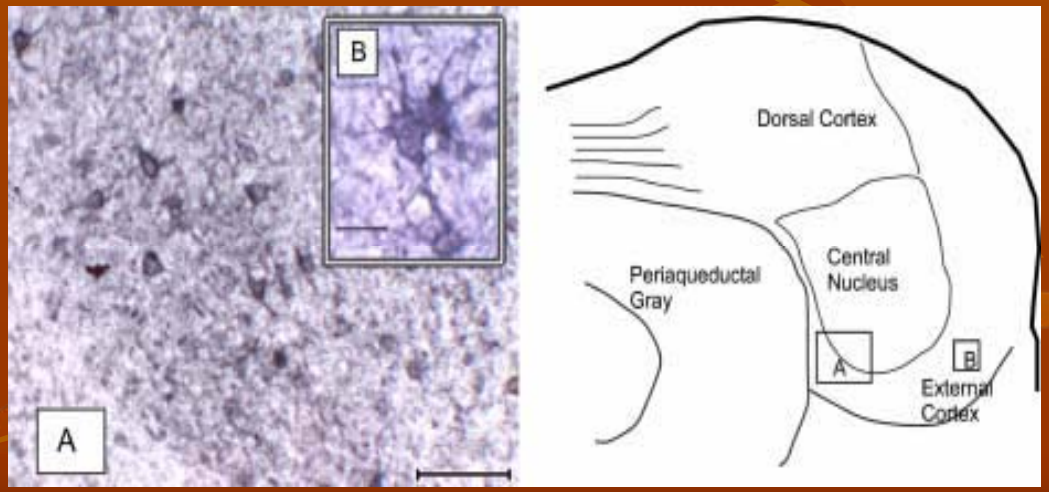


Upregulation of Serotonin Receptors with Age and Hearing Loss in the Inferior Colliculus – Auditory Midbrain

Gene Expression



Protein Expression



From: Tadros et al., *Neurobiology of Aging*, 2007

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

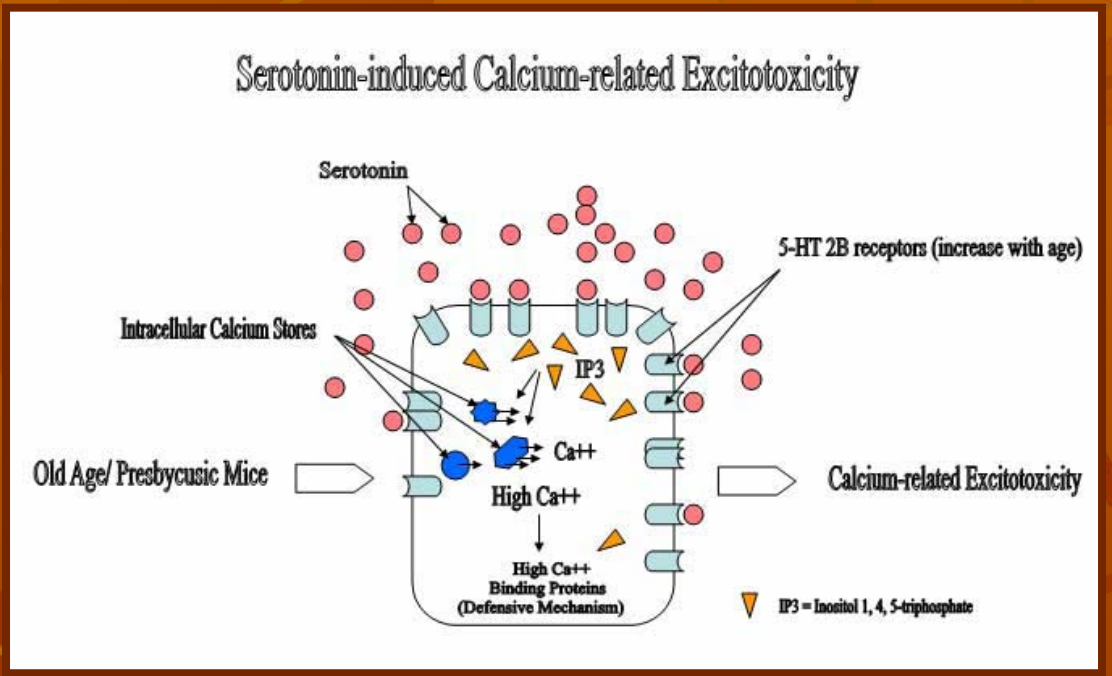
-Could help compensate for declines in Serotonin with age

