The Development of NHP Models for Cochlear Gene Therapy

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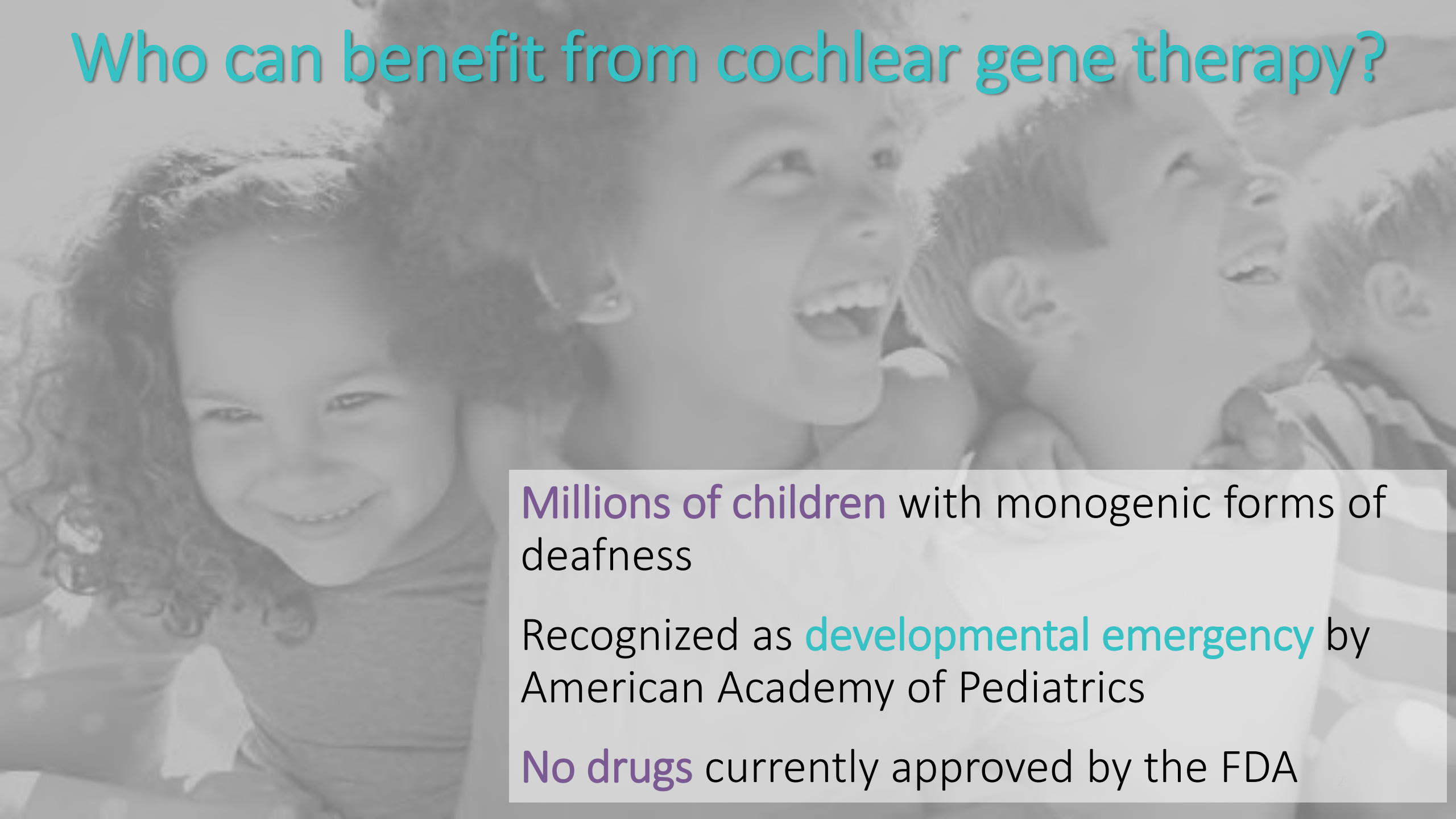
Who can benefit from cochlear gene therapy?



