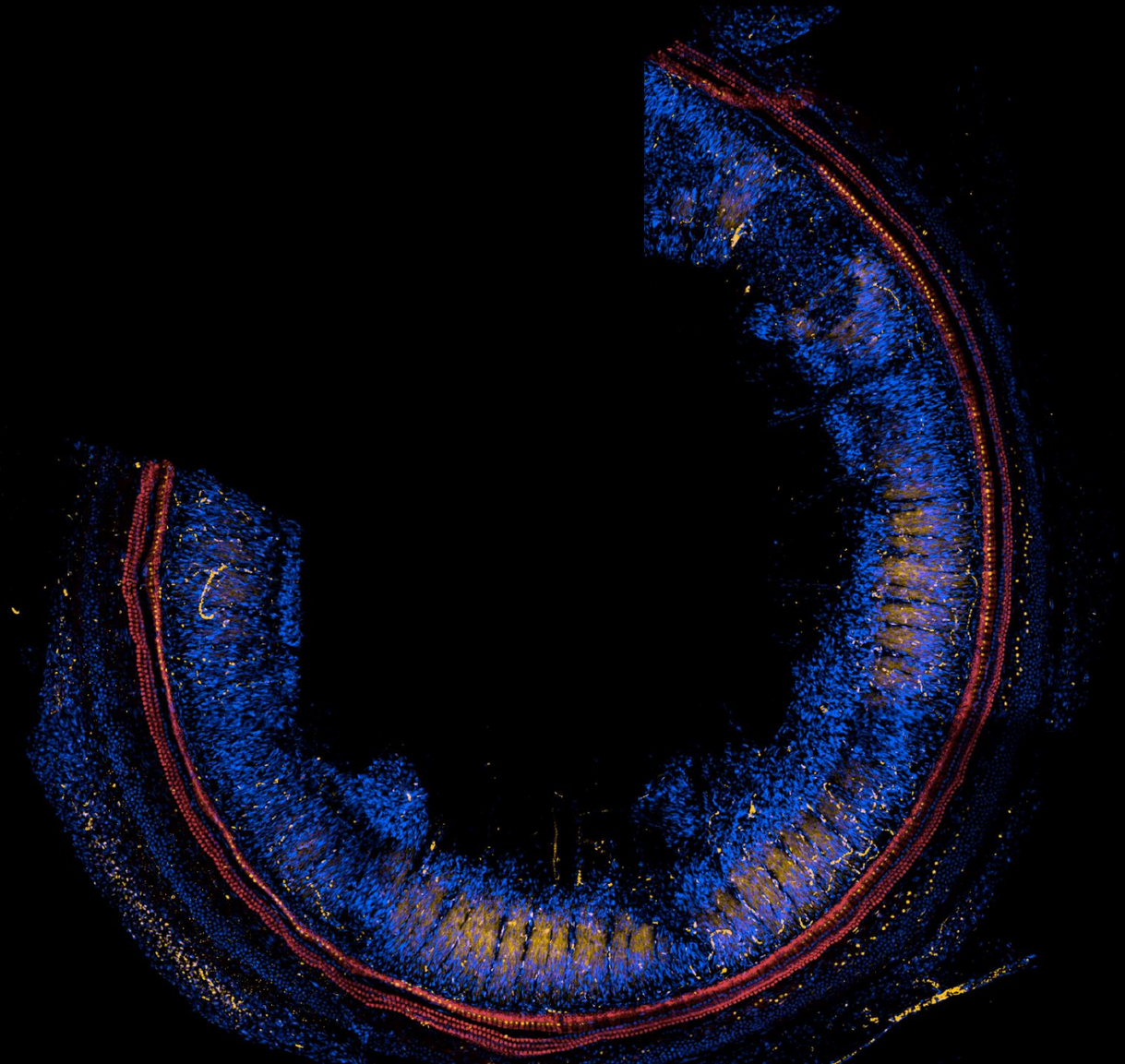
Sensorion

Sensorion Gene Therapy R&D Day

April 6, 2023

Institut de l'Audition
Institut Pasteur Center
Paris, France

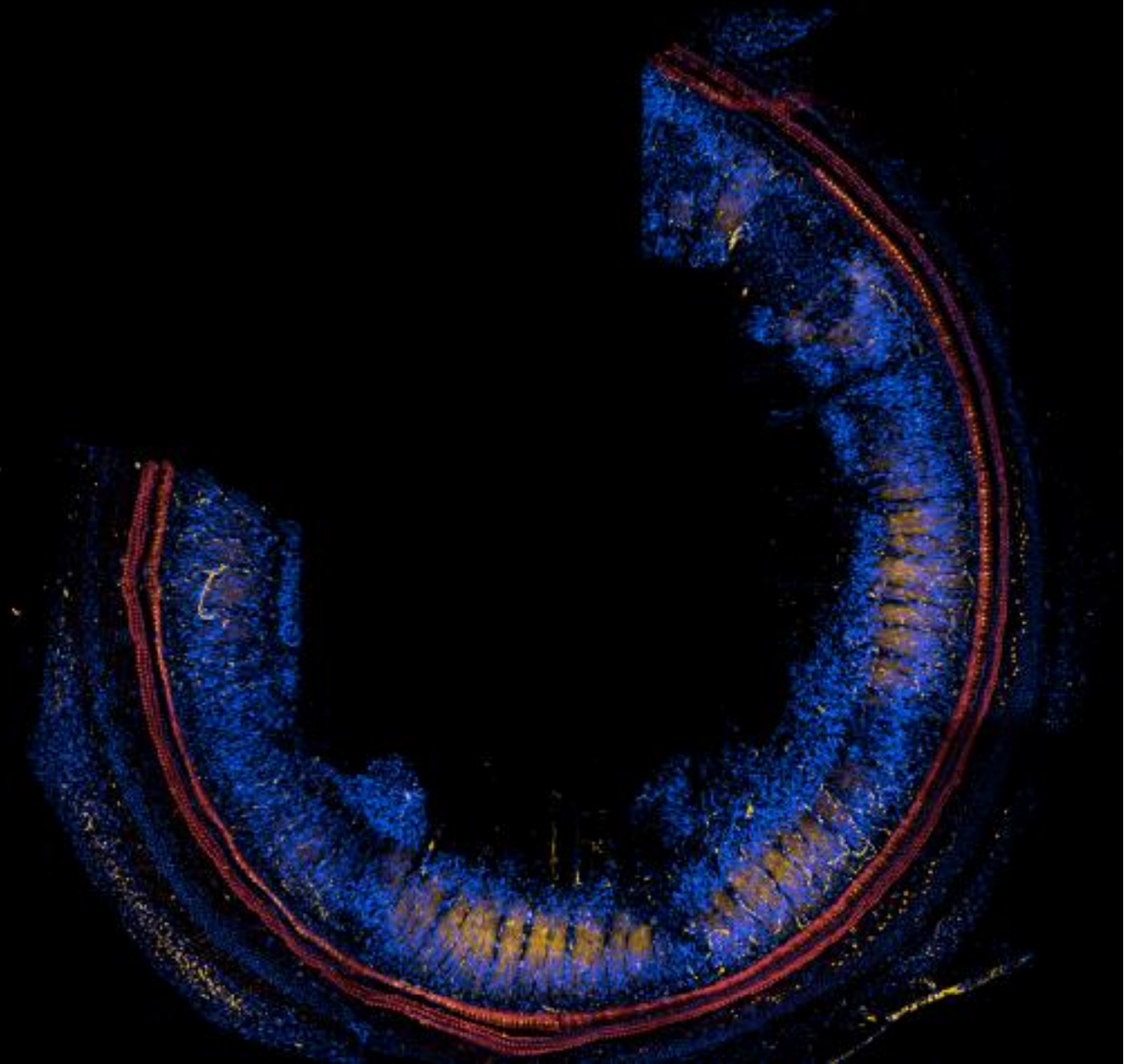


Sensorion

WELCOME AND INTRODUCTION

Nawal Ouzren
CEO, Sensorion

April 6, 2023



Agenda

Nawal Ouzren - Sensorion	Welcome and Introduction
Barbara Kelley - HLAA	Incorporating the Patient Voice for Tomorrow’s Care
Christine Petit - The Institut Pasteur	Deafness: from Genetic Architecture to Gene Therapy
Laurent Désiré - Sensorion	GJB2-GT Program: Data to Drive Next Steps
Géraldine Honnet - Sensorion	GJB2-GT Program: Natural History Studies to Prepare Execution of Clinical Trials

Agenda

Natalie Loundon - Necker Hospital

Laurent Désiré - Sensorion

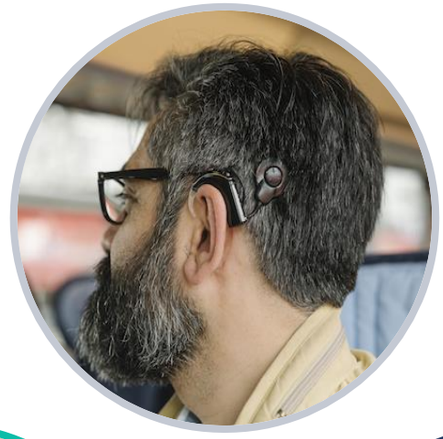
Christine Le Bec - Sensorion

Nawal Ouzren - Sensorion

- Otoferlin Defiency: Approaches Towards Hearing Restoration
- OTOF-GT Program: SENS-501 Sensorion’s Lead Gene Therapy Program
- Enabling Reliable Gene Therapy Manufacturing and Analytical Control
- Q&A Session and Closure

Transforming Lives, Connecting People

Our vision is to help people with inner ear hearing disorders to live life with unlimited connections





Hearing Loss is a Massive Global Health Issue

Hearing loss is the most frequently occurring congenital sensory deficit, the largest modifiable risk factor for dementia and has a significant impact as people live longer.[1-4]

