AKOUOS

# Translation of Potential Genetic Medicines for the Inner Ear

February 24, 2021

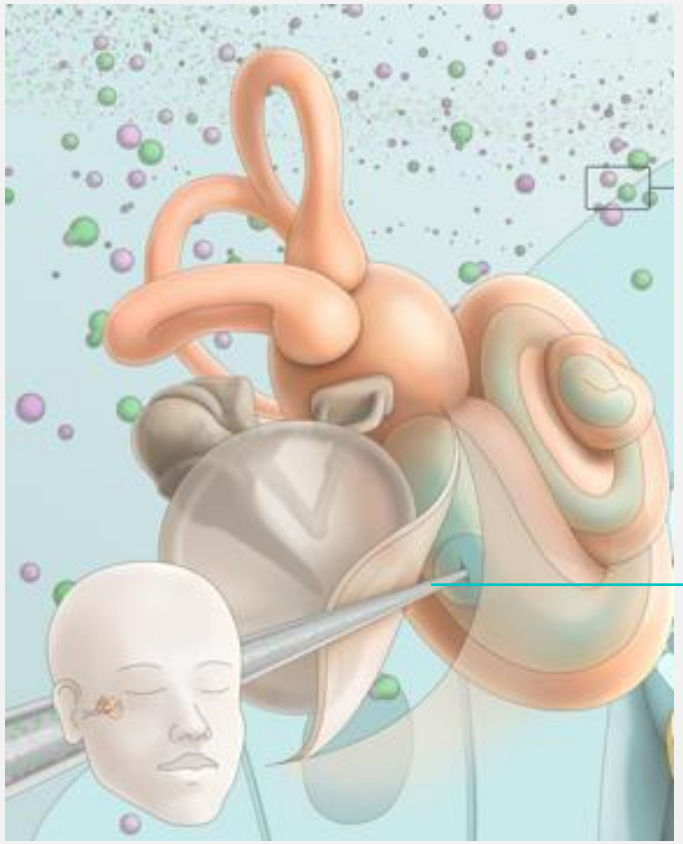
Michelle D. Valero

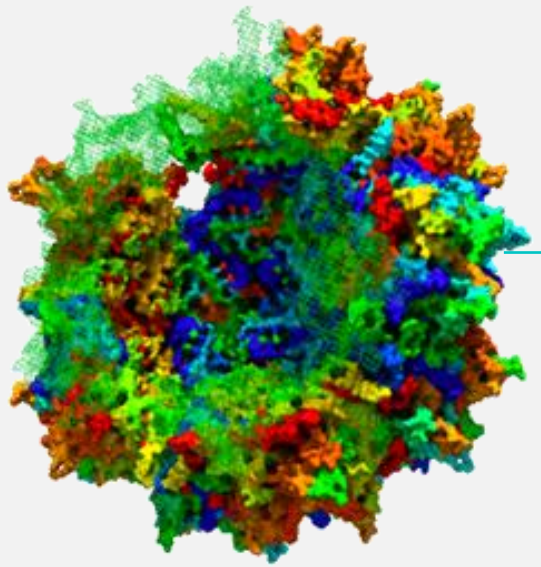
# Forward Looking Statements

This presentation includes “forward-looking statements” within the meaning of, and made pursuant to the safe harbor provisions of, the Private Securities Litigation Reform Act of 1995, including, but not limited to: the ability of our product candidates to potentially restore, improve, and preserve high-acuity physiologic hearing for people worldwide who live with disabling hearing loss. These forward-looking statements may be accompanied by such words as “aim,” “anticipate,” “believe,” “could,” “estimate,” “expect,” “forecast,” “goal,” “intend,” “may,” “might,” “plan,” “potential,” “possible,” “will,” “would,” and other words and terms of similar meaning. These statements involve risks and uncertainties that could cause actual results to differ materially from those reflected in such statements, including: the initiation, timing, progress, and results of our current and future nonclinical studies and clinical trials and our research and development programs, including our expectation that we will submit an IND application for AK-OTOF, our lead product candidate, for otoferlin gene (*OTOF*)-mediated hearing loss to the U.S. Food and Drug Administration in 2021; our estimates regarding expenses, future revenue, capital requirements, need for additional financing, and the period over which we believe that our existing cash, cash equivalents, and investments will be sufficient to fund our operating expenses and capital expenditure requirements; our plans to develop and, if approved, subsequently commercialize our product candidates; the timing of and our ability to submit applications for, and obtain and maintain regulatory approvals for, our product candidates; our expectations regarding our regulatory strategy; our expectations regarding our ability to fund our operating expenses and capital expenditure requirements with our cash, cash equivalents, and marketable securities; the potential advantages of our product candidates; the rate and degree of market acceptance and clinical utility of our product candidates; our estimates regarding the potential addressable patient population for our product candidates; our commercialization, marketing, and manufacturing capabilities and strategy; our expectations regarding our ability to obtain and maintain intellectual property protection for our product candidates; our intellectual property position; our ability to identify additional products, product candidates, or technologies with significant commercial potential that are consistent with our commercial objectives; the impact of government laws and regulations; our competitive position and expectations regarding developments and projections relating to our competitors and any competing therapies that are or become available; developments and expectations regarding developments and projections relating to our competitors and our industry; the impact of the COVID-19 pandemic on our business, results of operations, and financial condition; our ability to maintain and establish collaborations or obtain additional funding; and the other risks and uncertainties that are described in the Risk Factors section of our most recent filings with the U.S. Securities and Exchange Commission. These statements are based on our current beliefs and expectations as of the date of this presentation. We do not undertake any obligation to publicly update any forward-looking statements except as required by law. By attending or receiving this presentation, you acknowledge that: you are cautioned not to place undue reliance on these forward-looking statements; you will be solely responsible for your own assessment of the market and our market position; and you will conduct your own analysis and be solely responsible for forming your own view of the potential future performance of Akouos, Inc.