Millions of children with monogenic forms of deafness

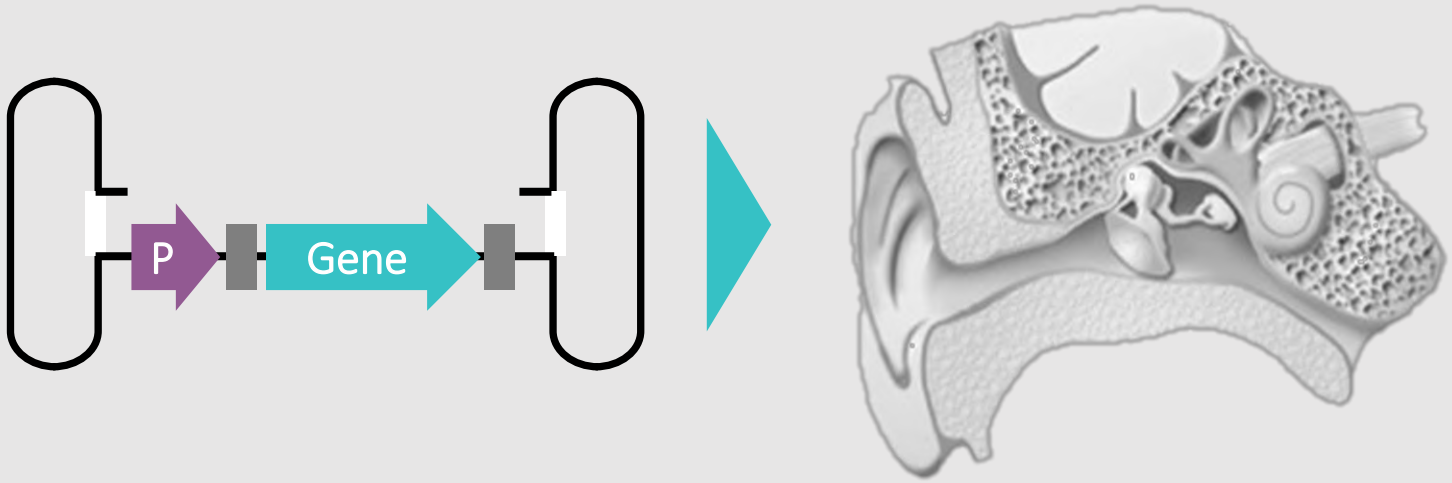
Recognized as developmental emergency by American Academy of Pediatrics

No drugs currently approved by the FDA

In vivo Gene Therapy Delivers Genetic Material to Target Cells

Direct delivery of a **functional gene copy** to the ear

→ **Functional protein produced by target cells** → **Restored hearing**



The Adeno-Associated Virus (AAV) Anc80 can package target genes for efficient delivery to cells

We Developed an Approach for Intracochlear Administration

The **approach(es)** for local delivery was developed using cadaveric specimens.

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Outer Hair Cells

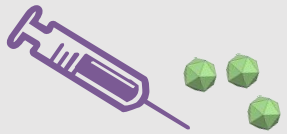
Cochlear Amplifier

Inner Hair Cells

Relay Signals to Auditory Nerve Fibers

AAVAnc80-eGFP was Tested in 2 NHP Species

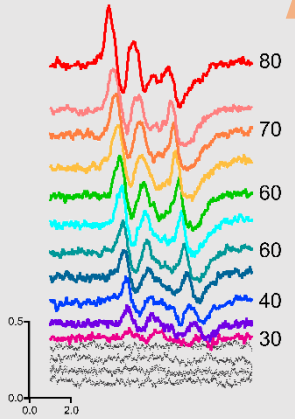
Model	N	AAVAnc80-eGFP Dose
Baboon	2	High
Cynomolgus Macaque	2	High
	2	Mid
	2	Low



Intracochlear Injections

Day 0

Day 21



Inclusion Criteria:

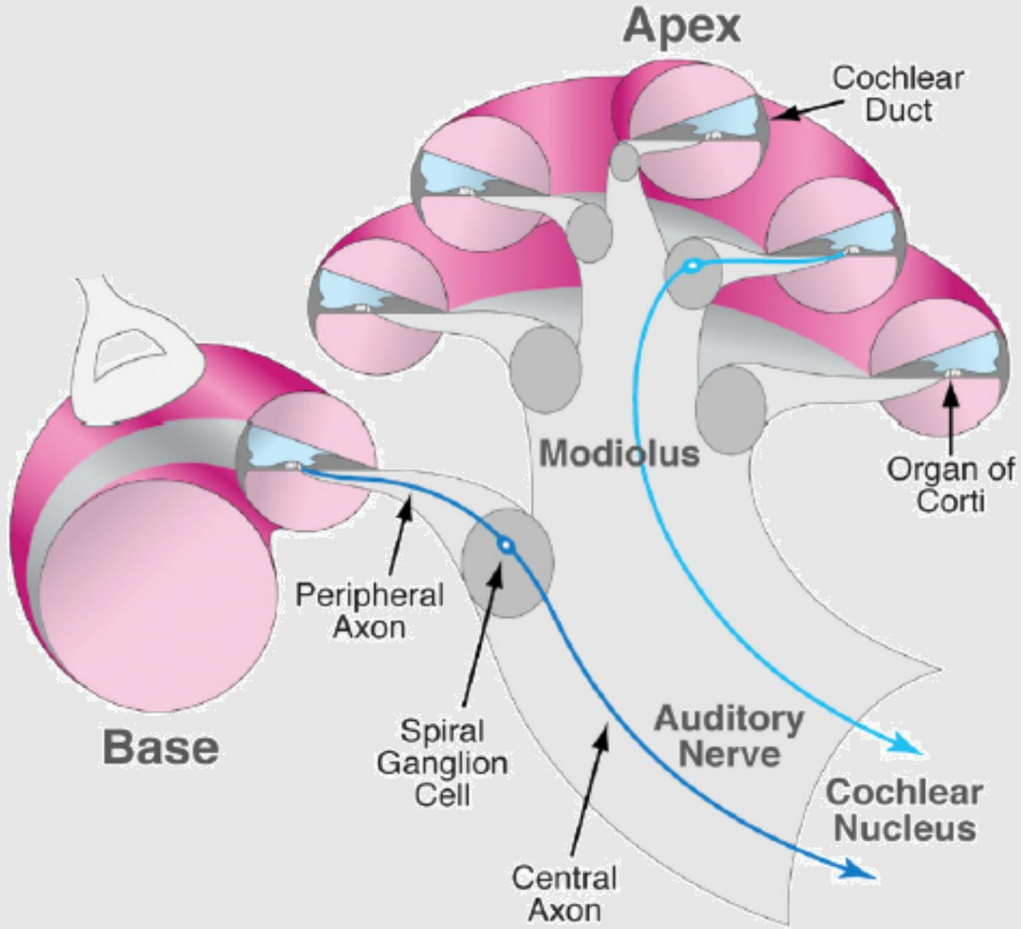
Cochlear Function Test (Baboon)

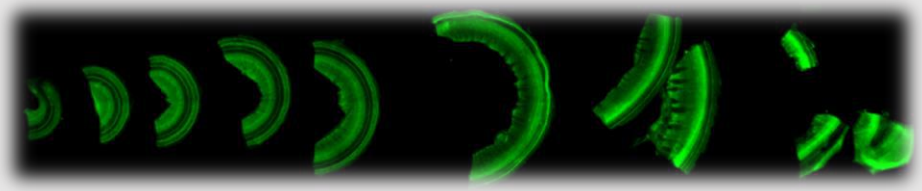
Endpoint:

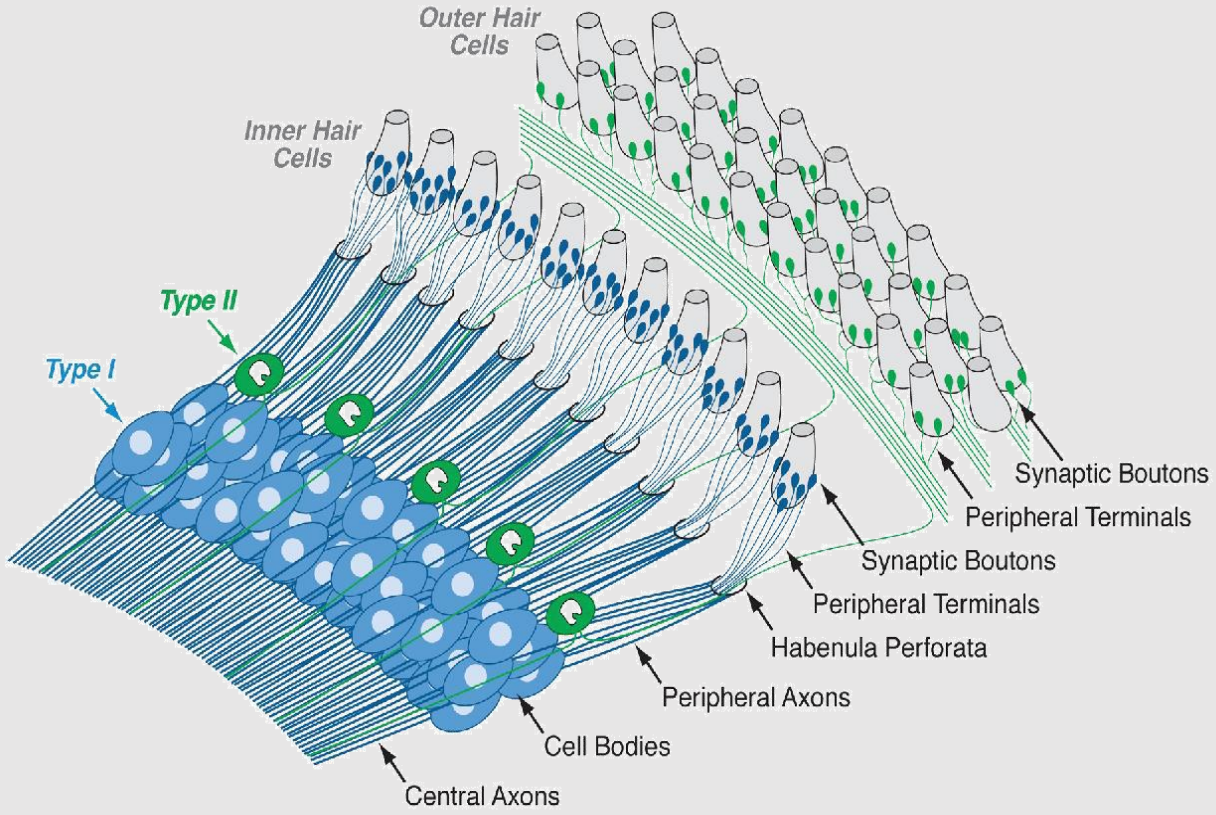
Cochlea, Organ Collection

Histopathology

Cochleae were Dissected into Half-turns & Immunostained







Images by MC Liberman

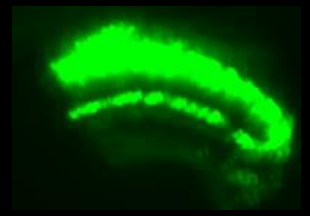
In Baboon Cochleae, Hair Cells and Supporting Cells Expressed GFP

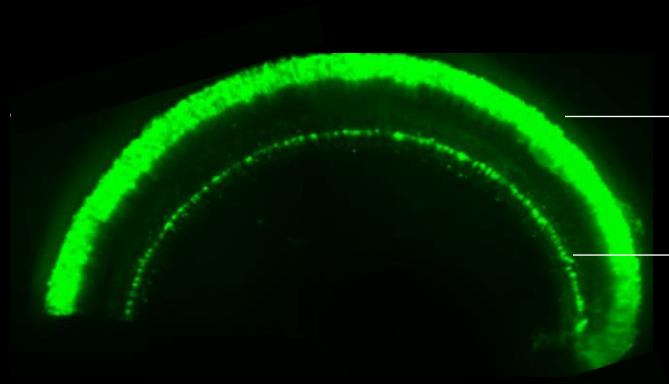
Baboon 1

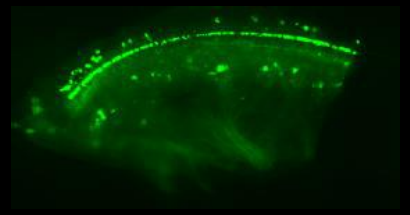
Baboon 2

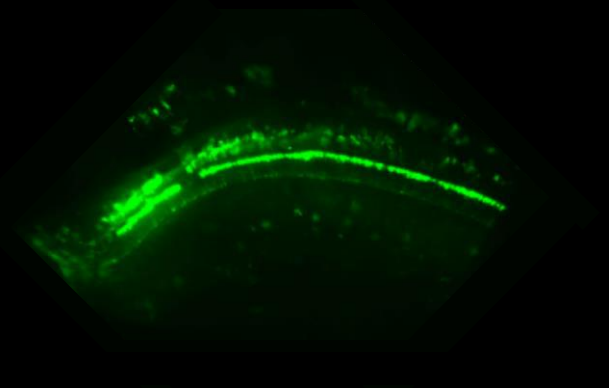
Apex

Base









Lateral Supporting Cells

Inner Hair Cells

Highly efficient transduction!!