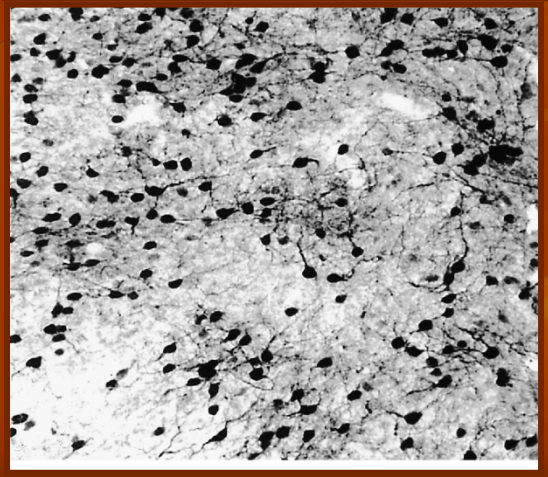
- Could result in age-related Ca++ toxicity by increasing the intracellular concentration of IP3

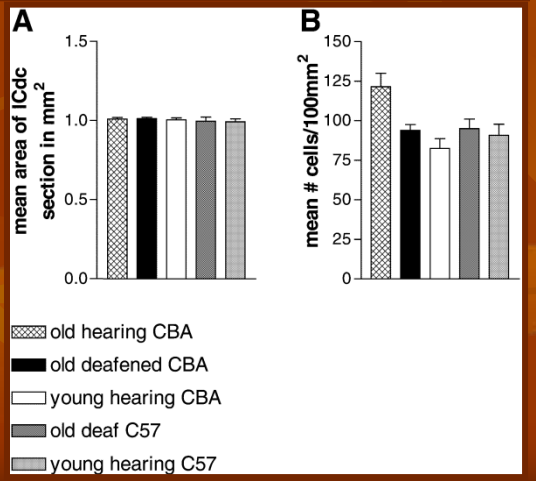
- Compensatory up-regulation of calretinin

From: Tadros et al., *Neurobiology of Aging*, 2007

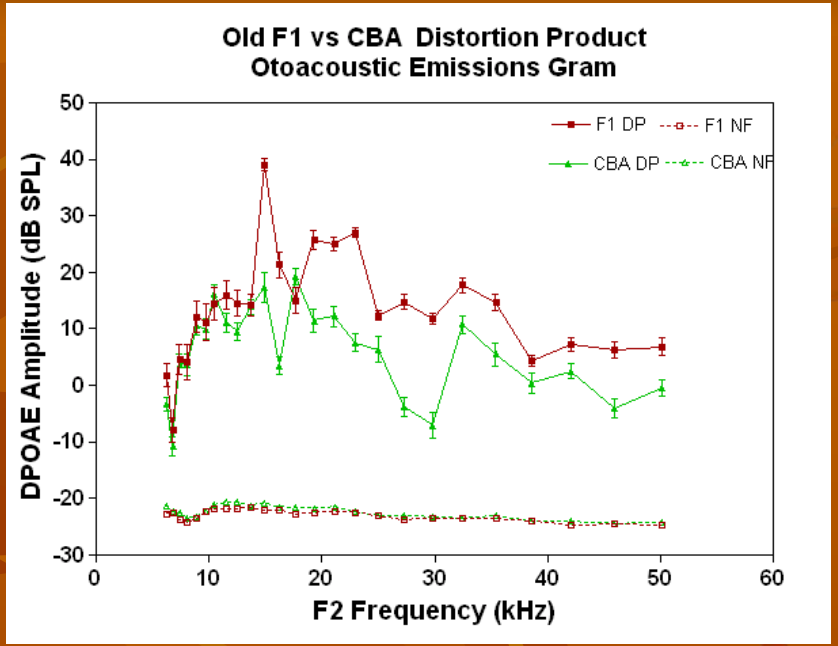
From: Zettel et al., *Hearing Res.* 2001