# *The Akouos Precision Genetic Medicine Platform*

| Novel Delivery Approach | Proprietary AAV Vector Library | Multimodal Capabilities |
|---|---|---|





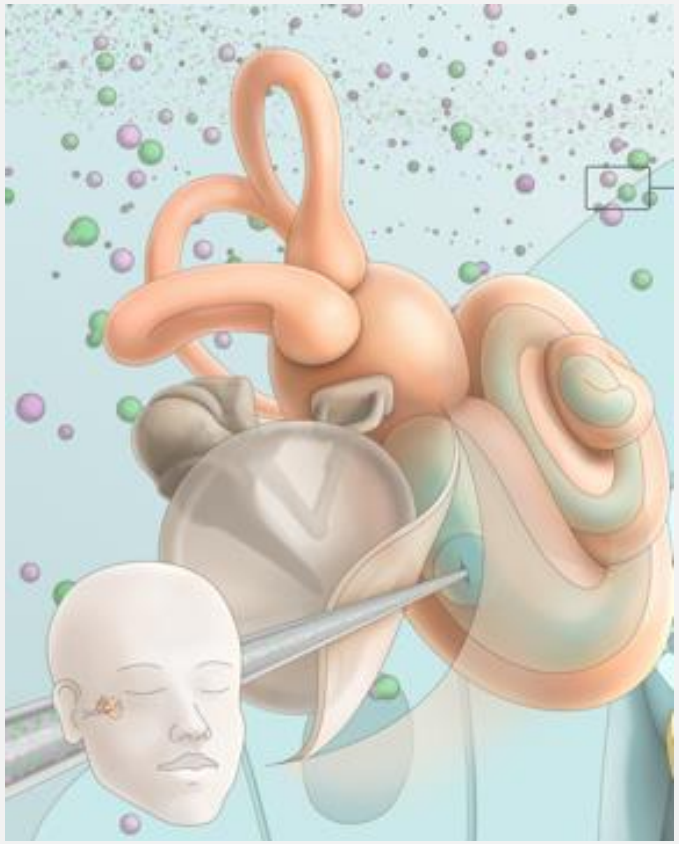
**Gene transfer** targeting loss-of-function mutations

**Gene knockdown or editing** targeting toxic gain-of-function or dominant negative mutations

**Therapeutic protein expression (e.g., monoclonal antibody)** targeting disease pathways responsible for non-monogenic hearing loss