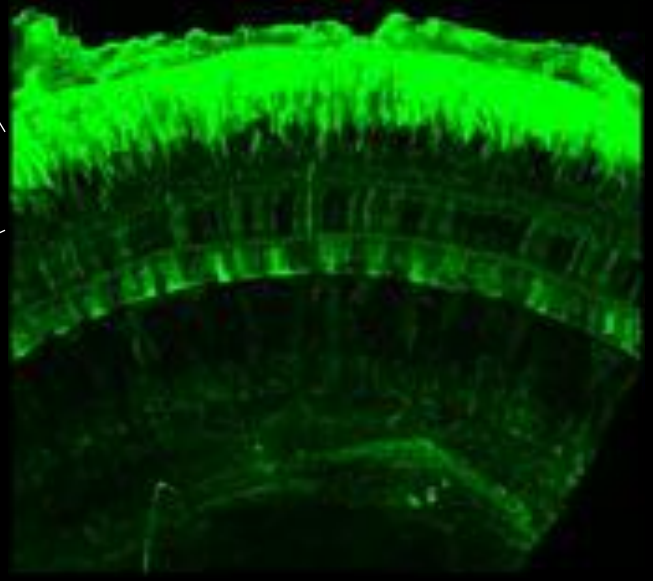
In Cyno Cochleae, Hair Cells and Supporting Cells Expressed GFP

