AKOUOS

NIDCD Workshop 1, Research and Development Workshop:
Translating Pre-Clinical Findings Into Successful Clinical Trials

Development of Potential Genetic Medicines for Inner Ear Conditions

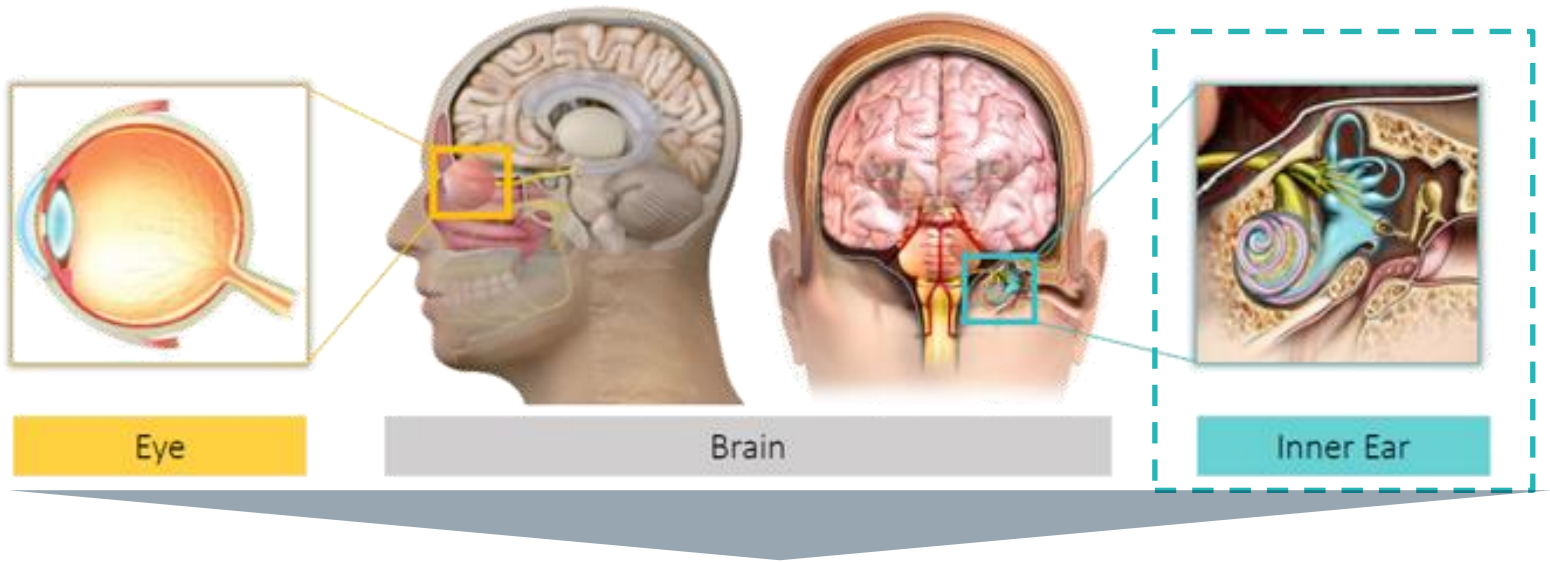
February 19, 2021

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: our expectation about timing and execution of anticipated milestones, including our planned IND submissions and initiation of clinical trials; our expectations about our collaborators’ and partners’ ability to execute key initiatives; our expectations regarding our regulatory strategy; and 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 FDA 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 Anatomy and Biology of the Inner Ear Are Ideal for One-Time Genetic Medicines

Opportunity to Leverage Learnings from Development of Genetic Medicines for the Eye and Brain



- **Enclosed compartments** → opportunity for local, targeted delivery
- **Reduced immune surveillance** → lower impact of neutralizing antibodies
- **Non-dividing target cells** → potential for one-time delivery to provide life-long benefit

Unique Advantages of the Inner Ear

- **Fewer target cells and smaller delivery volume** → less vector required for meaningful transgene expression
- **Anatomy is fully developed at birth** → more favorable benefit-risk profile in pediatric populations

While the unique anatomical challenges of delivering to the inner ear have hindered genetic medicine development for inner ear conditions and hearing loss, we believe Akouos is uniquely positioned to overcome these delivery challenges