# *Considerations in Development of a Novel Delivery Approach*

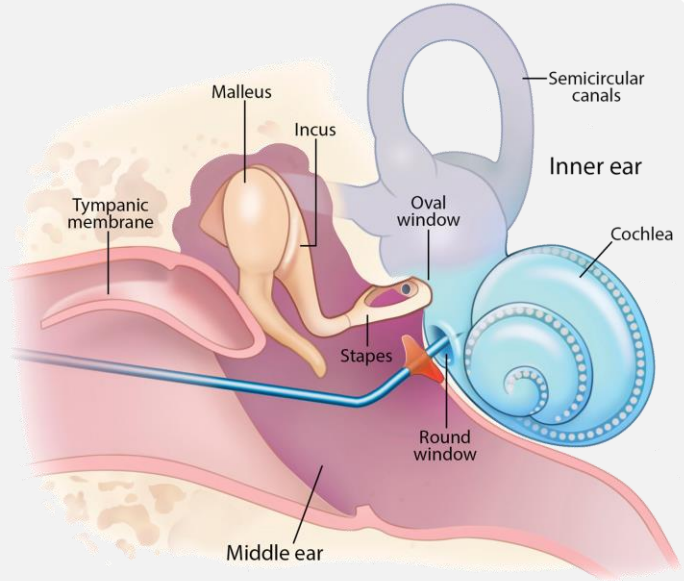
Novel
Delivery Approach

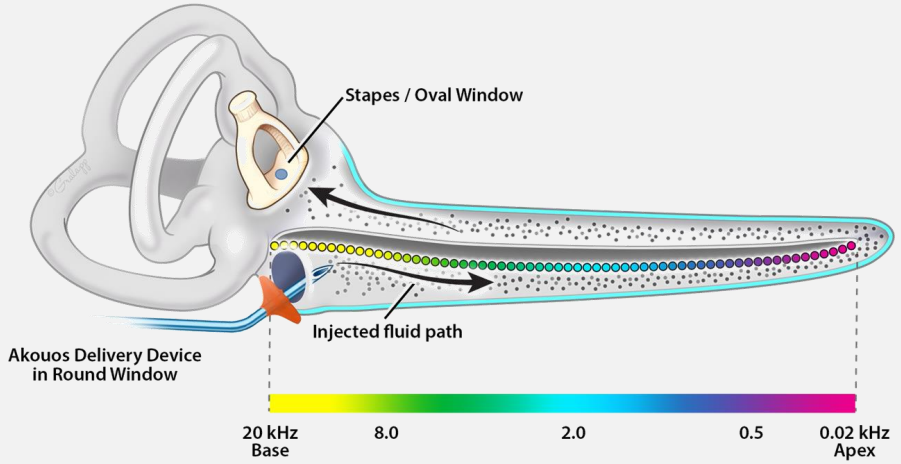


- Product candidates should uniformly access target cells across the entire length of the cochlea
- Surgical approach and intracochlear administration should be as minimally invasive as feasible
- Surgical approach and use of the device should be familiar to otologic surgeons
- Duration of direct intracochlear administration should be limited
- Delivery approach in animal models should closely mimic the intended clinical delivery approach

# *Akouos's Approach for Delivery to the Human Cochlea Leverages Common Otologic Techniques*

- Minimally invasive approach via the external auditory canal
  - Standard transcanal tympanotomy approach for middle ear surgeries
  - No need for mastoidectomy (*i.e.,* drilling through the mastoid bone)
  - Provides clear visual access to the oval and round windows
- Direct intracochlear administration via the round window membrane (RWM)
  - Device designed to guide positioning through the RWM
  - Product candidate delivered in a fixed volume and at a controlled rate
- Fenestration of the stapes footplate serves as a vent
  - Stapedotomy is a routine otologic procedure
  - Product candidates can access target cells along the full length of the cochlea
  - Minimizes potential for backflow through the RWM