Lateral Supporting Cells

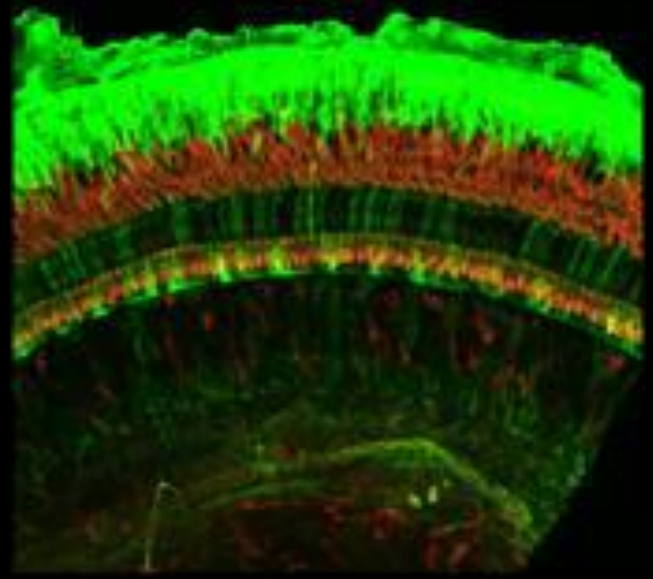
OHCs

IHCs

GFP

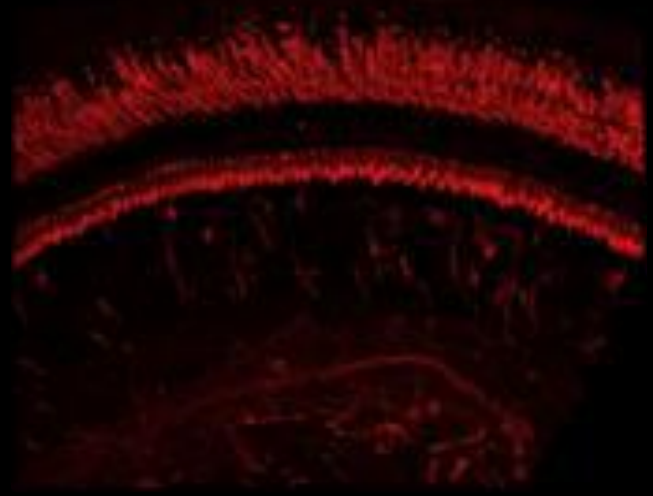


Merge

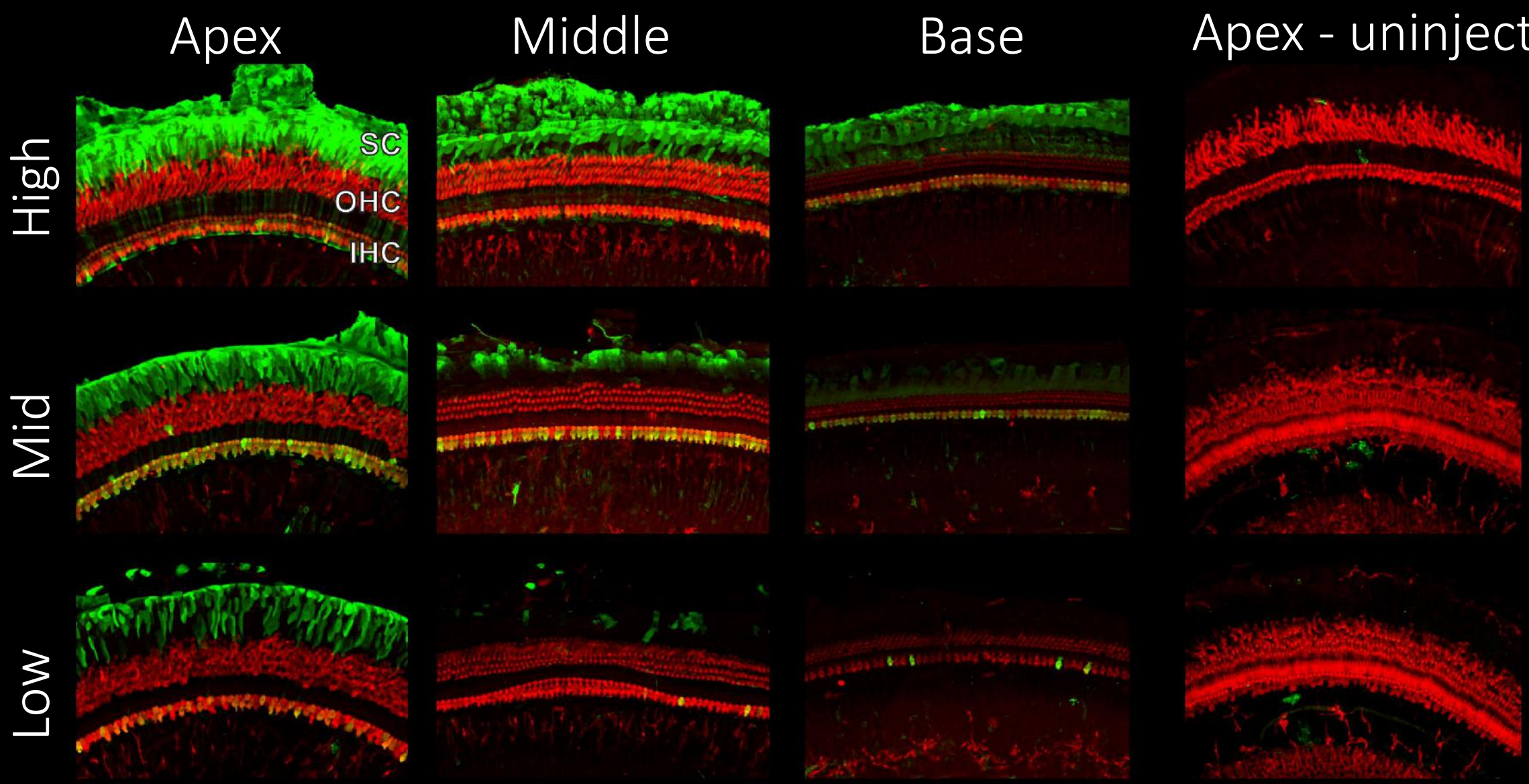


Myo7a // iba-1

(Hair cell // macrophage)