Challenges Associated with Development of Genetic Medicines for the Inner Ear

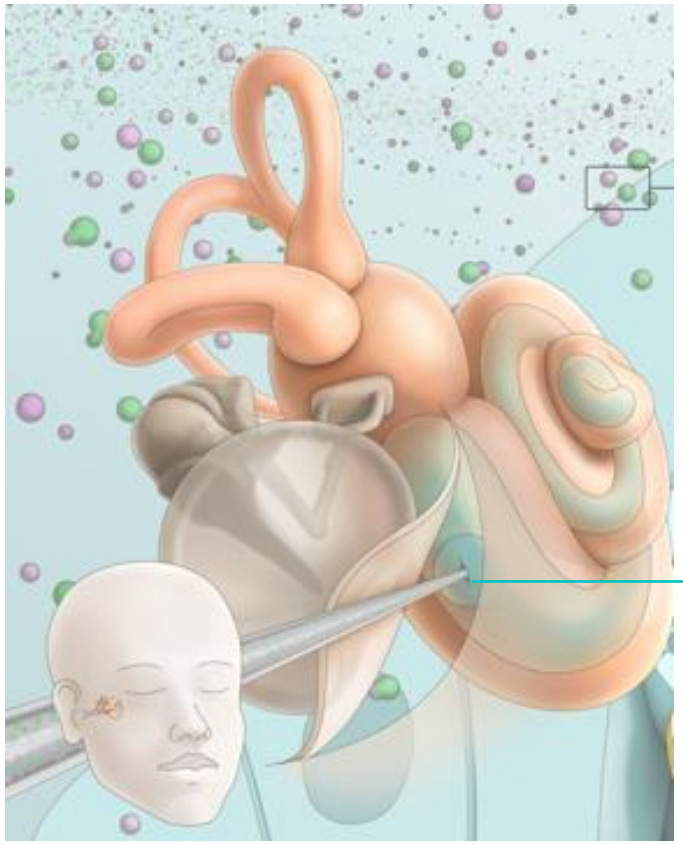
1. Gene therapy product candidate design (e.g., capsid, promoter, transgene) should be tailored for each specific condition

2. Direct delivery to the inner ear requires a novel delivery approach

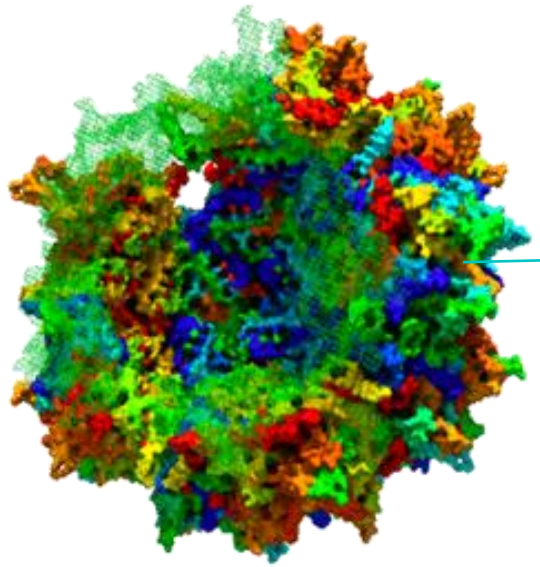
3. The selection of appropriate animal models is important for successful translation to a clinical development program designed to enable potential for broad access

The Akouos Precision Genetic Medicine Platform

Novel Delivery Approach



Proprietary AAV Vector Library



Multimodal Capabilities

Gene transfer targeting loss-of-function mutations

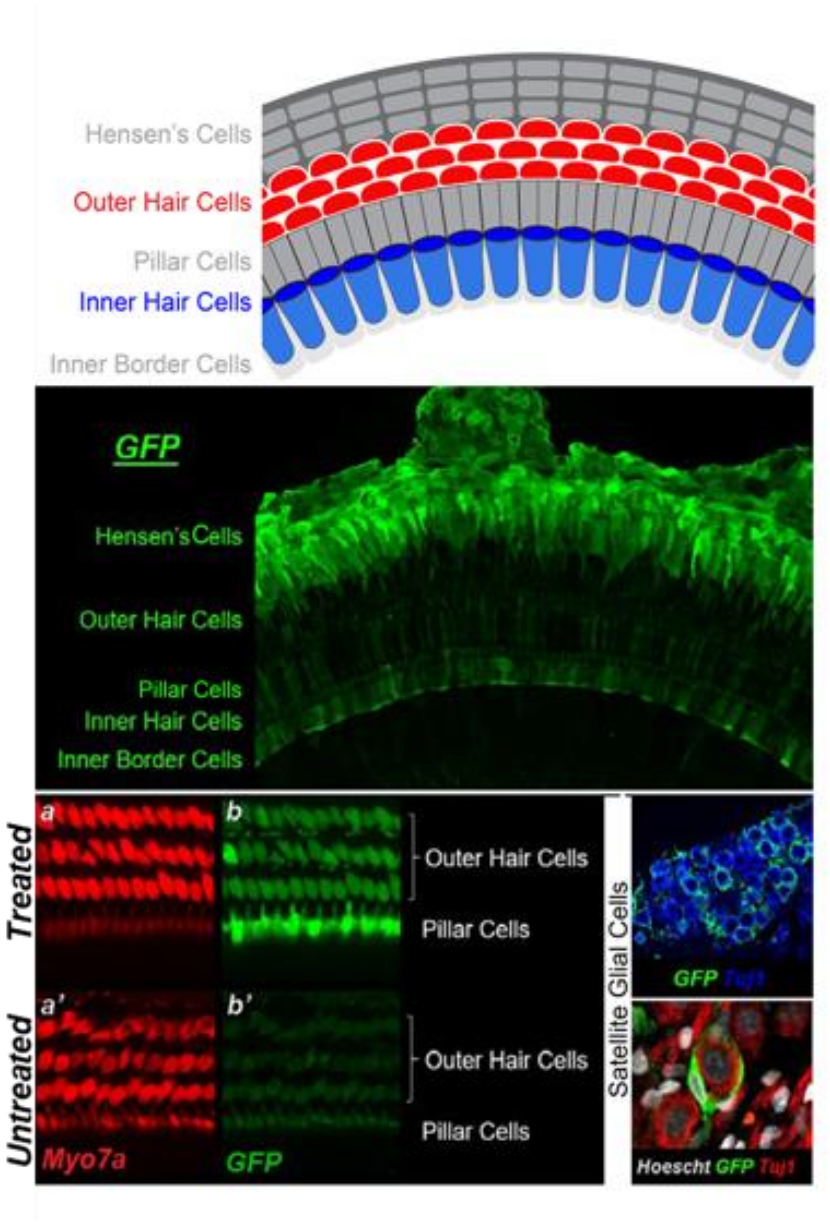
Gene knockdown or editing targeting toxic gain-of-function or dominant negative mutations