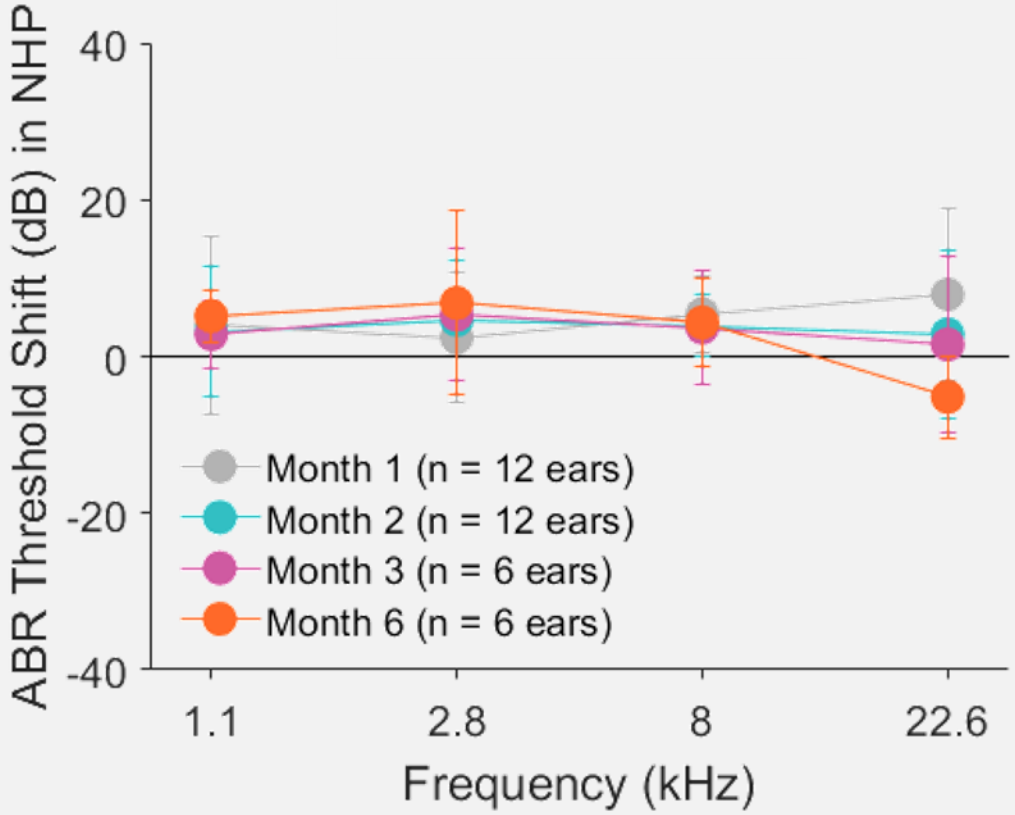




Frequency Distribution Along the Cochlea

# *Nonclinical Studies in Non-human Primates Follow a Different Surgical Approach, but Same Route of Administration*

| *Key Attributes of the Delivery Approach* | *Akouos's Planned Delivery Approach for Humans* | *Akouos's Delivery Approach for Non-human Primates* |
|---|---|---|
| *Minimally Invasive Surgical Approach* | ✓<br>Transcanal Tympanotomy<br>(*i.e.,* through the external auditory canal) | ✗<br>Post-auricular Transmastoid / Facial Recess<br>(*i.e.,* drilling into mastoid bone) |
| *Visualization of Oval Window* | ✓ | ✗ |
| *Venting: Fenestration of Stapes Footplate* | ✓ | ✓ |
| *Akouos Delivery Device* | ✓ | ✓ |
| *Round Window Membrane Administration* | ✓ | ✓ |

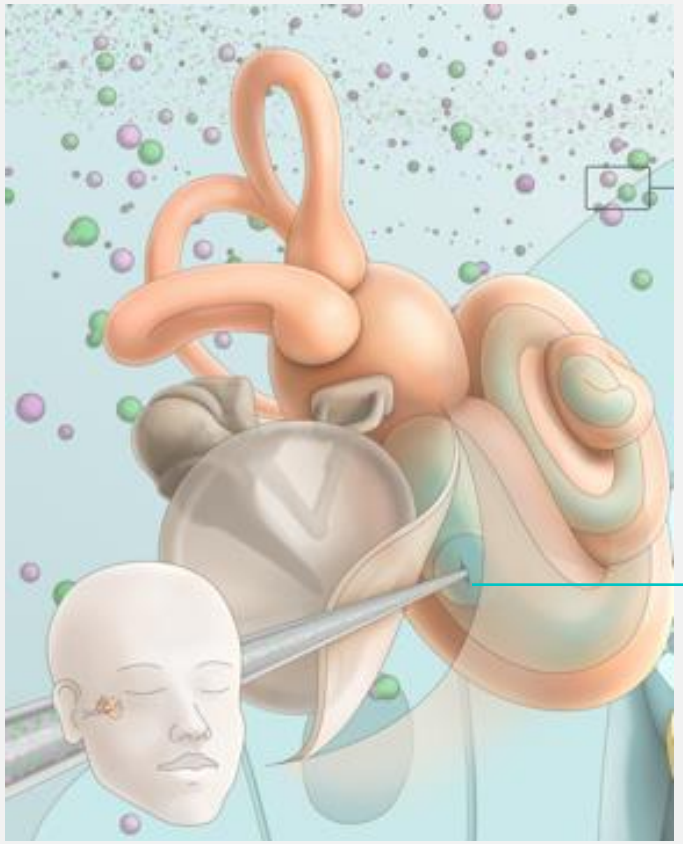
# *Intracochlear Administration of AAVAnc80 is Well Tolerated in Non-human Primates*