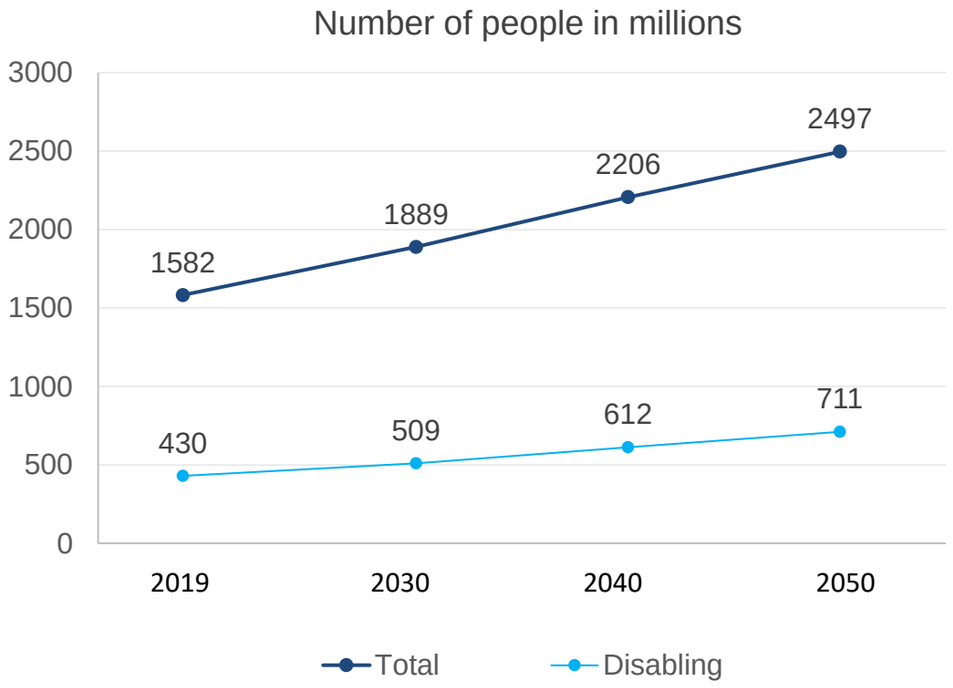
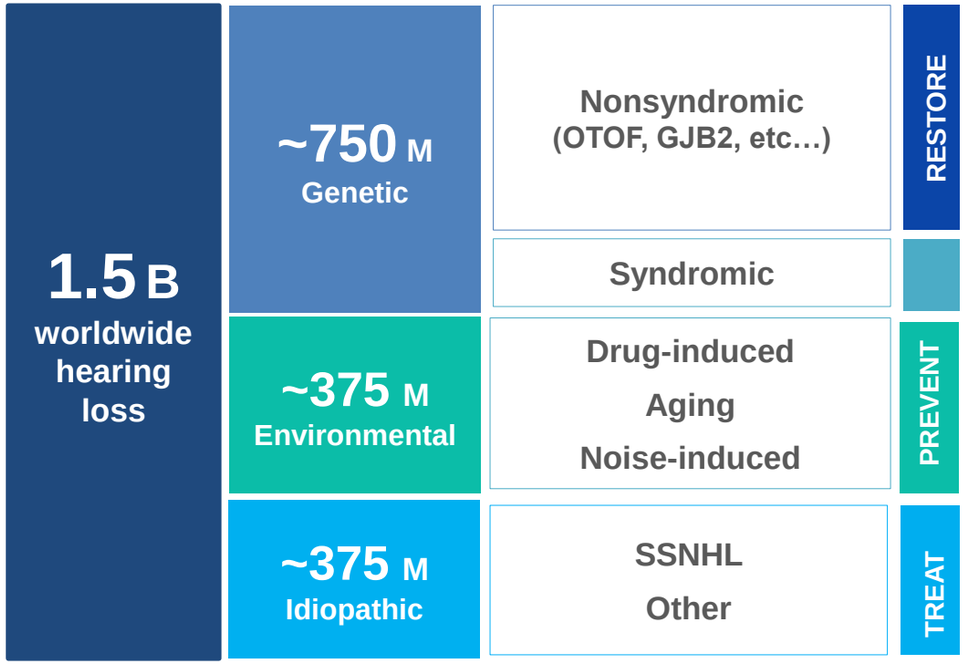


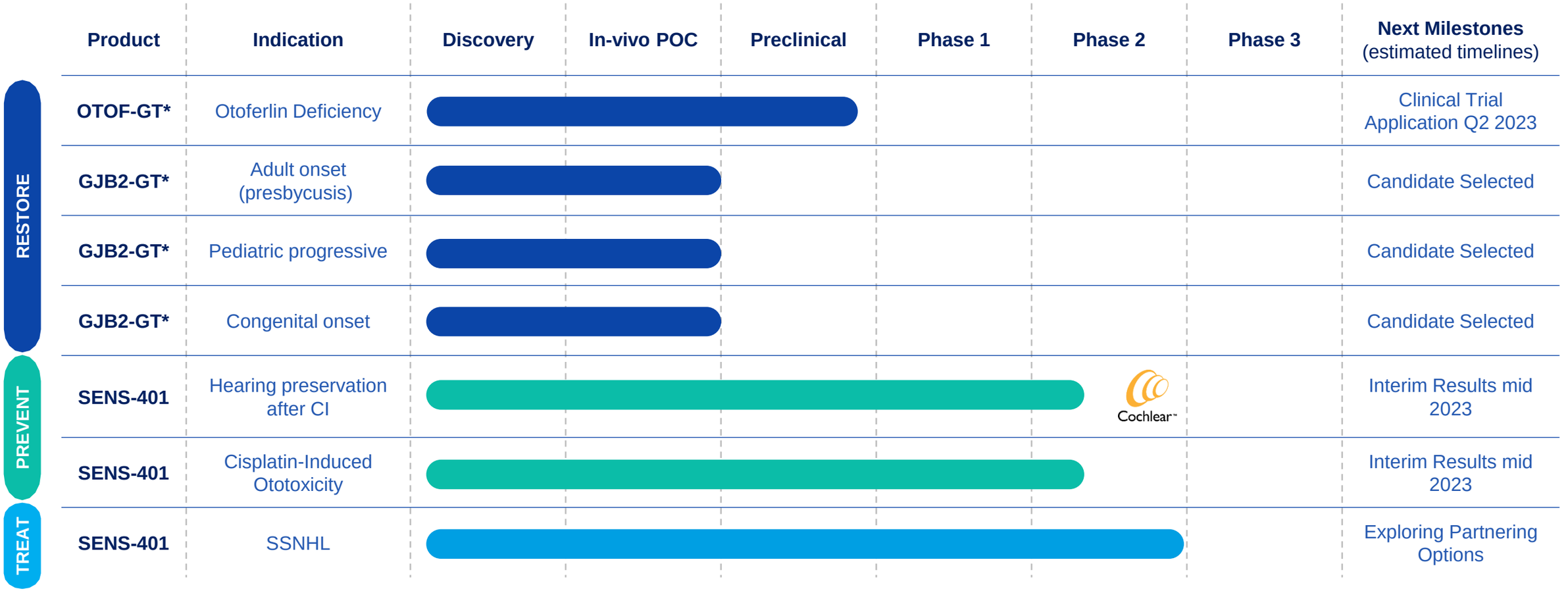
*Chart adapted from World Report on Hearing. Geneva: World Health Organization; 2021.



Sources: Petit C et al., 2001, Snoeckx RL et al., 2005, Iizuka 2015 Human Molecular Genetics, World report on hearing. Geneva: World Health Organization; 2021

1. Amieva H et al., 2018; 2. Loughrey DG et al., 2018: 3. Hilgert N et al., 2008 ; 4. Livingston G et al. 2017

Sensorion's Pipeline: A Comprehensive Franchise Of Advanced Hearing Loss Therapies

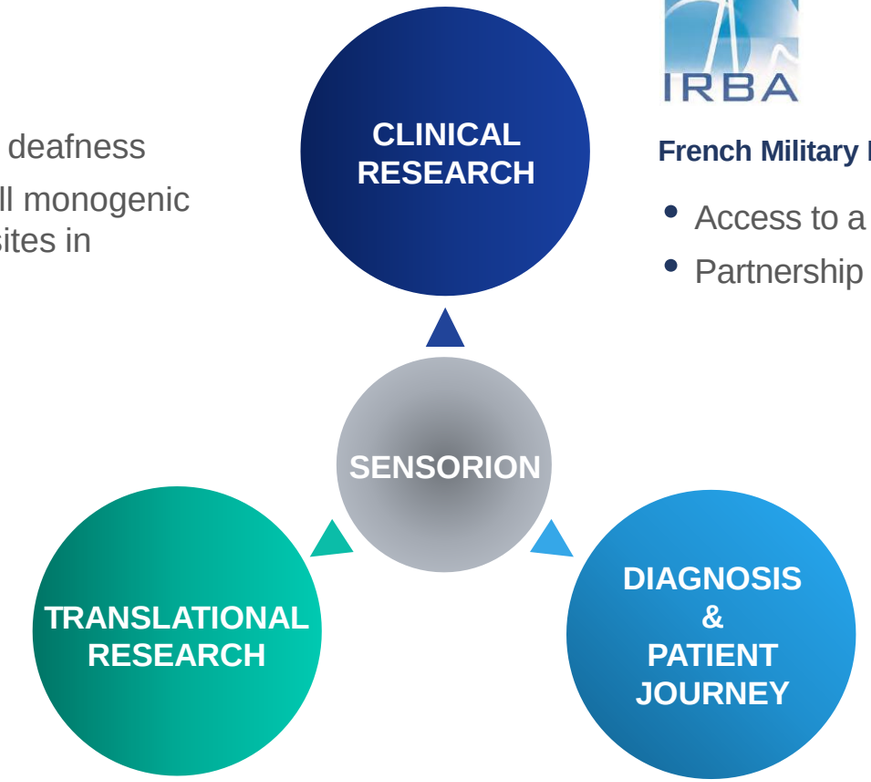


3SBio has a right of first refusal with respect to licensing in Greater China of SENS-401 (except in combination with cochlear implants) and OTOF-GT

**Option to obtain a licence from the Institut Pasteur (pre-defined financial terms and other terms to be negotiated)*

Our Strategic Partnerships Support the Franchise

- EU reference center for monogenic forms of deafness
- Natural History Study currently running for all monogenic forms of deafness; extension in EU clinical sites in preparation (OTOCONEX study)



French Military Biomedical Research Institute

- Access to a military population at risk of noise-induced hearing loss
- Partnership to identify biomarkers for noise-induced hearing loss

- Interdisciplinary approach to the mechanisms of hearing and its damage
- Research in deafness therapies and preclinical studies
- Exclusive option over programs developed at the Institut Pasteur

- Global leader in implantable hearing solutions
- Currently developing a drug/ device combination to maintain residual hearing after CI surgery

- Biggest hearing retail chains in the world
- A significant shareholder in Sensorion
- Collaboration to initiate Natural History in presbycusis

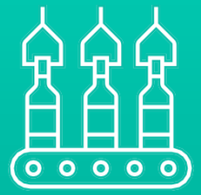
We Have Established Strong Internal Capabilities to Ensure Successful Execution

PRECLINICAL CAPABILITIES FOR SMALL MOLECULES & GT PROGRAMS

- **Cell Model Platform**: assays development, target & drug discovery, biomarkers
- **Animal Pharmacology platform**: from the POC to the dose-finding studies in disease-relevant rodent models, surgery
- **Technology & Innovation platform**: design and select the best drug candidate (capsid & promoter selection)

CLINICAL EXPERIENCE

- 400 people enrolled in Sensorion led clinical trials
- Set-up audio tests in different countries, languages
- Central reading of audiometry testing
- In-house audiology expertise of more than 20 years for the pediatric and adult populations and cochlear implants



CMC GENE THERAPY FACILITIES

- **Process development**: non-GMP manufacturing from small scale up to 50L in bioreactor
- **Analytical development**: development of product-specific analytical methods, in-house generic assays to support process development and AAV manufacturing

REGULATORY EXPERTISE

- Develop regulatory strategies to ensure expedited product development including gene therapy
- Regulatory Agency interaction (EU/US)
- Shape the treatment guidelines and standardize clinical endpoints