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

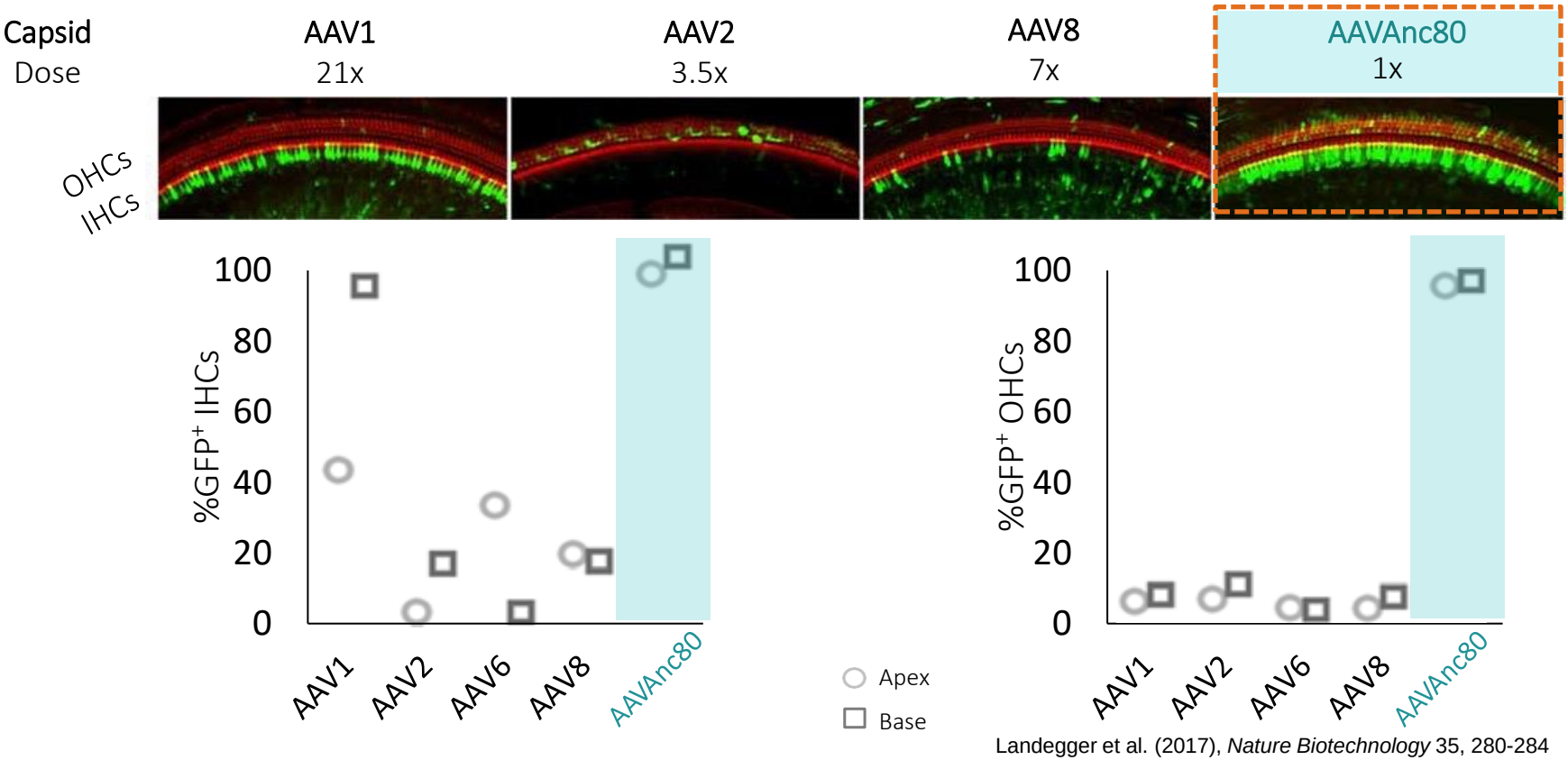
AAVAnc80 has shown significant advantages over commonly used AAV vectors:

- ✓ Broad tropism across inner ear cell types, which further expands target landscape
- ✓ Superior transduction efficiency in inner ear cells, which paves the way for dual vector delivery of large transgenes and more available targets
- ✓ Tropism and transduction advantages open new opportunities to address broader target landscape



AAVAnc80 Exhibits High Transduction Efficiency Compared to Other AAV Capsids

AAVAnc80 Transduces Cochlear Hair Cells More Efficiently than Other AAV Capsids



Landegger et al. (2017), *Nature Biotechnology* 35, 280-284

Multiple independent investigations have shown increased hair cell transduction efficiency of AAVAnc80 relative to other AAV capsids in mouse and non-human primate models