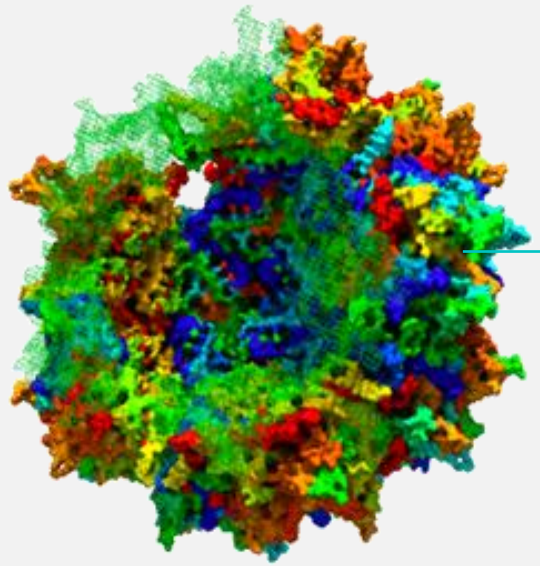

- Intracochlear administration of AK-antiVEGF
  - antiVEGF is a secreted protein driven by a ubiquitous promoter intended for treatment of vestibular schwannoma
- An independent group assessed auditory function and cochlear histology
  - Auditory brainstem responses (ABRs) were measured prior to surgery and up to four times following surgery (1, 2, 3, 6 months)
  - Tone-burst stimuli presented in ~1.5-octave steps from 1.1 to 22.6 kHz
- Auditory function and hair cell integrity was preserved for the duration of the study

# *The Akouos Precision Genetic Medicine Platform*

## Novel Delivery Approach



## Proprietary AAV Vector Library



## Multimodal Capabilities

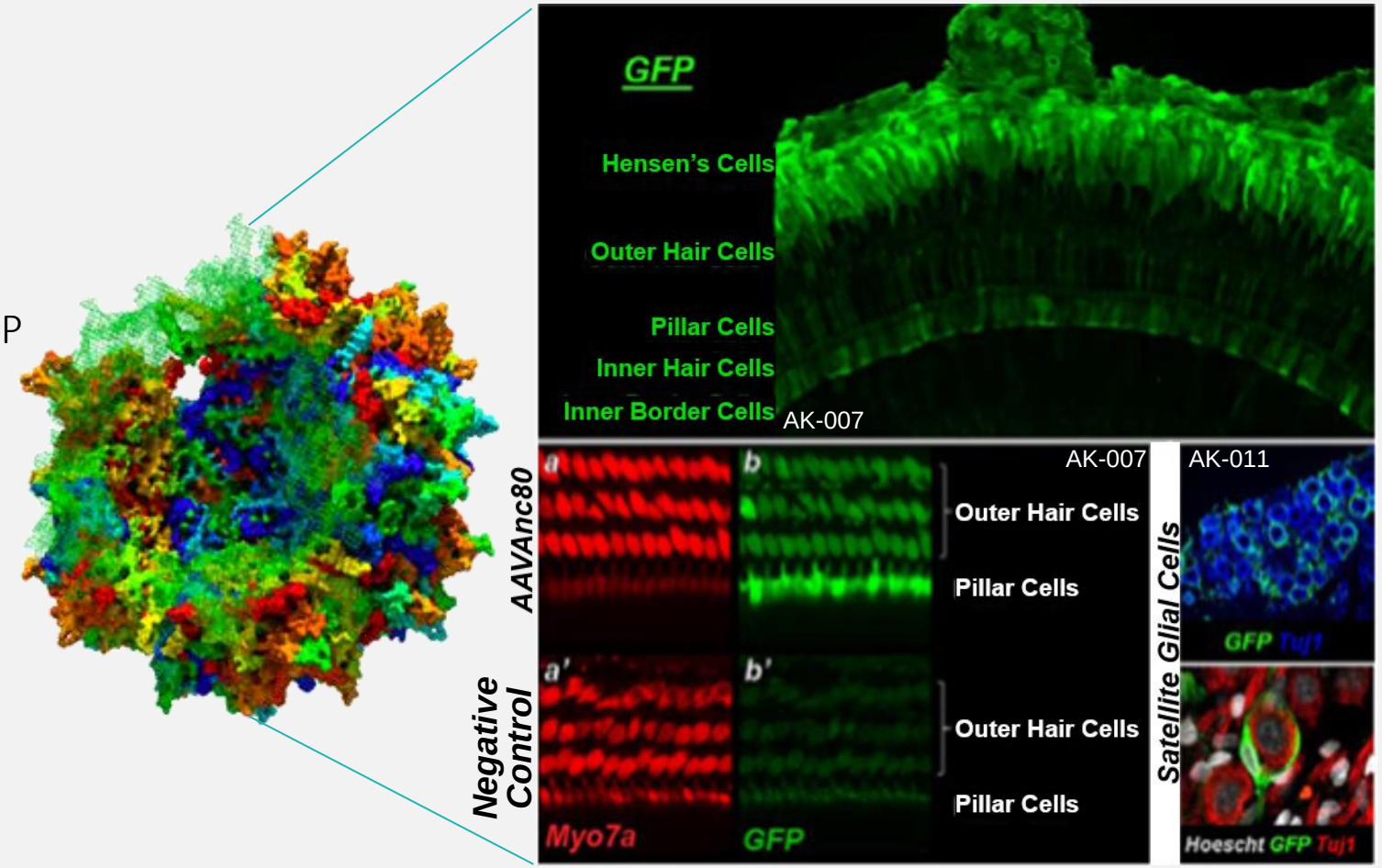
Gene transfer targeting loss-of-function mutations