Our Team has Significant Experience in Gene Therapy Clinical Development

The team has been involved in 15+ programs from preclinical to BLA filing…

10	4	1
Preclinical	Clinical	BLA filing

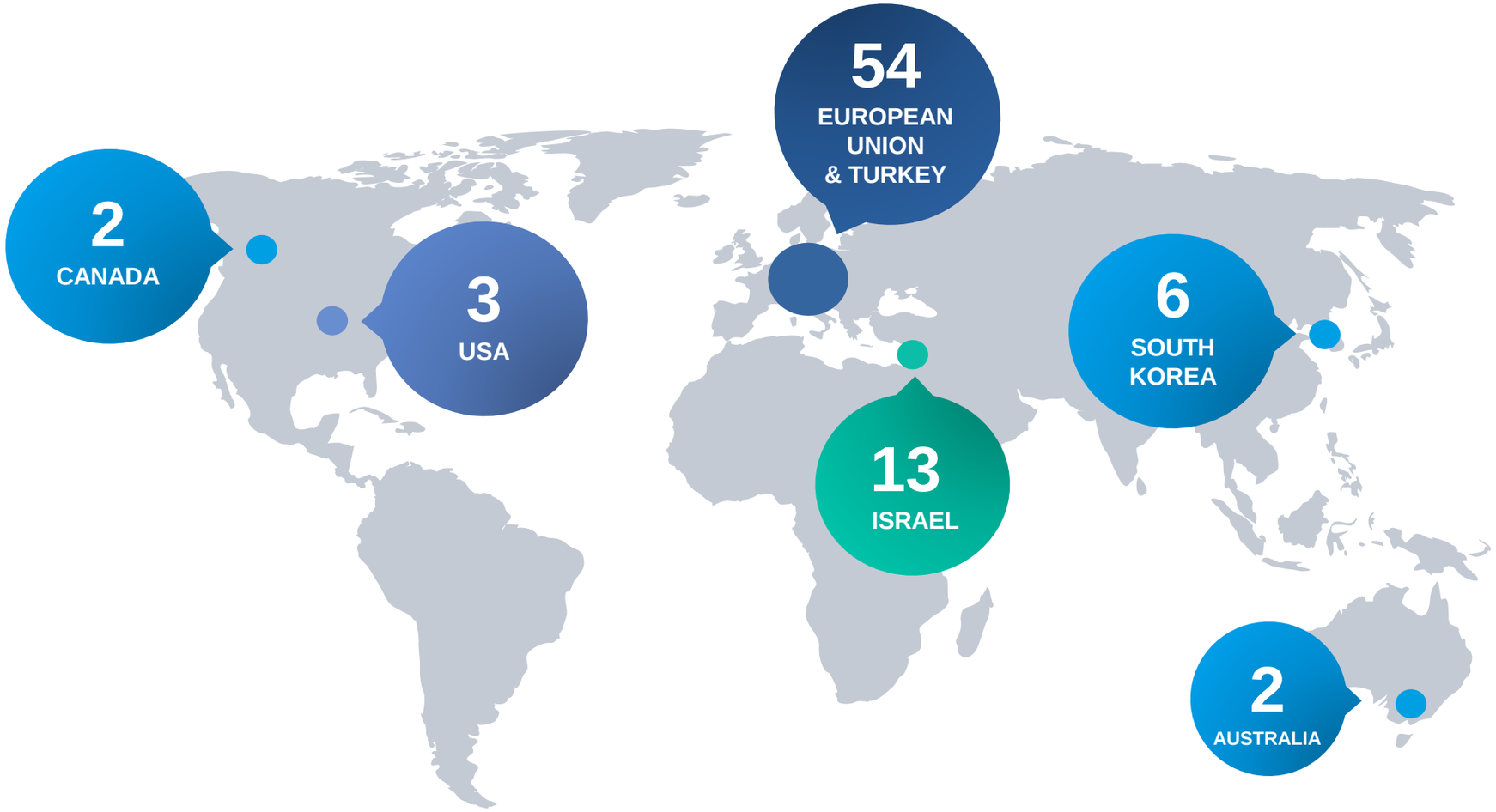
… using different technologies…

15	1	1
Gene therapy (AAVs / LVs)	Cell therapy	Gene editing

… across different organs and indications…

… with multiple organizations

We Have Established a Robust, Global Clinical Network



Our Vision: A Global Franchise Establishing Leadership in The Hearing Space

PORTFOLIO

ECOSYSTEM

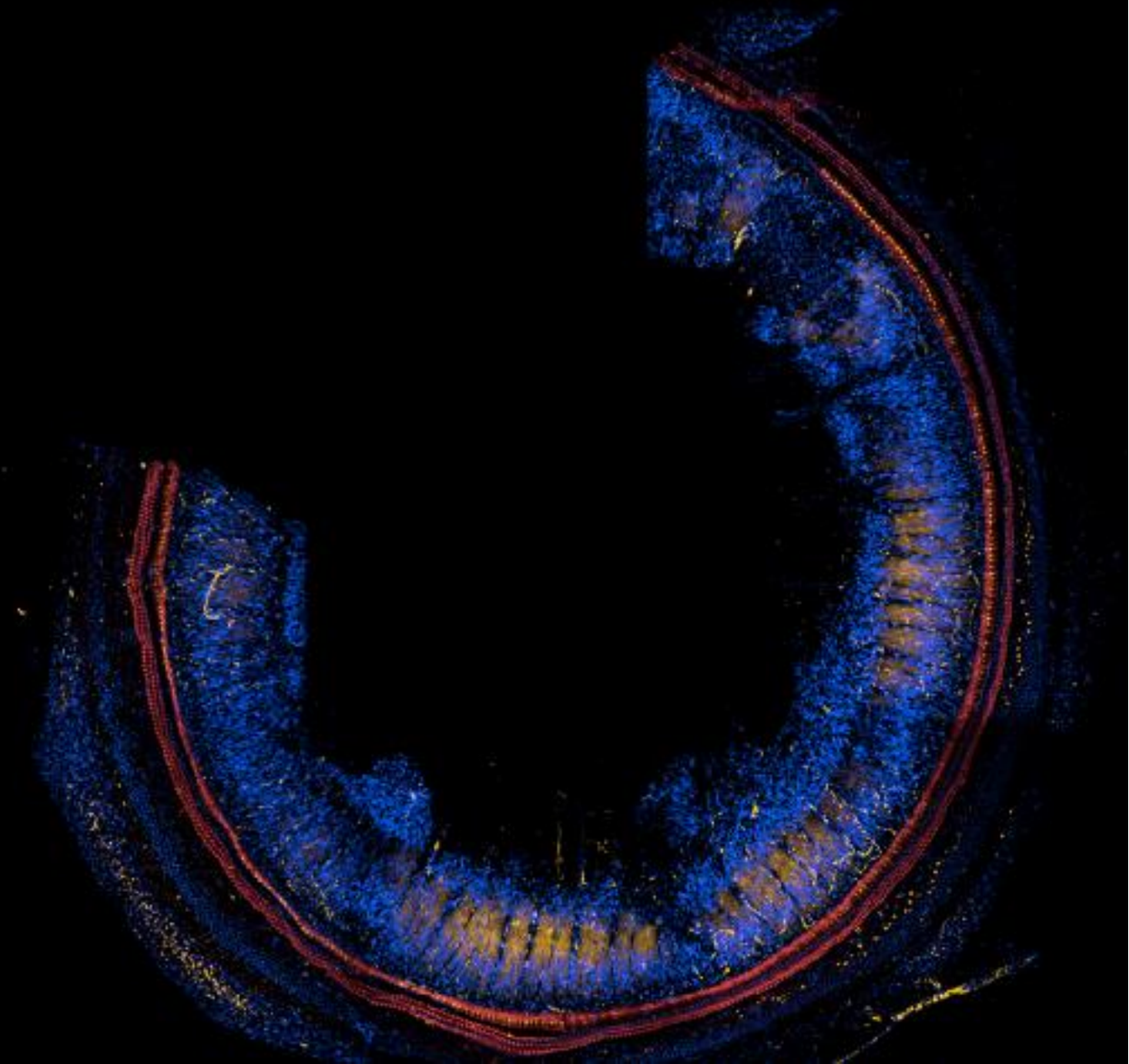
- Natural History Studies
- Key Opinion Leaders
- Centers of Excellence
- Patient Groups
- Partners
  - EU
  - US
  - ROW

Sensorion

INCORPORATING THE PATIENT VOICE FOR TOMORROW'S CARE

Barbara Kelley
Executive Director, HLAA

April 6, 2023



HLAA

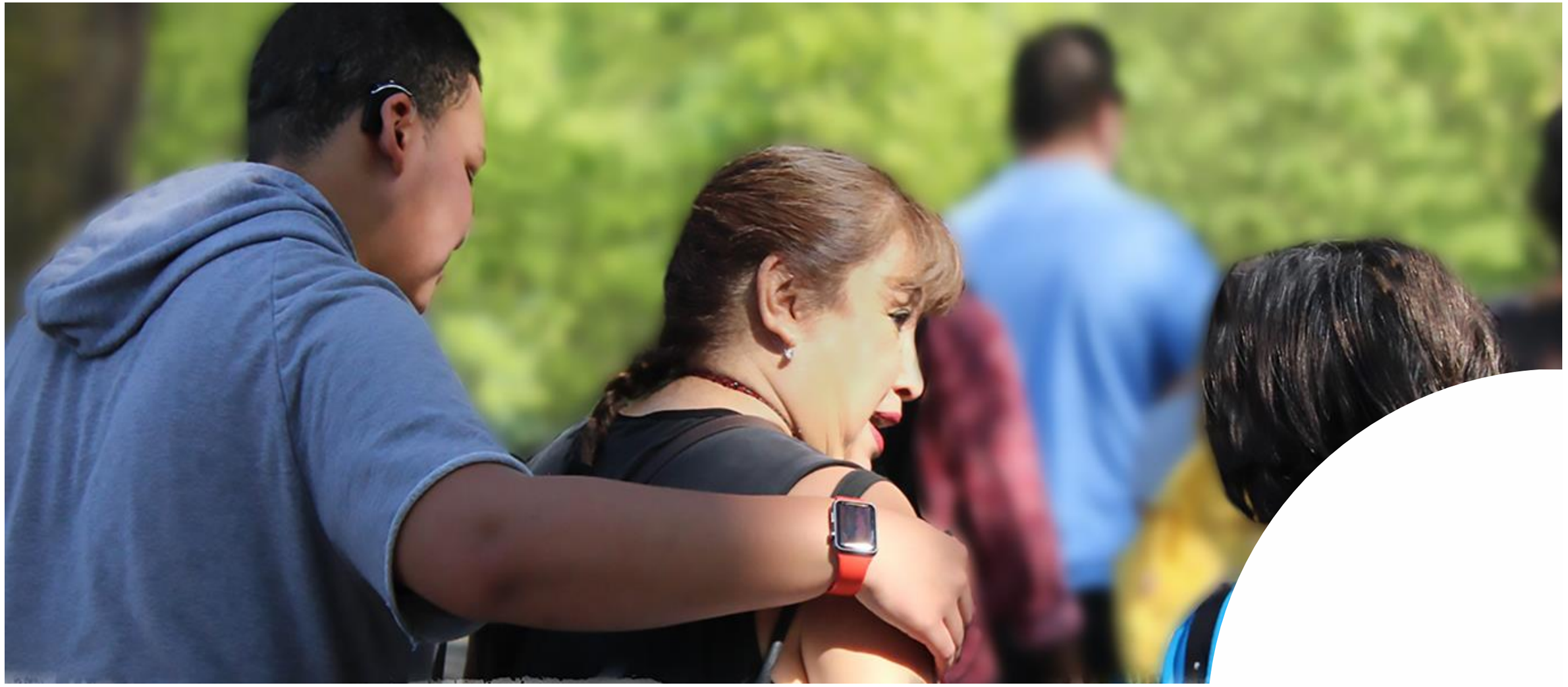
Hearing Loss Association of America

The mission of HLAA is to open the world of communication to people with hearing loss by providing information, education, support and advocacy.