OHCs = outer hair cells; IHCs = inner hair cells; GFP = green fluorescent protein

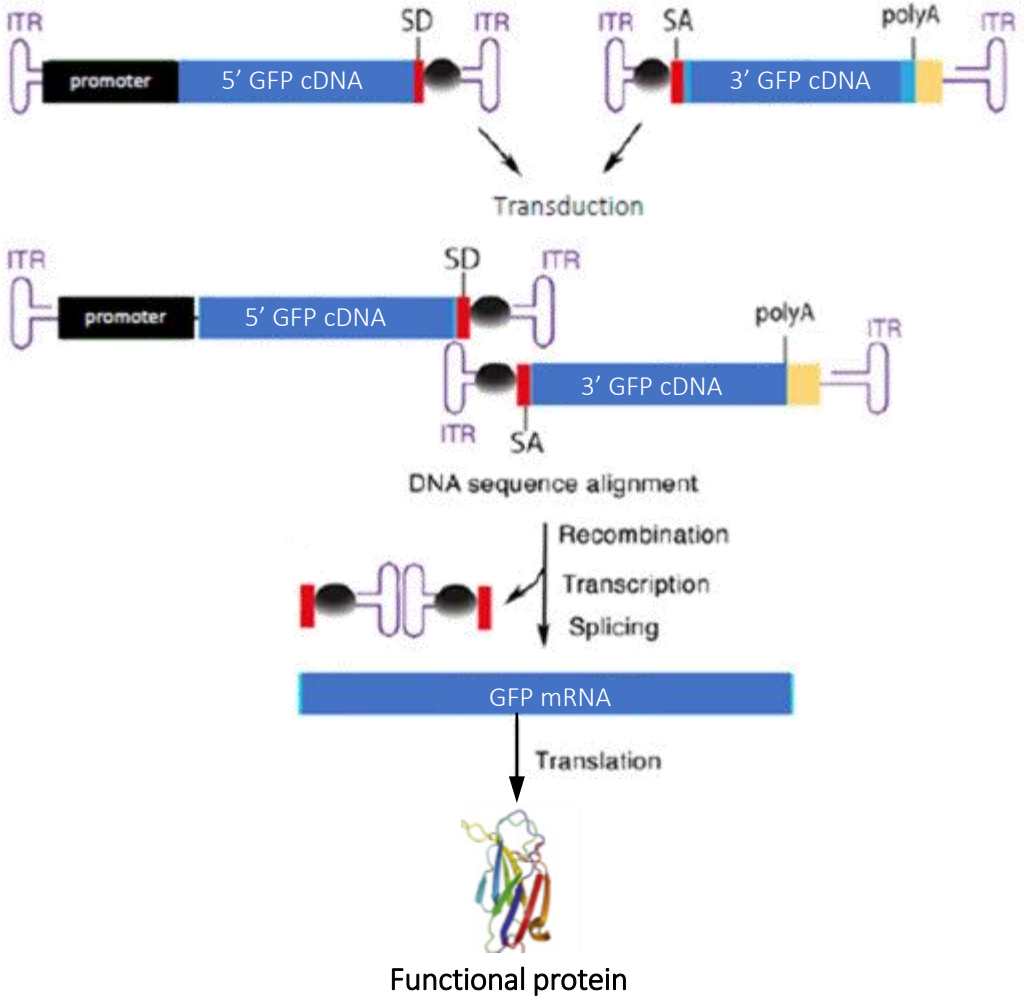
Ubiquitous Promoters Can Provide Safe, Effective, and Durable Gene Expression

Examples of Ubiquitous Promoter - AAV Gene Therapy

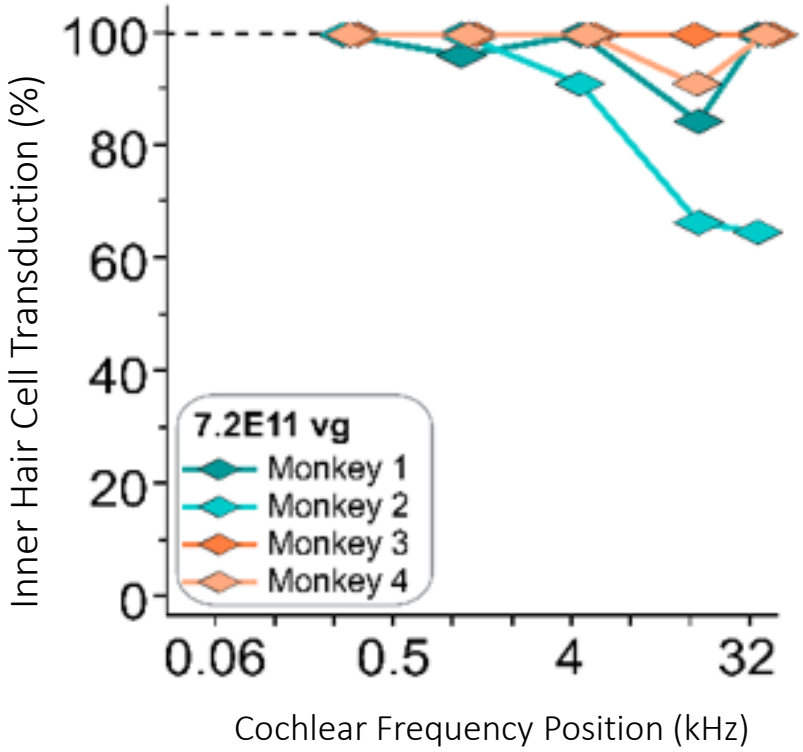
Sponsor	Condition	Phase	AAV	Regulatory	Transgene
Adverum	Diabetic Macular Edema	II	2.7m8	CMV	Aflibercept
Agilis / PTC	AADC Deficiency	II	2	CMV	AADC
Ceregne / Sangamo	Idiopathic Parkinson's	II	2	CBA	Neurturin
Voyager	Parkinson's	II	2	CMV	AADC
Gensight Biologics	Leber Hereditary Optic Neuropathy	III	2	CMV, Cox10-3UTR	ND4
Lysogene	MPS IIIA	III	rh10	CAG	SGSH
Nightstar / Biogen	Choroideremia	III	2	CBA, WPRE	REP1
Approved					
Avexis / Novartis	Spinal Muscular Atrophy	2019	9	CBA	SMN1
Spark / Roche / Novartis	*RPE65*-mediated IRD	2017	2	CBA	RPE65
Uniqure *	Lipoprotein Lipase Deficiency	2012	1	CMV, WPRE	LPL
* withdrawn by Sponsor					