AAVAnc80 Transduction is Dose-Dependent



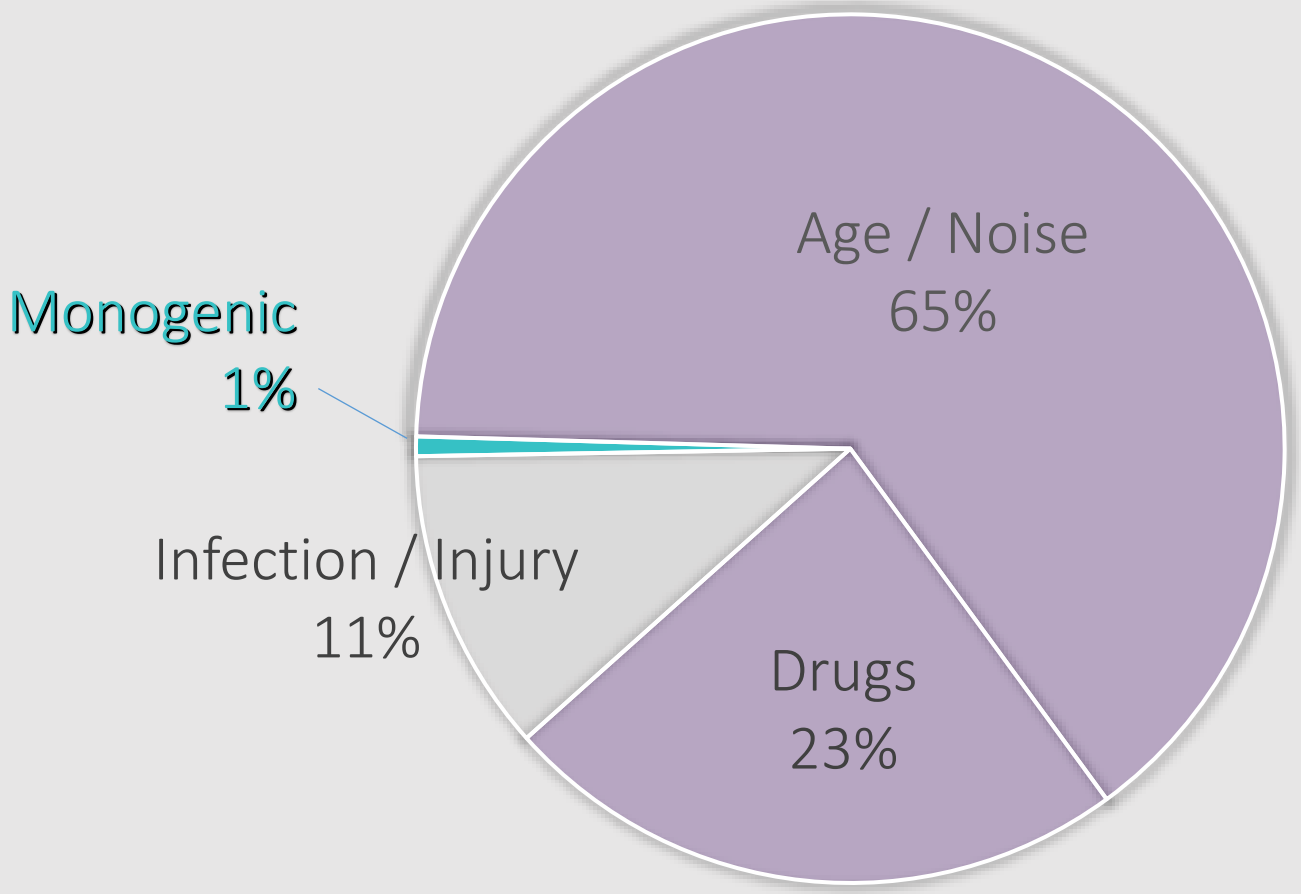
Summary

- Efficient transduction of AAVAnc80 in relevant cochlear cells in rhesus (Andres-Mateos et al., 2019), cynomolgus macaques, and baboons.
- Transduction is dose-dependent
- The intracochlear delivery was well tolerated in primates

➢ Together, these data support a strategy of intracochlear administration of AAVAnc80 to address genetic hearing loss

Who can benefit from cochlear gene therapy?

- *360 million with Disabling Hearing Loss worldwide*
  - *50 Million in the U.S.*



- Genetic Risk Factors
- Protective Gene Products
- Gene Therapy-Mediated Regeneration

Thank you

Blindness separates us from **things**
Deafness separates us from **people**
~ Helen Keller ~

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