hearingloss.org

Technology Users - Staying in the Hearing World

Because the Comfort of Community Is More Than Something You Hear



Sow Joy. Nurture Community

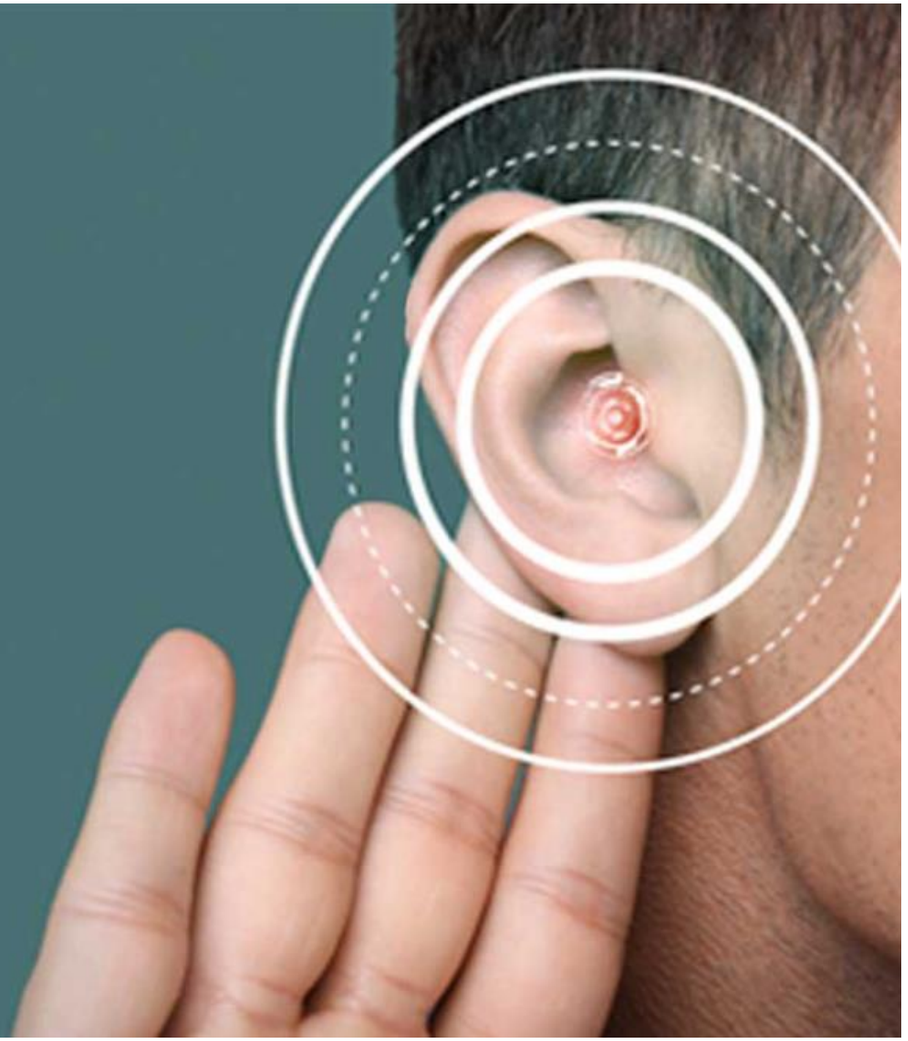
BELONGING
IT MAKES ALL
THE DIFFERENCE

FILM
Here we GO

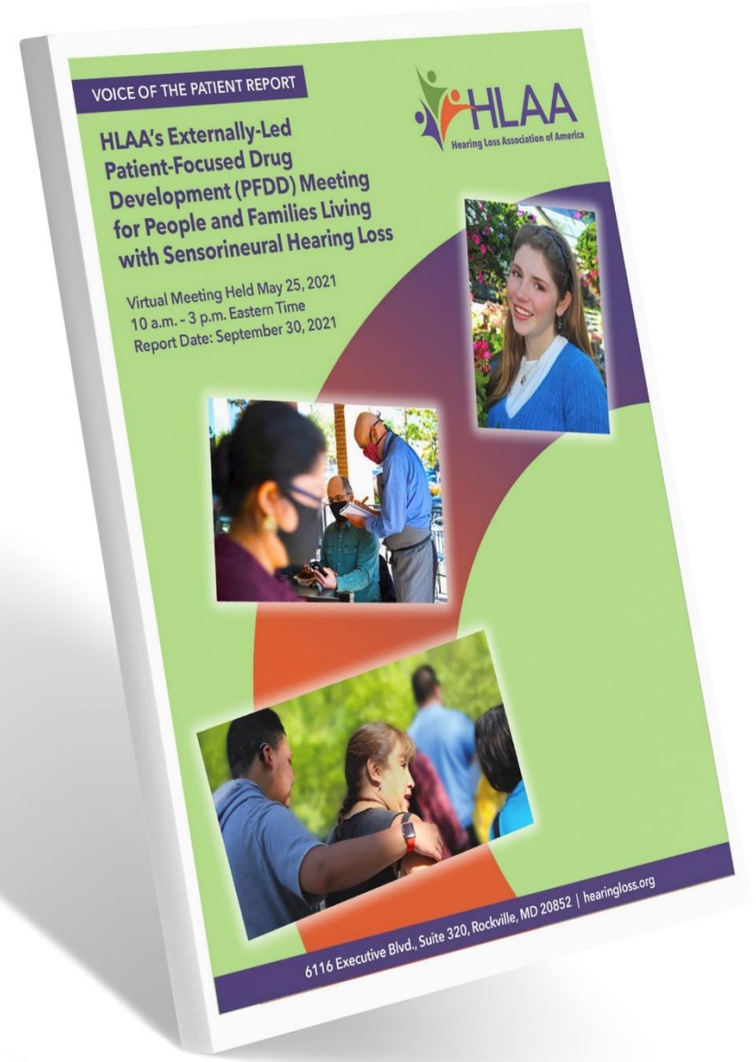
Increased Access to Influencing Change

With permission from the U.S. Food and Drug Administration
May 25, 2021

EXTERNALLY-LED PATIENT-FOCUSED DRUG DEVELOPMENT MEETING FOR PEOPLE AND FAMILIES LIVING WITH SENSORINEURAL HEARING LOSS



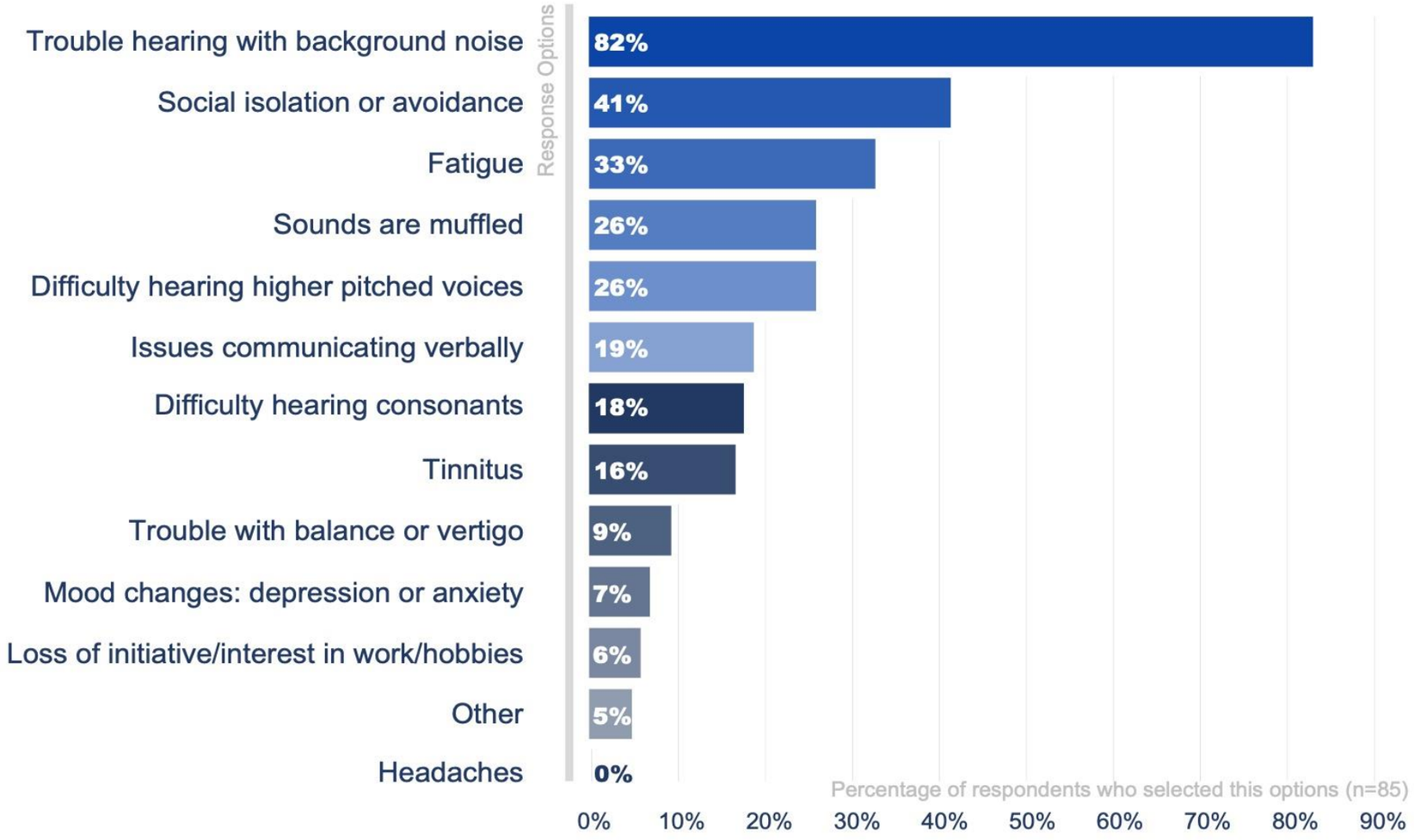
Qualitative Data - Hearingloss.org and Fda.gov



Voice of the Patient: Most Troublesome Hearing Loss Related Concerns

Topic 1, Q2.