- The benefit of using ubiquitous promoters in AAV gene therapy (GT) is to achieve rapid onset, and robust and durable expression in transduced cells
- Both CMV and CBA promoters have been widely used for late-stage clinical trials and approved AAV GT products
  - For Luxturna®, the CBA promoter has demonstrated a safe and durable effect in Phase 3 trial participants (sustained for 4 years with observations ongoing; Maguire *et al.,* American Academy of Ophthalmology 2019)

The High Transduction Efficiency of AAVAnc80 Coupled with Local Delivery to the Inner Ear Compartment Allows for a Dual Vector Approach for Larger Transgenes

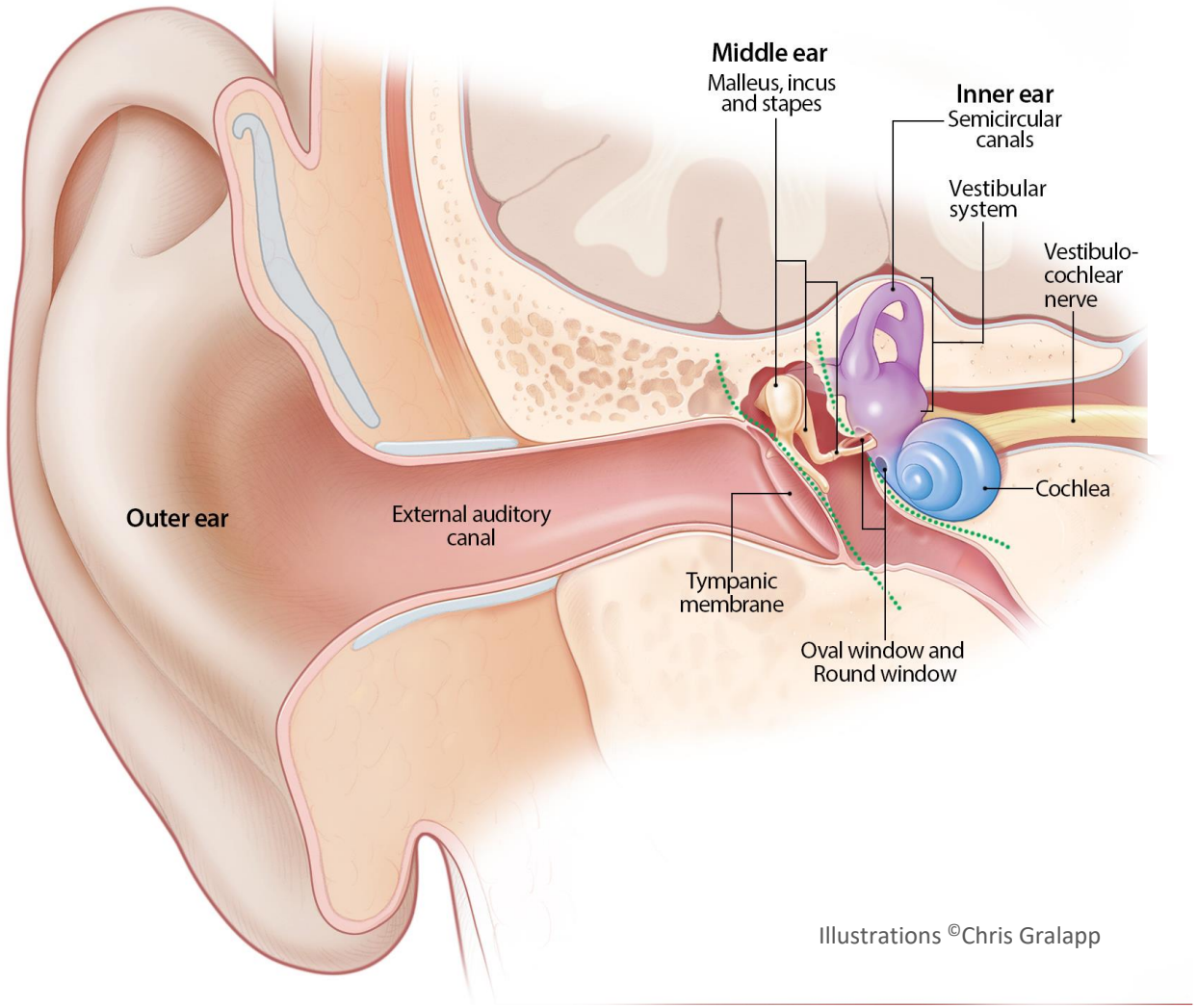


Percentage of Inner Hair Cells Expressing Transgene Three Weeks Following Administration of Dual AAVAnc80 Vectors