Gene knockdown or editing targeting toxic gain-of-function or dominant negative mutations

Therapeutic protein expression (e.g., monoclonal antibody) targeting disease pathways responsible for non-monogenic hearing loss

# AAVAnc80 Efficiently Transduces Multiple Cell Types in the Inner Ear

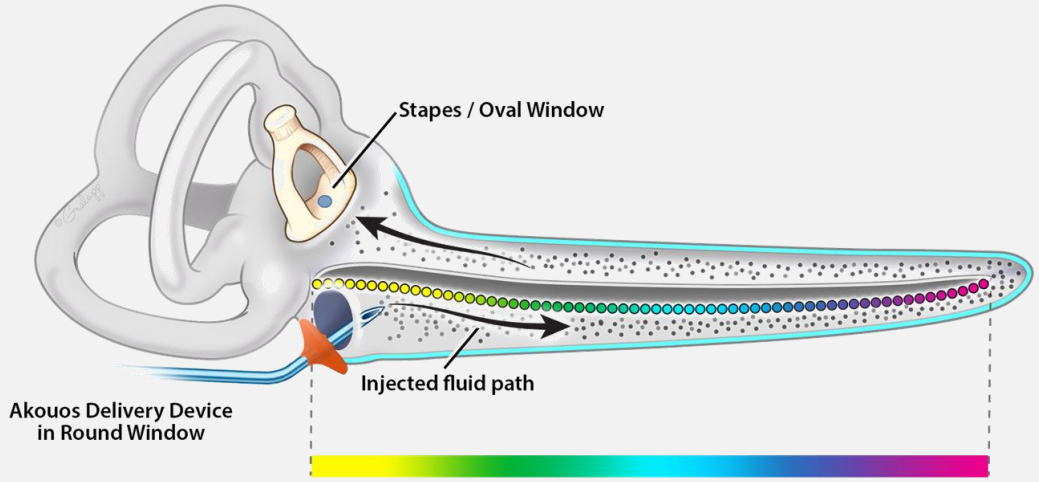
- ✓ Conducted nonclinical studies across three different non-human primate models using GFP as a reporter gene delivered by AAVAnc80
- ✓ AAVAnc80 can efficiently transduce multiple target cell populations throughout the cochlea in the primate inner ear



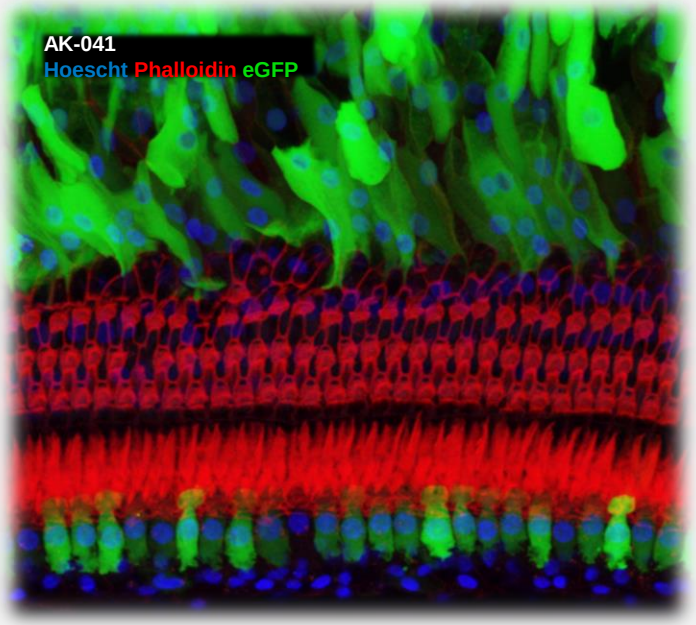

GFP: green fluorescent protein; Myo7a: Myosin VII a; Tuj1: class III beta-tubulin