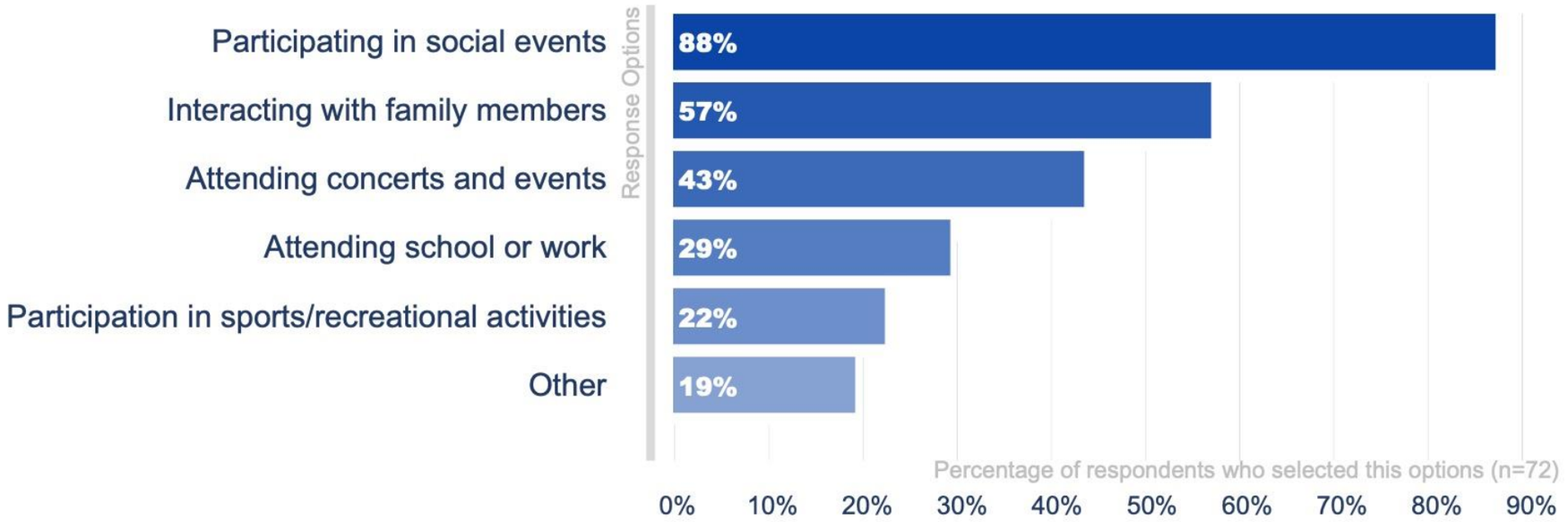
Select the TOP 3 most troublesome hearing loss-related health concerns that you have or have had



Voice of the Patient: Top Struggles of Daily Life Due To Hearing Loss

Topic 1, Q3.

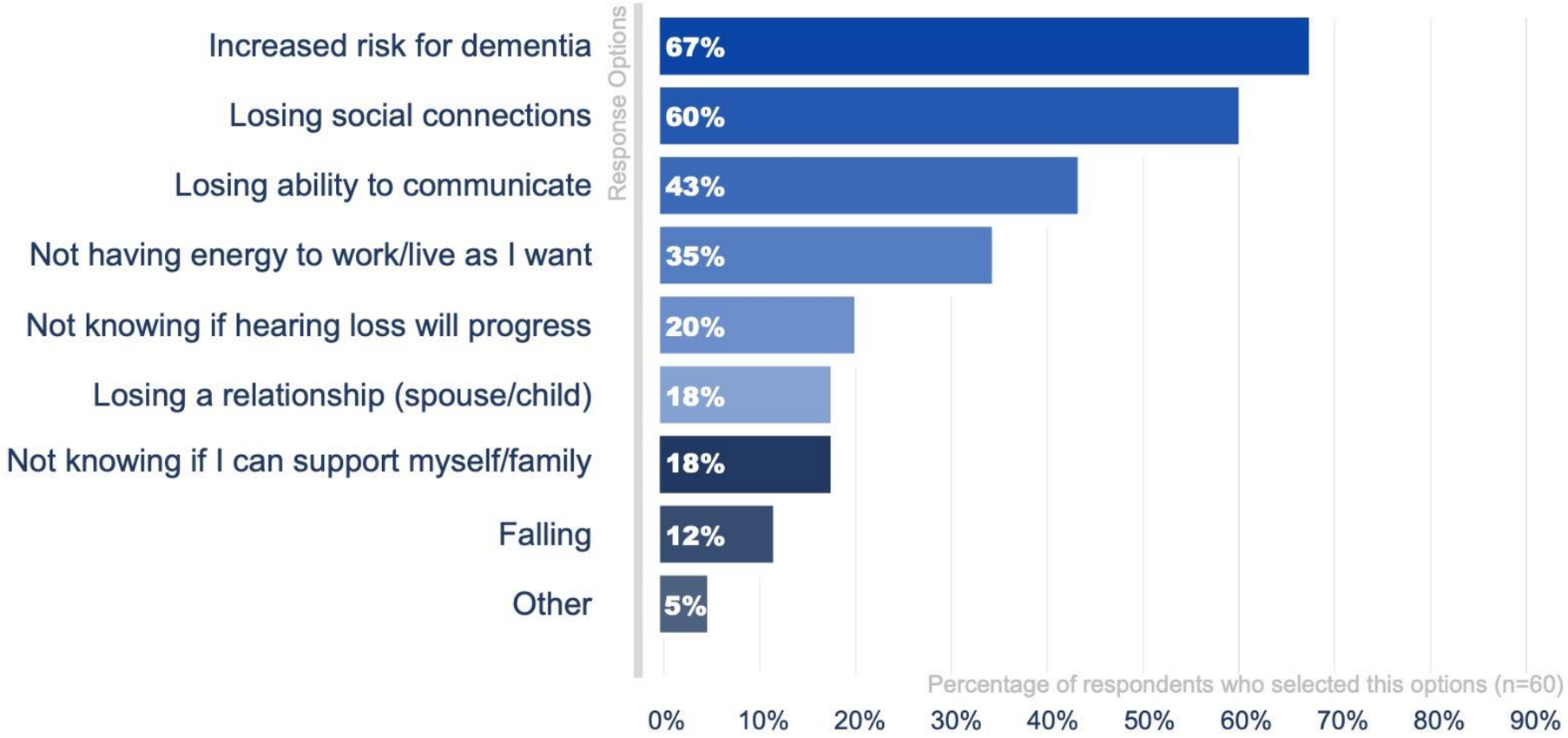
What specific activities of daily life are most important to you are NOT able to do or you struggle with due to hearing loss? Select TOP 3



Voice of the Patient: Worries About the Future

Topic 1, Q4.

What worries you most about you or your loved one's condition in the future? Select TOP 3



“I’m sorry” she said. You Could Have Heard a Pin Drop…

Conclusions

- People with hearing loss described many worries for the future
- Hearing loss profoundly impacts all activities of daily life
- Hearing loss leads to social exclusion and diminished quality of life
- Hearing loss is heavily stigmatized
- Many hide their hearing loss, are intentionally excluded and misperceived as less intelligent
- Many described feelings of denial or shame, which made them reluctant to seek treatment
- Hearing loss accommodation is not recognized as essential, and many environments are inaccessible including hospitals, airports, schools and workplaces

Prospects for the Future

- Hoping for hearing restoration, improved hearing, decreased background noise and slowing and stopping hearing loss
- Are hopeful for new options to restore or improve their hearing and many express a wish to participate in clinical trials

Today. Tomorrow. Together

CREATING A FUTURE OF PROMISE

THANK YOU

Barbara Kelley
Executive Director
bkelley@hearingloss.org

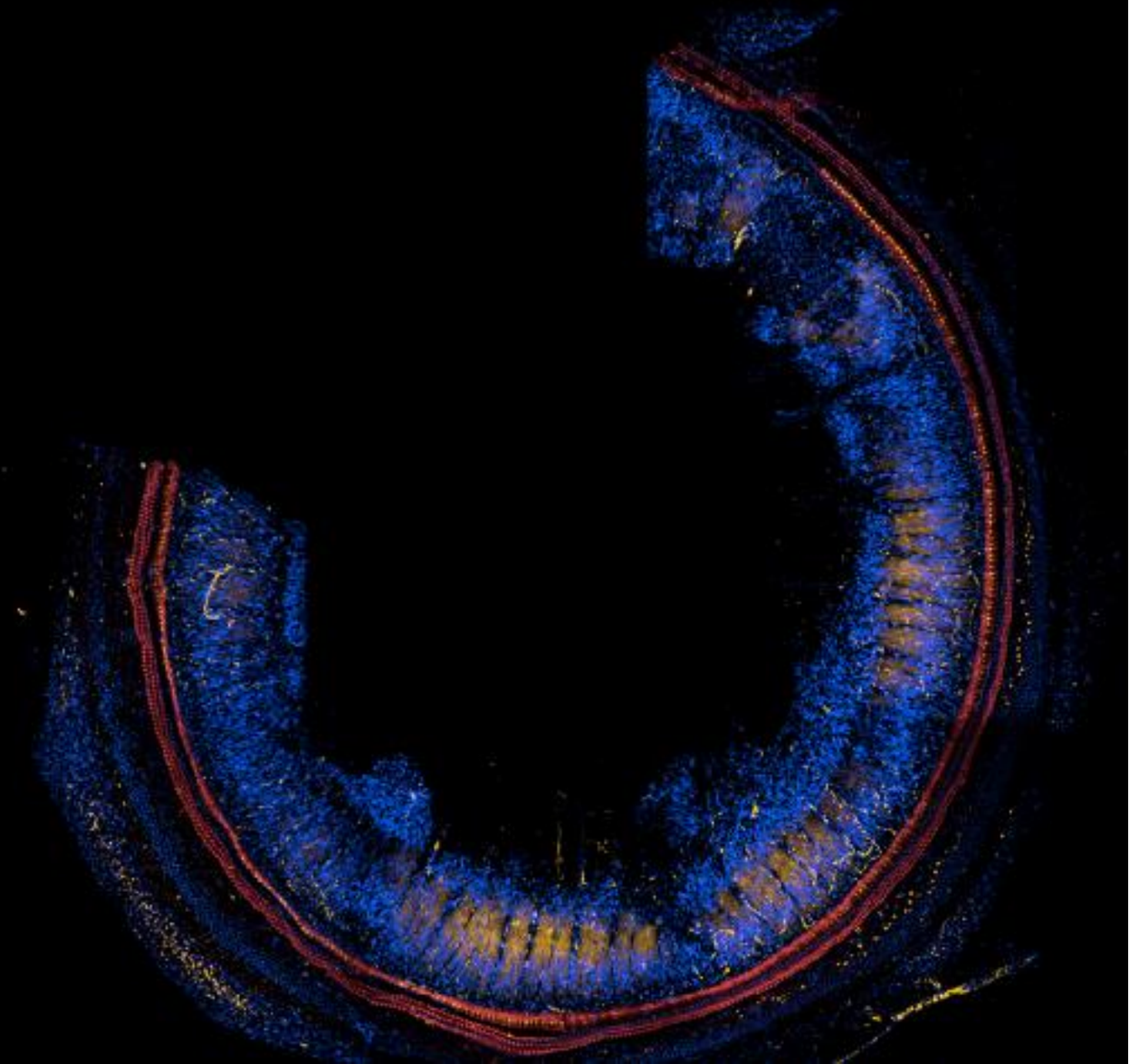
Hearing Loss Association of America
hearingloss.org