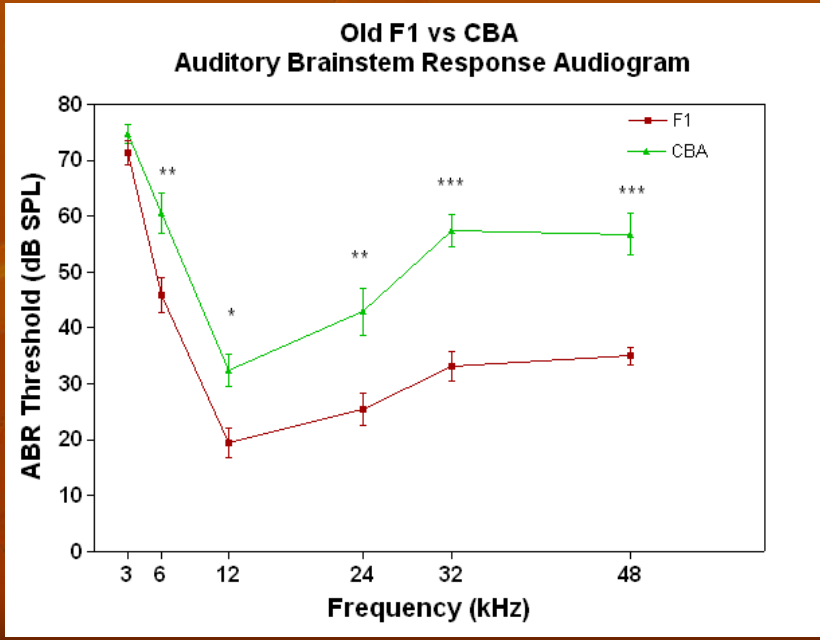




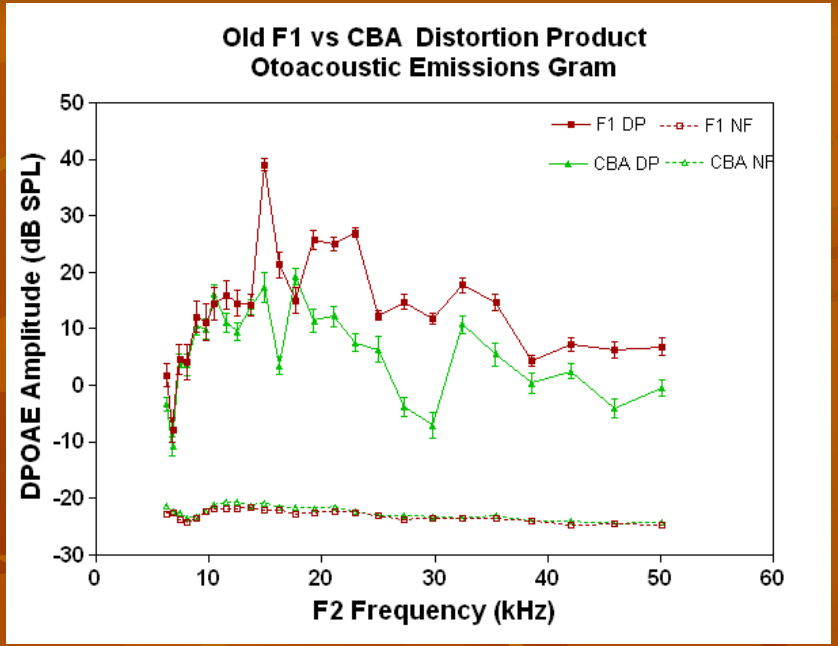
Genetically Cross the CBA and C57 Mouse Strains:
Discovered a new mouse model for aged human listeners who have audiograms within the normal hearing range: mice with “Golden Ears”



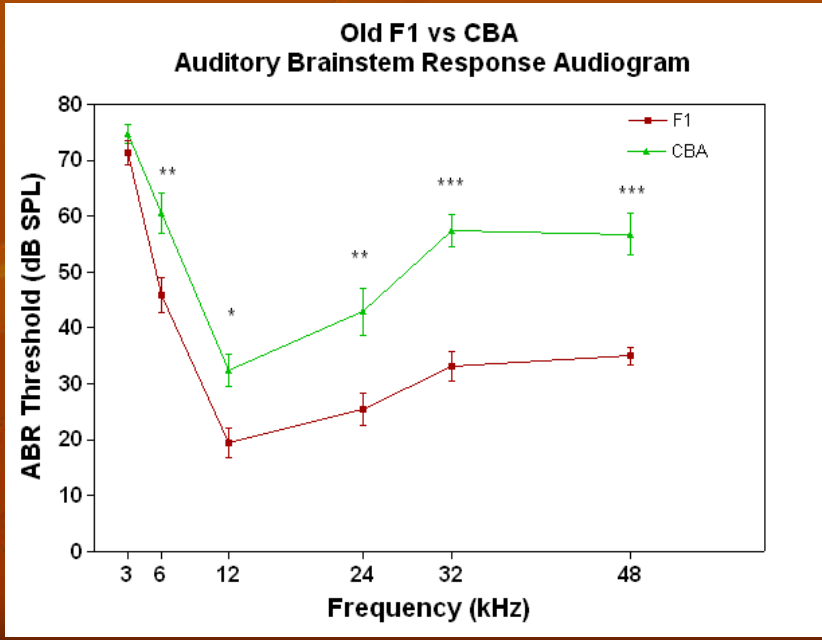
From: Frisina et al., *Neurobiology of Aging*, On Line