Ability to deliver transgenes that are larger than 5 kilobases in size creates the potential for broader treatment of genetically-driven hearing loss

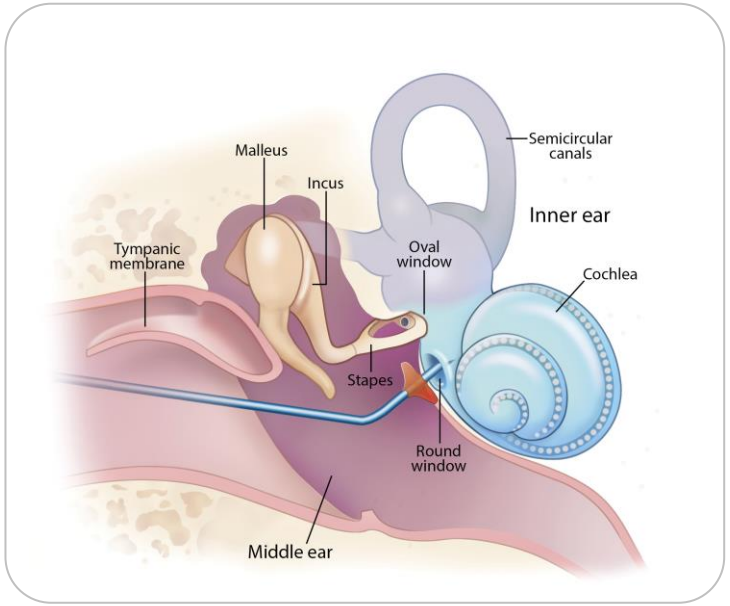
Uniform Intracochlear Delivery is Important to Address Inner Ear Conditions

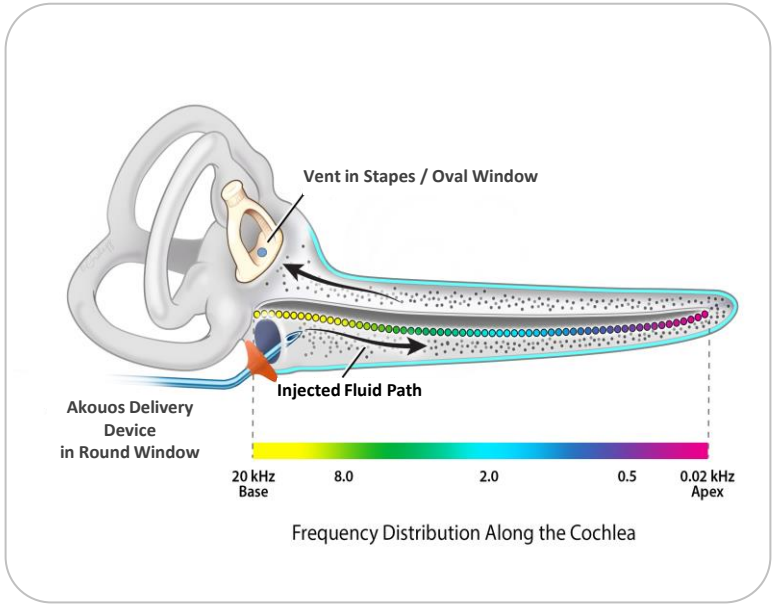


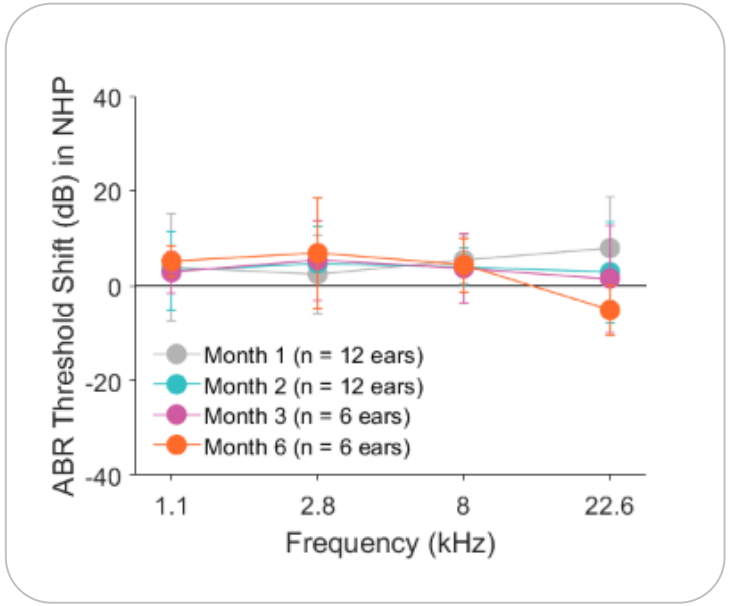
Illustrations ©Chris Gralapp

- Target cells are within the inner ear
- Blood-cochlea barrier prevents ready access to cochlea
- Direct administration with uniform distribution throughout the cochlea requires a novel delivery approach
- Less systemic exposure due to local administration and lower doses supports potential for improved safety