Sensorion

DEAFNESS:
FROM GENETIC ARCHITECTURE TO GENE THERAPY

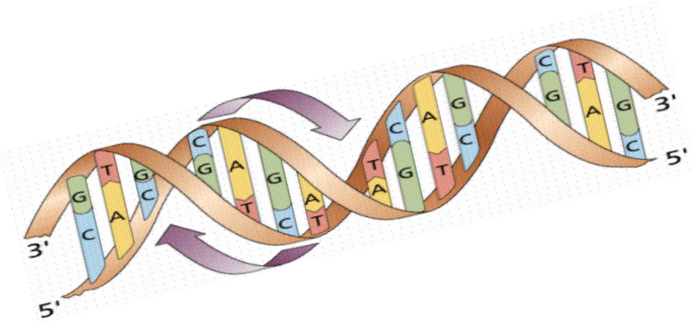
Pr. Christine Petit
Director of the Laboratory for
Innovation in hearing therapies
The Institut Pasteur, Hearing Institute

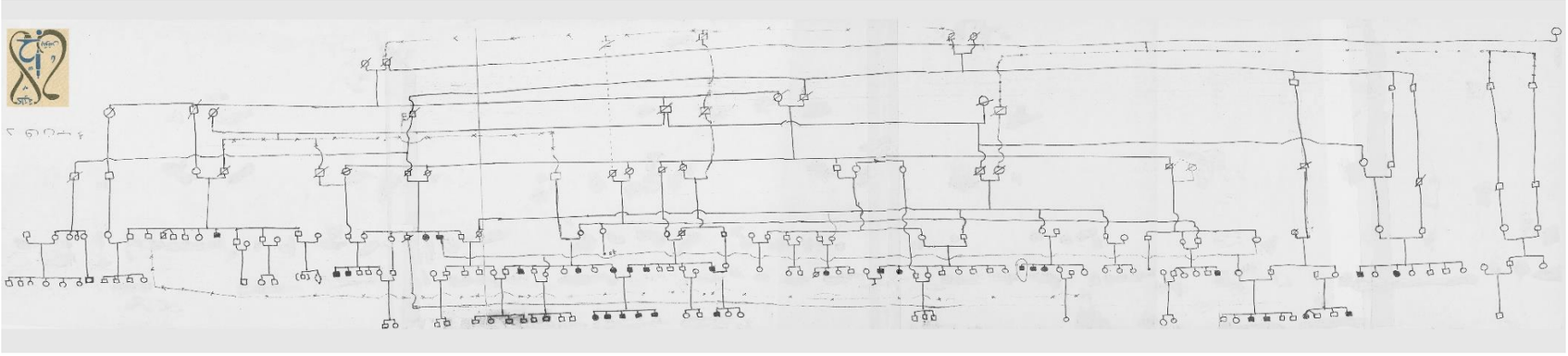
April 6, 2023



Hearing Institute

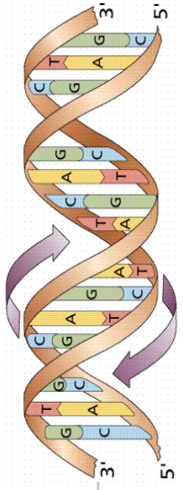
Causal Gene for Deafness





Genetic Architecture of Sensorineural Deafness

Casual genes for monogenic forms of deafness (early & late onset) **and predisposing genes to age-related hearing loss, noise induces hearing loss…**



CAUSAL GENES:

- ~ **130 causal genes for monogenic isolated forms of deafness** (congenital/prelingual/ pre-adulthood –onset forms); a few causal genes responsible for monogenic forms of noise-induced-induced hearing loss.
- **77 genes are responsible for autosomal recessive forms** (DFNB forms), 52 are responsible for dominant forms (DFNA forms) and 11 of them are responsible for both DFNA and DFNB forms.

Most cases of severe-to-profound early-onset-deafness, are hereditary in western countries.

- ~ **300 causal genes for monogenic syndromic forms of deafness,** in which other symptoms are associated with hearing impairment of various degrees of severity.

CANDIDATE SUSCEPTIBILITY GENES (GENETIC RISK FACTORS):

- ~ **120 candidate genes conferring a predisposition to age-related forms of deafness or noise-induced hearing loss**

A Genetic Continuum from Early Onset Deafness to Some Forms of Age-Related Hearing Loss (Presbycusis)