# Nonclinical Studies in NHPs to Support Akouos's Novel Delivery Approach

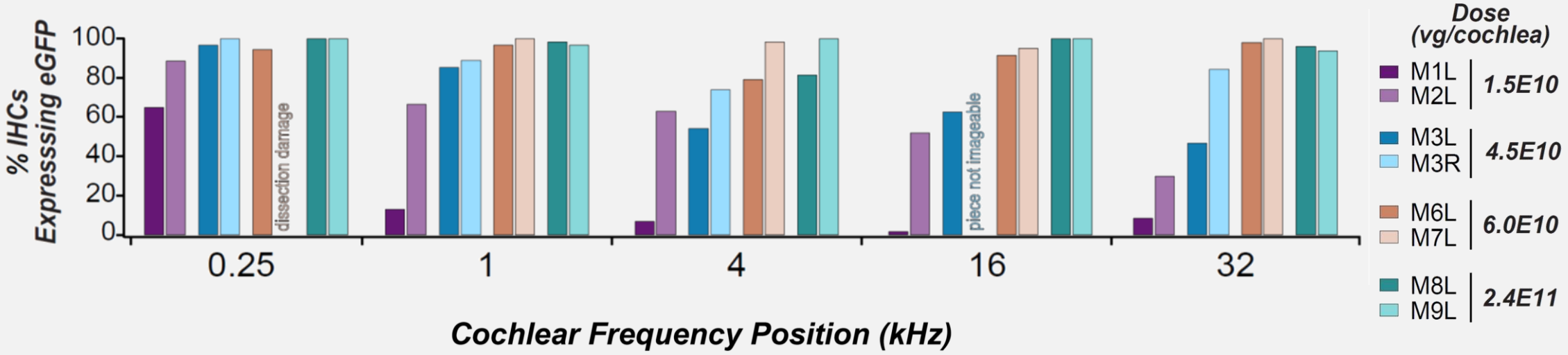
- Seven NHPs underwent intracochlear (RWM) administration of AAVAnc80-eGFP *with* venting of the stapes footplate (6 unilateral, 1 bilateral)
- Two NHPs underwent intracochlear (RWM) administration of AAVAnc80-eGFP *without* venting of the stapes footplate (bilateral)
- Cochleae were analyzed for eGFP expression in inner hair cells following a 3-week in-life duration




**Frequency Distribution Along the Macaque Cochlea**



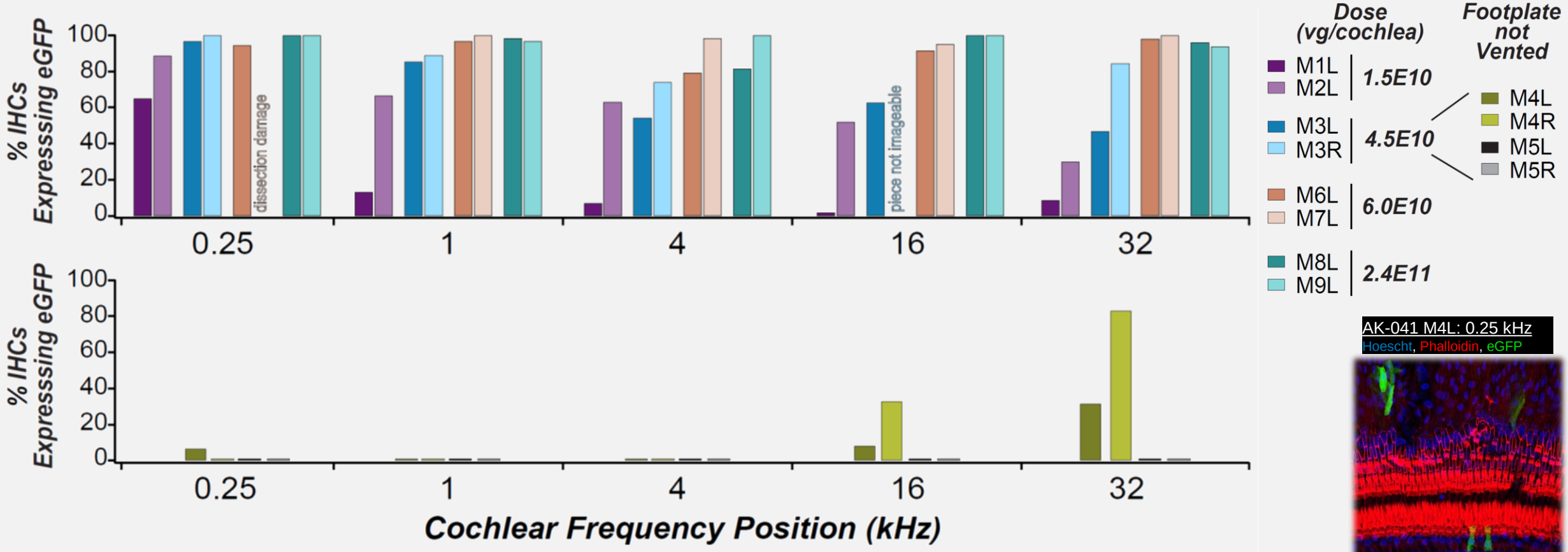
# AAVAnc80 Efficiently Transduces Inner Hair Cells of Non-human Primates