Novel, Minimally Invasive Delivery Approach Designed to Enable Efficient Access to Target Cells and Uniform Distribution of Product Candidates Throughout the Cochlea



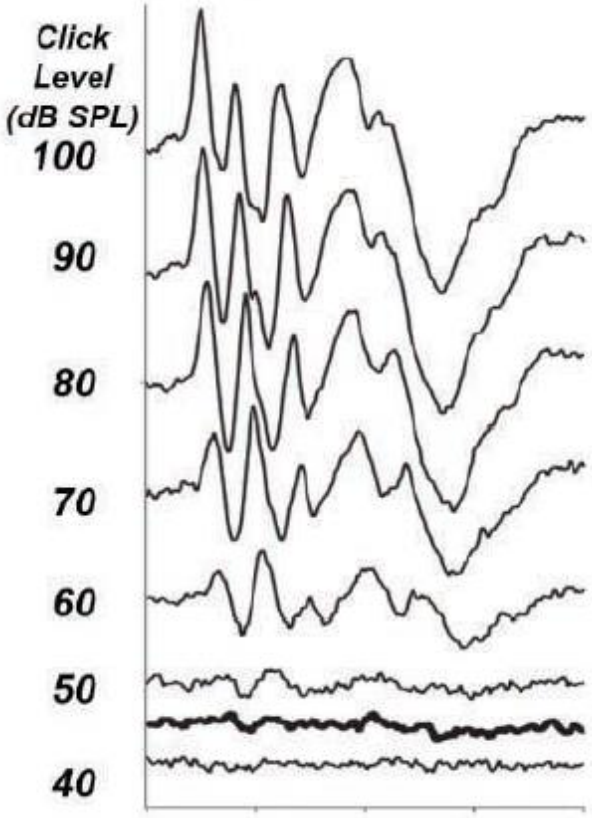




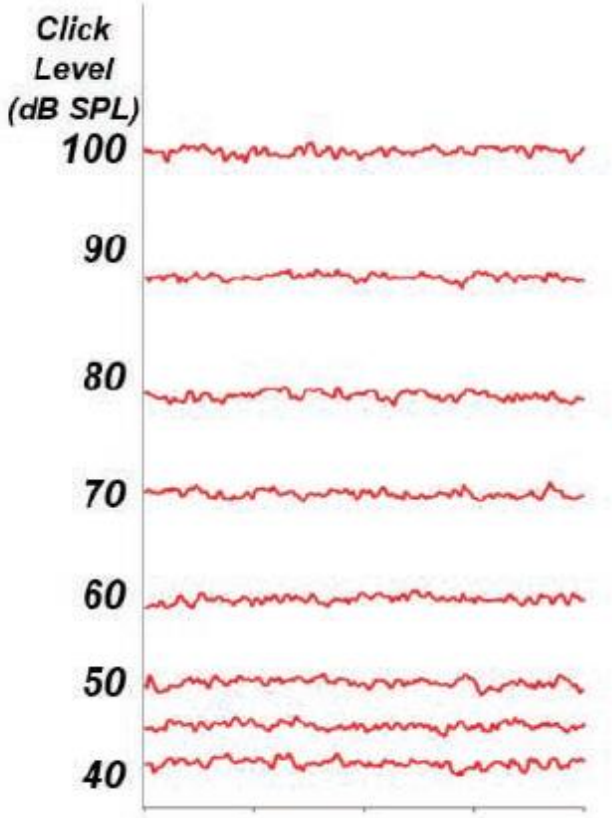
- Designed to allow for the safe and effective delivery of product candidates through the round window membrane
- Minimally invasive device delivers product candidates in a fixed volume and at a controlled flow rate
- Design allows for distribution of product candidates across the full length of the cochlea
- Auditory brainstem response (ABR) data in NHPs demonstrate intracochlear administration is well-tolerated

A Single Dose of AK-OTOF (AAVAnc80-hOTOF) Restored Auditory Function in Mature Mice Lacking Otoferlin