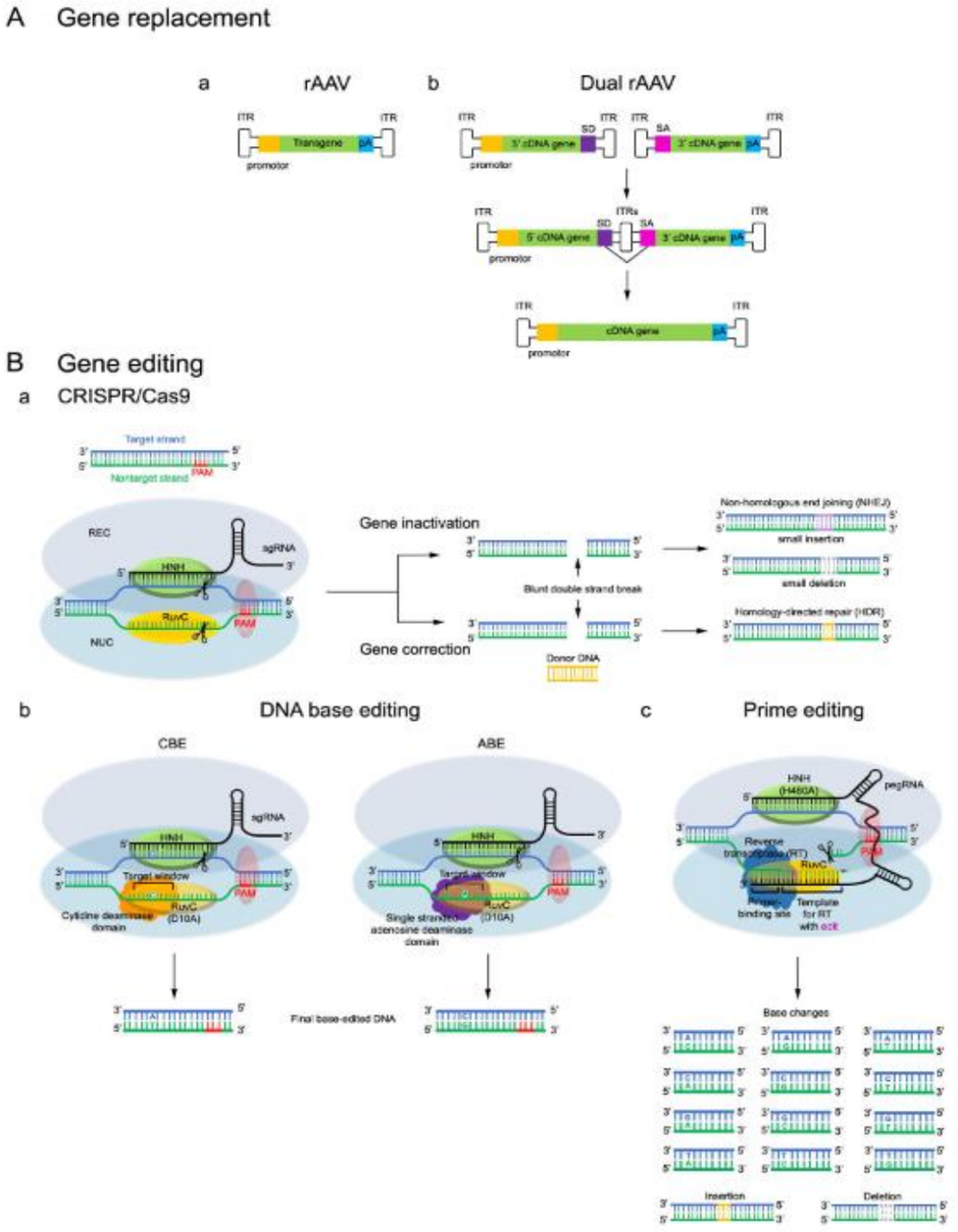
Prelingual deafness DFNB forms

Young adult onset deafness DFNA forms

Monogenic forms of presbycusis

Five Major Groups of Cochlear Functions Each Defective in Several Deafness Forms

Gene symbol	Protein name	Deafness form	OMIM identifier
	AUDITORY MECHANOELECTRICAL TRANSDUCTION MACHINERY		
CDHR15	Cadherin-related 15	DFNB23 USH1F	605514
CDHR23	Cadherin-related 23	DFNB12 USH1D	602092
CIB2	Calcium and integrin-binding family member 2	DFNB48	605564
CLRN1#	Clarin-1	USH3A	606397
CLRN2	Clarin-2	DFNB117	619174
LHFPL5	LHFPL tetraspan subfamily member 5 protein	DFNB66/67	609427
LRTOMT	Transmembrane O-methyltransferase	DFNB63	612414
*MYO7A**	Unconventional myosin-VIIa	DFNB2/DFNA11 USH1B	276903
TMC1	Transmembrane channel-like protein 1	DFNB7/11/DFNA36	606706
TMIE	Transmembrane inner ear expressed protein	DFNB6	607237
USH1C	Harmonin	DFNB18 USH1C	605242
USH1G#	Scaffold protein containing ankyrin repeats and SAM domain	USH1G	607696
	TRANSCRIPTIONAL REGULATION AND POST-TRANSCRIPTIONAL MODIFICATIONS		
BDP1	Transcription factor TFIIIB component B double prime 1 homolog	DFNB112	607012
ESRP1	Epithelial splicing regulatory protein 1	DFNB109	612959
ESRRB	Steroid hormone receptor ERR2	DFNB35	602167
EYA4	Eyes absent homolog 4	DFNA10	603550
GRHL2	Grainyhead-like protein 2 homolog	DFNA28	608576
LMX1A	LIM homeobox transcription factor 1-alpha	DFNA7	600298
MIR96	miRNA96	DFNA50	611606
POU3F4	POU domain, class 3, transcription factor 4	DFNX2	300039
POU4F3	POU domain, class 4, transcription factor 3	DFNA15	602460
REST	RE1-silencing transcription factor	DFNA27	600571
SIX1	Homeobox protein SIX1	DFNA23	601205
TRRAP	Transformation/transcription domain-associated protein	DFNA75	603015
WBP2	WW domain-binding protein 2	DFNB107	606962
	ACTIN CYTOSKELETON DYNAMICS AND ASSOCIATED PROTEINS		
ACTG1	Actin, cytoplasmic 2	DFNA20/26	102560
DIAPH1	Protein diaphanous homolog 1	DFNA1	602121
DIAPH3	Protein diaphanous homolog 3	AUNA1	609129
ELMOD3	ELMO domain-containing protein 3	DFNB88	615427
EPS8	Epidermal growth factor receptor kinase substrate 8	DFNB102	600206
EPS8L2	Epidermal growth factor receptor kinase substrate 8-like protein 2	DFNB106	614988
ESPN	Espin	DFNB36	606351
*HOMER2**	Homer protein homolog 2	DFNA68	604799
MYH9	Myosin-9	DFNA17	160775
MYH14	Myosin-14	DFNA4A	608568
MYO3A	Myosin-IIIa	DFNB30/DFNAi	606808
MYO6	Unconventional myosin-VI	DFNB37/DFNA22	600970
*MYO7A**	Unconventional myosin-VIIa	DFNB2/DFNA11 USH1B	276903
MYO15A	Unconventional myosin-XVa	DFNB3	602666
PLS1	Plastin-1 fimbrin	DFNA76	602734
RDX	Radixin	DFNB24	179410
RIPOR2	Rho family-interacting cell polarization regulator 2	DFNB104/DFNA21	611410
TPRN	Taperin	DFNB79	613354
TRIOBP	TRIO and F-actin-binding protein	DFNB28	609761
WHRN	Whirlin	DFNB31 USH2D	607928
	COCHLEAR ION HOMEOSTASIS		
ATP2B2	Plasma membrane calcium-transporting ATPase 2	DFNA82	108733
BSND	Barttin	DFNB73	606412
CLIC5	Chloride intracellular channel protein 5	DFNB103	607293
GJB2	Gap junction beta-2 protein	DFNB1A/DFNA3A	121011
GJB3	Gap junction beta-3 protein	DFNA2B	603324
HGF	Hepatocyte growth factor	DFNB39	142409
*HOMER2**	Homer protein homolog 2	DFNA68	604799
KCNQ4	Potassium voltage-gated channel subfamily KQT member 4	DFNA2A	603357
MET	Hepatocyte growth factor receptor	DFNB97	164860
P2RX2	P2X purinoceptor 2	DFNA41	600844
SLC12A2	Solute carrier family 12 member 2	DFNA78	600840
SLC22A4	Solute carrier family 22 member 4	DFNB60	604190
SLC26A4	Pendrin	DFNB4	605646
SLC26A5	Prestin	DFNB61	613865
TMPRSS3	Transmembrane protease serine 3	DFNB8/10	605511
	COCHLEAR ENERGY AND REDOX HOMEOSTASIS, INFLAMMATION AND IMMUNITY		
AIFM1	Apoptosis-inducing factor 1, mitochondrial	DFNX5	300169
CLPP	ATP-dependent Clp protease proteolytic subunit, mitochondrial	DFNB81	601119
DIABLO	Diablo homolog, mitochondrial	DFNA64	605219
GRXCR1	Glutaredoxin domain-containing cysteine-rich protein 1	DFNB25	613283
GRXCR2	Glutaredoxin domain-containing cysteine-rich protein 2	DFNB101	615762
GSDME	Gasdermin-E	DFNA5	608798
IFNLR1	Interferon lambda receptor 1	DFNA2C	607404
KARS1	Lysine--tRNA ligase	DFNB89	613916
MSRB3	Methionine-R-sulfoxide reductase B3	DFNB74	613719
MTRNR1	Mitochondrially encoded 12S RNA	-	561000
MTTS1	Mitochondrially encoded tRNA serine 1	-	590080
NARS2	Probable asparagine--tRNA ligase, mitochondrial	DFNB94	612803
NLRP3	NACHT, LRR and PYD domains-containing protein 3	DFNA34	606416
OSBPL2	Oxysterol-binding protein-related protein 2	DFNA67	606731
PJVK	Pejvakin	DFNB59	610219
PNPT1	Polyribonucleotide nucleotidyltransferase 1, mitochondrial	DFNB70	610316



Petit, C et al., Nature genetics reviews, *in press*

Gene Therapy Approaches of Sensorineural Deafness

46 POCs;
41 POCs with positive effects
21 deafness genes

DFNB forms: Cabp2, Gjb2, Kcne1, Kcnq1, Lhfpl5(Tmhs), Msrb3, Otof, Pcdh15, Pjvk, Slc26aA4, Slc26aA5, Strc, Syne4, Tmc1, Ush1c, Ush1g, Ush3a, Whrn and DFNA forms: Kcnq4, Myo6, Slc17a8(Vglut3)

Gene replacement

31 POCs (18 genes)
30/31: mouse models for congenital profound DFNB forms of deafness
1/31: a mouse model for a post-natal progressive DFNA form of deafness

Gene augmentation

3 POCs (2 genes)
3/3: mouse models for congenital severe/profound DFNB forms of deafness

CRISPR/Cas9

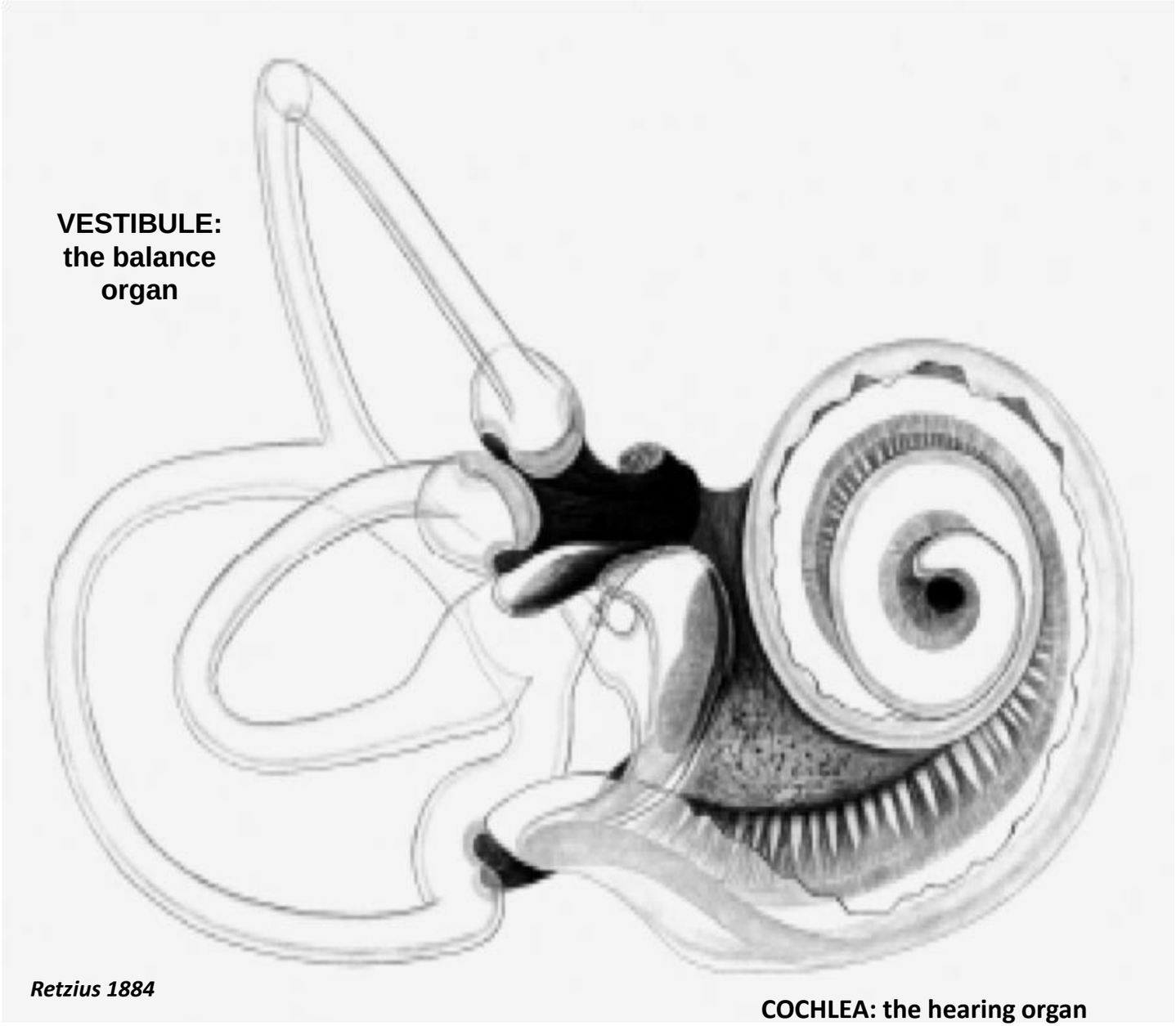
6 POCs (4 genes)
5/6: mouse models for post- natal progressive DFNA forms of deafness
1/6 a mouse model for congenital profound DFNB forms of deafness

Base editing (CBE)