Three weeks following intracochlear administration of AAVAnc80-eGFP with venting of the stapes footplate:

- Transduction efficiency of ~80% to 100% can be achieved in NHP inner hair cells at doses ≥ 6.0E10 vg/cochlea
- At lower doses, an apex-to-base gradient in eGFP expression is observed

# *In the Absence of Footplate Venting, Inner Hair Cell Transduction is Biased to the Base of the Cochlea*



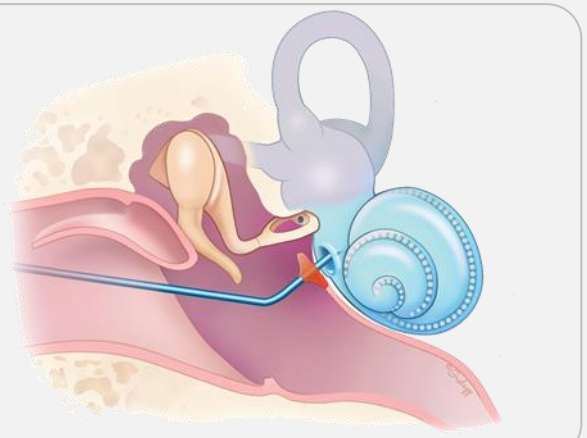


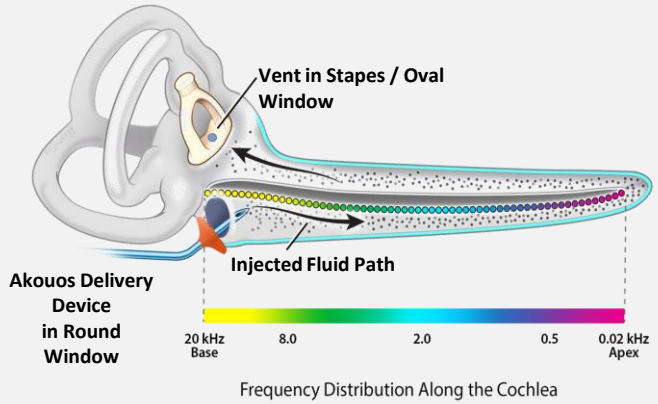


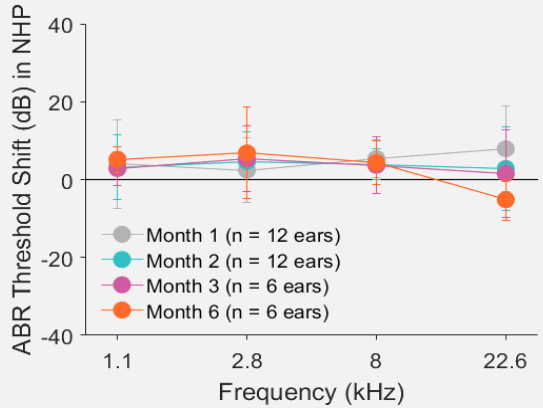
Three weeks following intracochlear administration of AAVAnc80-eGFP without venting of the stapes footplate:

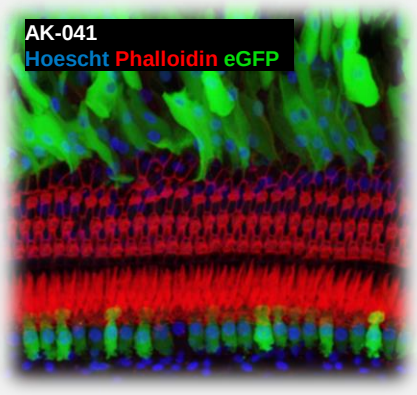
- Only sporadic transduction at cochlear regions in the apical 75% of the cochlea
- There may be potential to overcome this barrier by *e.g.*, increased dose, larger volume, and/or slower infusion, but these strategies may not be ideal for clinical development

# Summary






- Akouos's novel delivery approach is designed to allow for the safe and effective delivery of product candidates through the round window membrane (RWM)
  - The surgical approach (transcanal tympanotomy) and venting (stapedotomy) are minimally invasive and routine in standard otologic practice
  - Akouos's delivery device is designed to deliver product candidates in a fixed volume at a controlled flow rate and to be familiar to otologic surgeons
  - Direct intracochlear administration through the RWM, with venting of the stapes footplate, allows for distribution of product candidates across the full length of the cochlea
- Intracochlear administration of AAVAnc80 is well tolerated by non-human primates at doses that achieve efficient transduction of target cells across the full length of the cochlea


Thank you