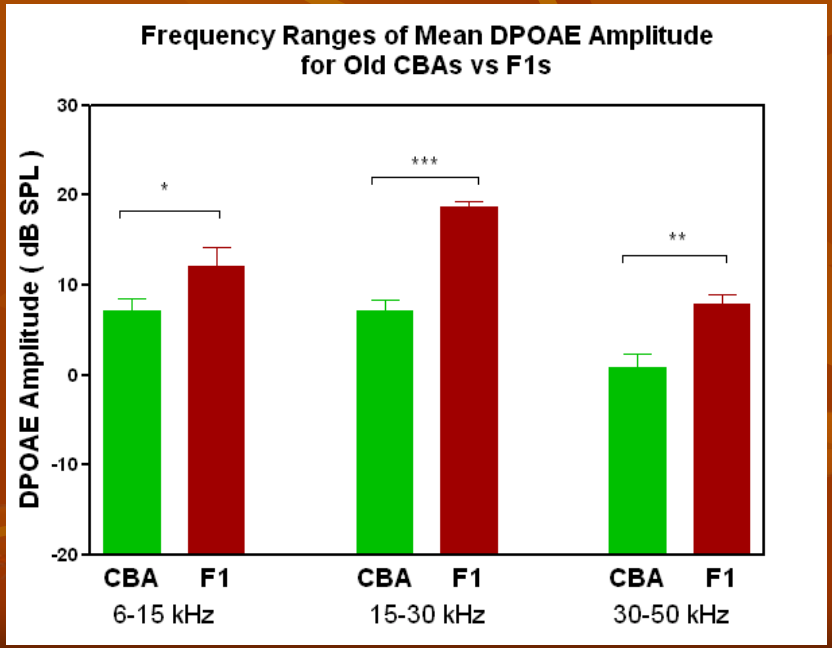


Genetically Cross the CBA and C57 Mouse Strains:
Discovered a new mouse model for aged human listeners who have audiograms within the normal hearing range: mice with “Golden Ears”



From: Frisina et al., *Neurobiology of Aging*, On Line






Work Supported by NIH:
National Institute on Aging,
Sensory and Motor Disorders of Aging,
Behavioral & Systems Neuroscience Branch,
Division of Neuroscience

National Institute on Deafness &

Communication Disorders

Rochester Hearing/Deafness Research Group

Otolaryngology - U. Rochester

- Dr. Kathy Barsz –Neurophysiol.
- Dr. Owen Brimijoin - Physiology
- Dr. Mary D'Souza – Molecular Biology, Gene Microarrays
- Susan Frisina, RN – Med. Genetics
- Dr. Robert Frisina -Neuroscience
- Dr. Patricia Guimaraes – Hormonal Effects on Audition
- Dr. U-Cheng Leong - Physiology
- Dr. Olga Vasilyeva – Pharmacol.
- Dr. Joseph Walton –Auditory Neurophysiology
- Martha Zettel, MS – Immunocytochemistry
- Dr. Xiaoxia Zhu – Emissions, ABRs, Micro-Surgery

University of Rochester

- Dr. Paul Allen - Behavior, Neurophysiology
- John Housel - Animal Core
- Dr. James Ison - Animal Behavior
- Dr. William O'Neill – ABRs, Auditory Neuroscience

Rochester Institute Technology

- Dr. Robert Frisina, Sr. – Speech Perception, PET, Audiology
- Dr. David Borkholder – Micro-Systems Bioengineering
- Dr. David Eddins - Psychoacoustics
- Fray Mapes, MA – Res. Audiology
- Dr. Dina Newman – Genetics