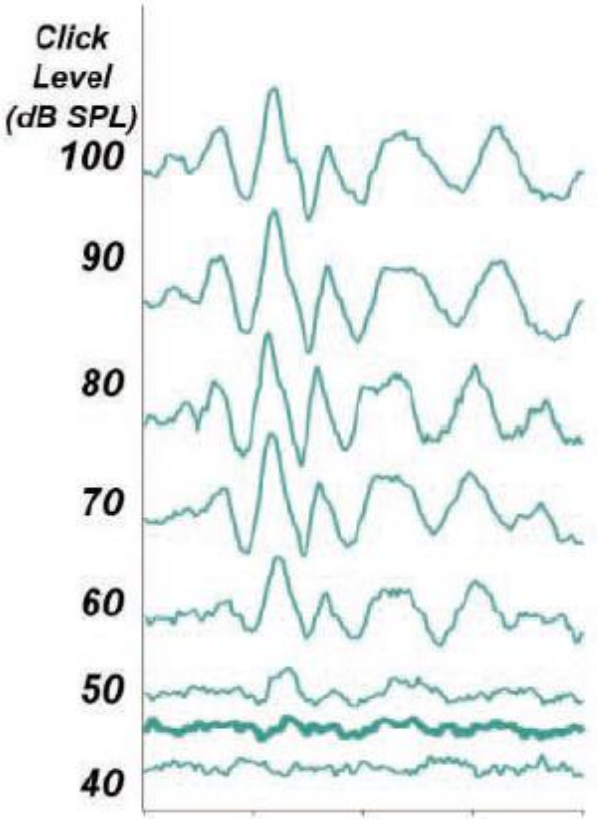
Wild-Type Vehicle Control



Otoferlin KO + Vehicle Control

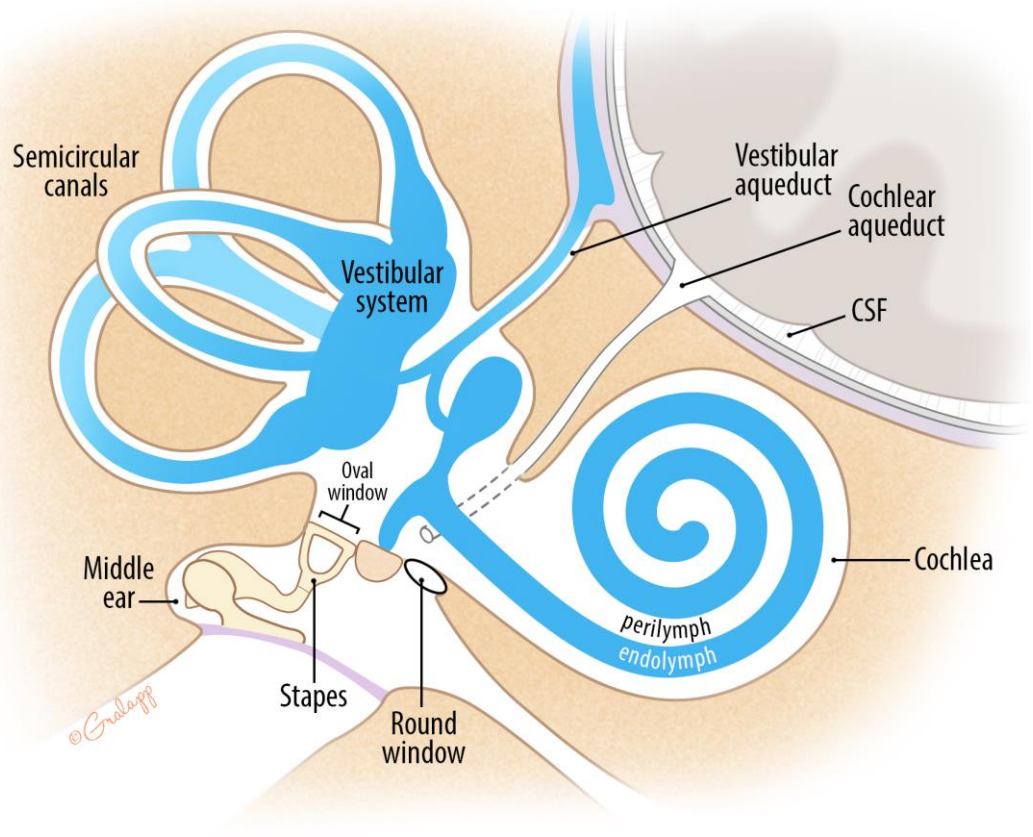


Otoferlin KO + AAVAnc80-hOTOF



In a nonclinical study, a single dose of AK-OTOF restored auditory function in mice lacking otoferlin

Non-Human Primates are the Most Relevant Model for the Translation of Intracochlear Administration



- Rodents may be used for efficacy models, but have a patent cochlear aqueduct that will likely result in a different distribution of the vector compared to humans
- NHP cochlear aqueduct patency is similar to that in human (i.e., a closed system)
- Shape of NHP cochlea is similar to that of human
  - Macaque cochlea is 1/3rd the size of human
  - Equivalent intracochlear route of administration between NHPs and humans (delivery through the RWM with oval window venting)
- AAV tropism and transduction efficiency is expected to be similar between NHPs and humans
- NHPs are the relevant animal model to determine reasonable safety and biodistribution of gene therapy product candidates following intracochlear delivery

Nonclinical Activities are Important for Translating Inner Ear Genetic Medicines with the Potential to Support Broad Patient Access

1. AAV gene therapy is well suited for the inner ear

2. Product candidate design is a key consideration towards potentially effective gene therapies for inner ear conditions

3. The development of potential genetic medicines for inner ear conditions is challenging due to anatomical access; uniform distribution to relevant cochlear cells may be important for successful therapeutic activity

4. The selection of appropriate animal models enables a clinical development program with the potential to support broad patient access.
   - Rodent models representing human inner ear conditions can be important for determining biological activity and dose recommendations.
   - Studies in non-human primates are important for determining feasibility of intended ROA and reasonable safety following intracochlear delivery due to an anatomical similarity with humans