1 POC a mouse model for congenital profound DFNB forms of deafness

Petit, C et al., Nature genetics reviews, *in press*

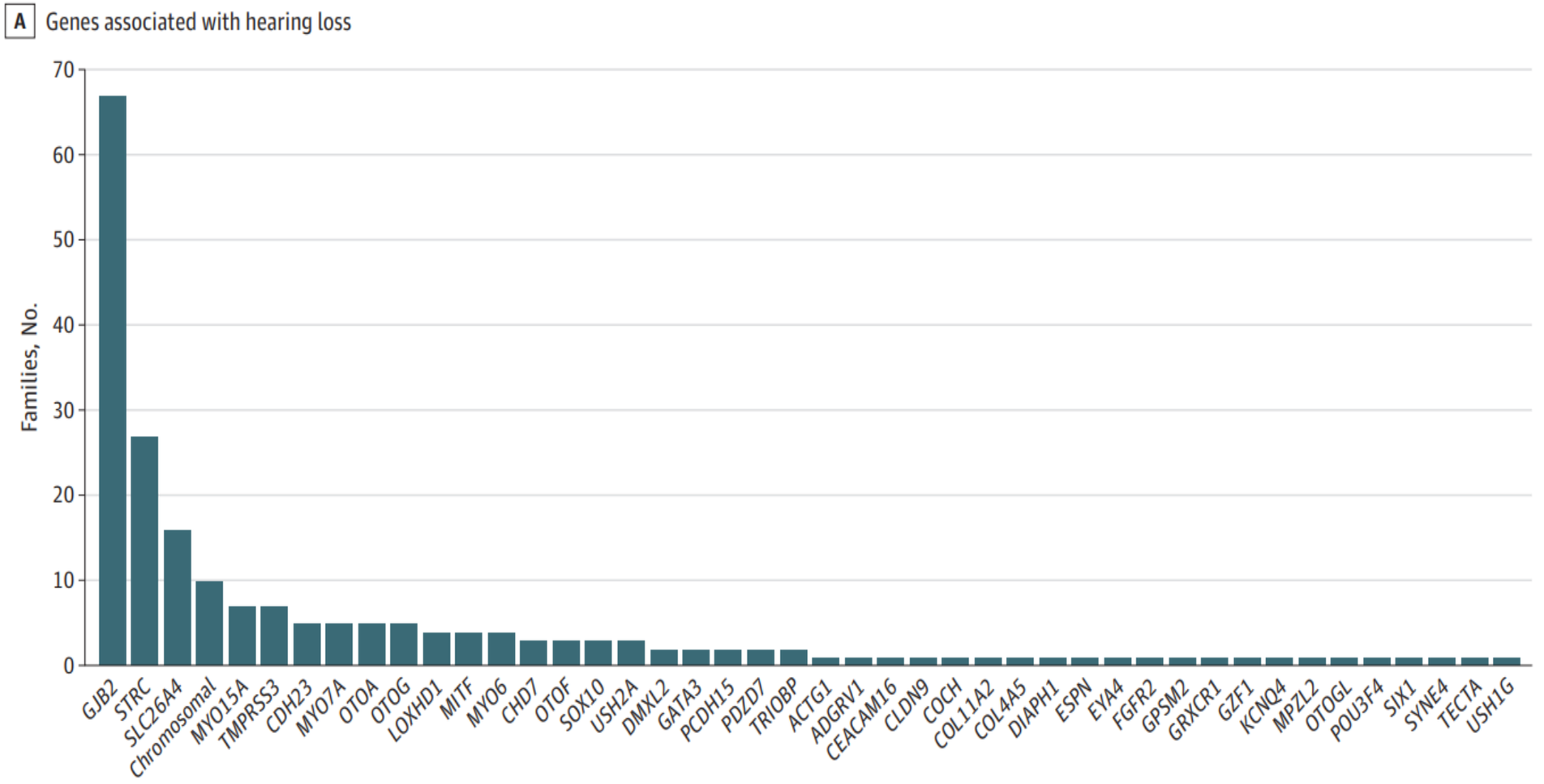
VESTIBULE: the balance organ



Retzius 1884

COCHLEA: the hearing organ

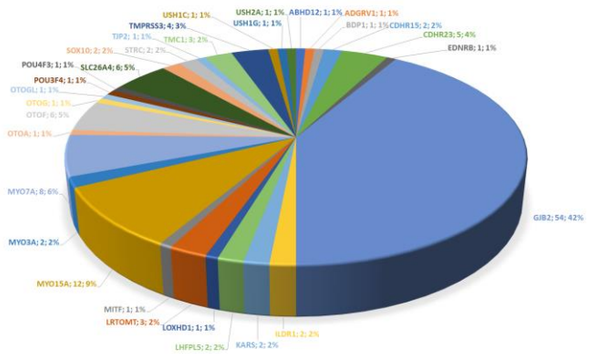
Figure 1. Genetic Diagnoses For Participants, With Variants in 43 Genes



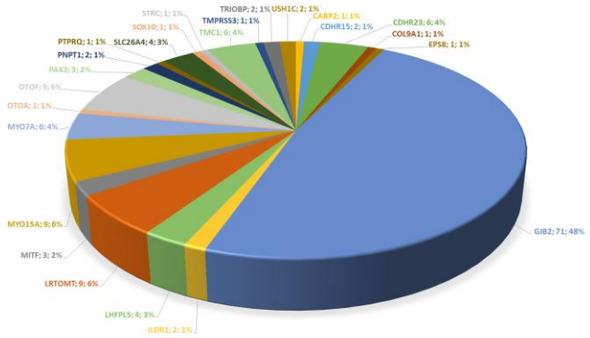
Carson et al., 2023, JAMA Otolaryngol Head Neck Surg

GJB2: The Most Frequent Causal Deafness Gene in North Africa

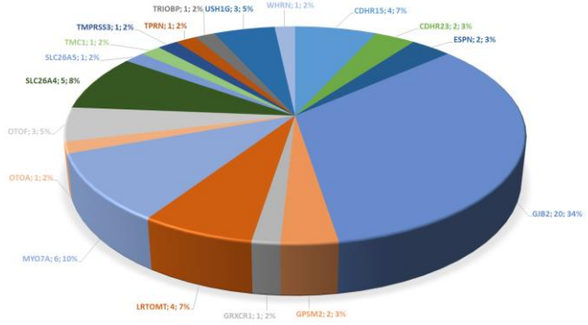
TUNISIA



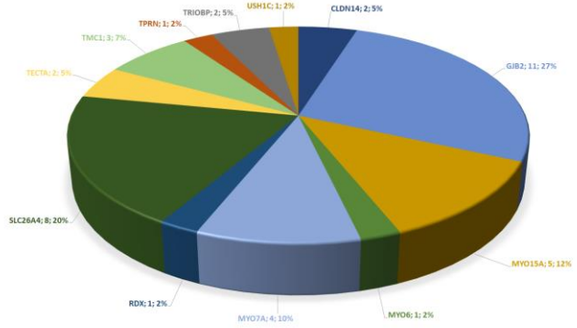
ALGERIA



MOROCCO

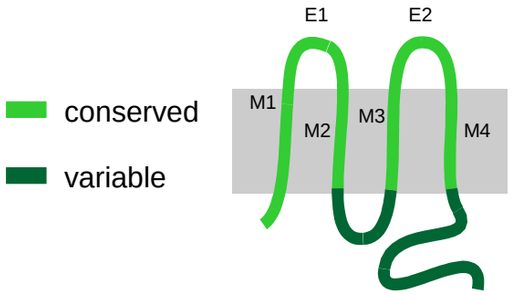


JORDAN

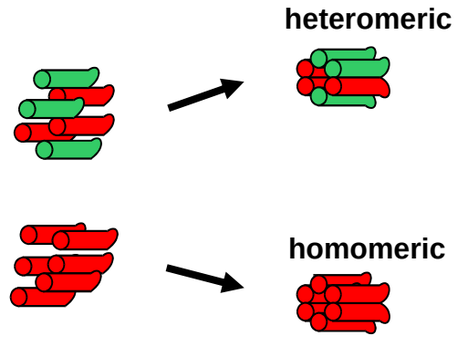


From Connexins to Connexons and Gap Junction Channels

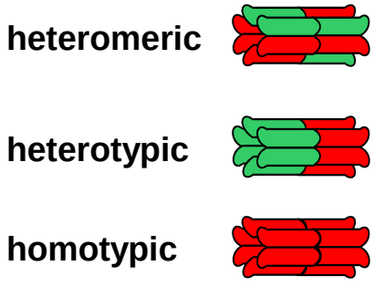
- 428 pathogenic or likely pathogenic *GJB2* variants have been reported.
- 90% of these variants are associated with early onset DFNB1 forms, in which biallelic variants are present.
- In addition, in late-onset forms of deafness, especially in some cases of age-related hearing loss, biallelic, pathogenic *GJB2* variants are also the causal variants.



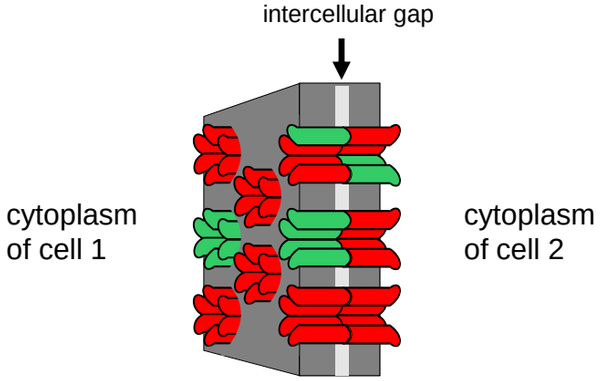
Topology of a generic connexin



connexins connexon



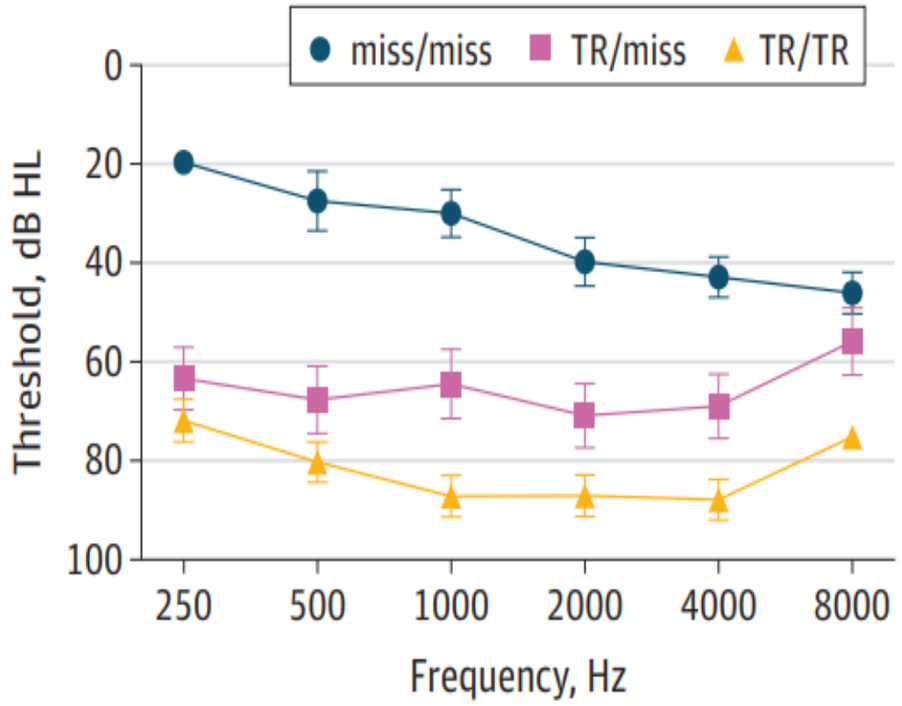
Intercellular channels



Gap junction

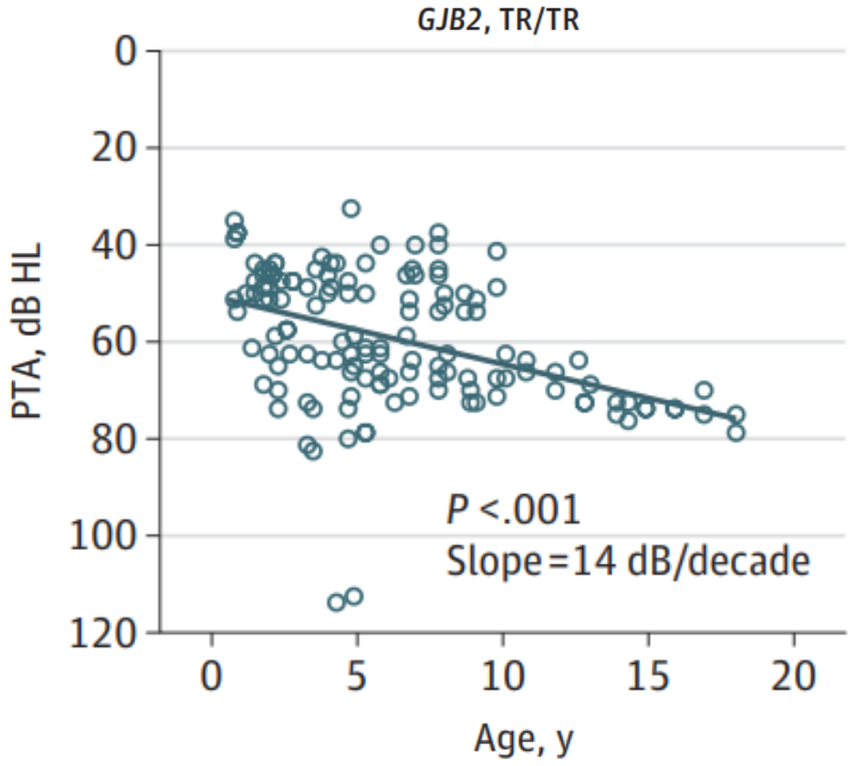
Variations in Audiogram Thresholds by Genotype and Progressivity of Hearing Loss

GJB2-ASSOCIATED HEARING LOSS



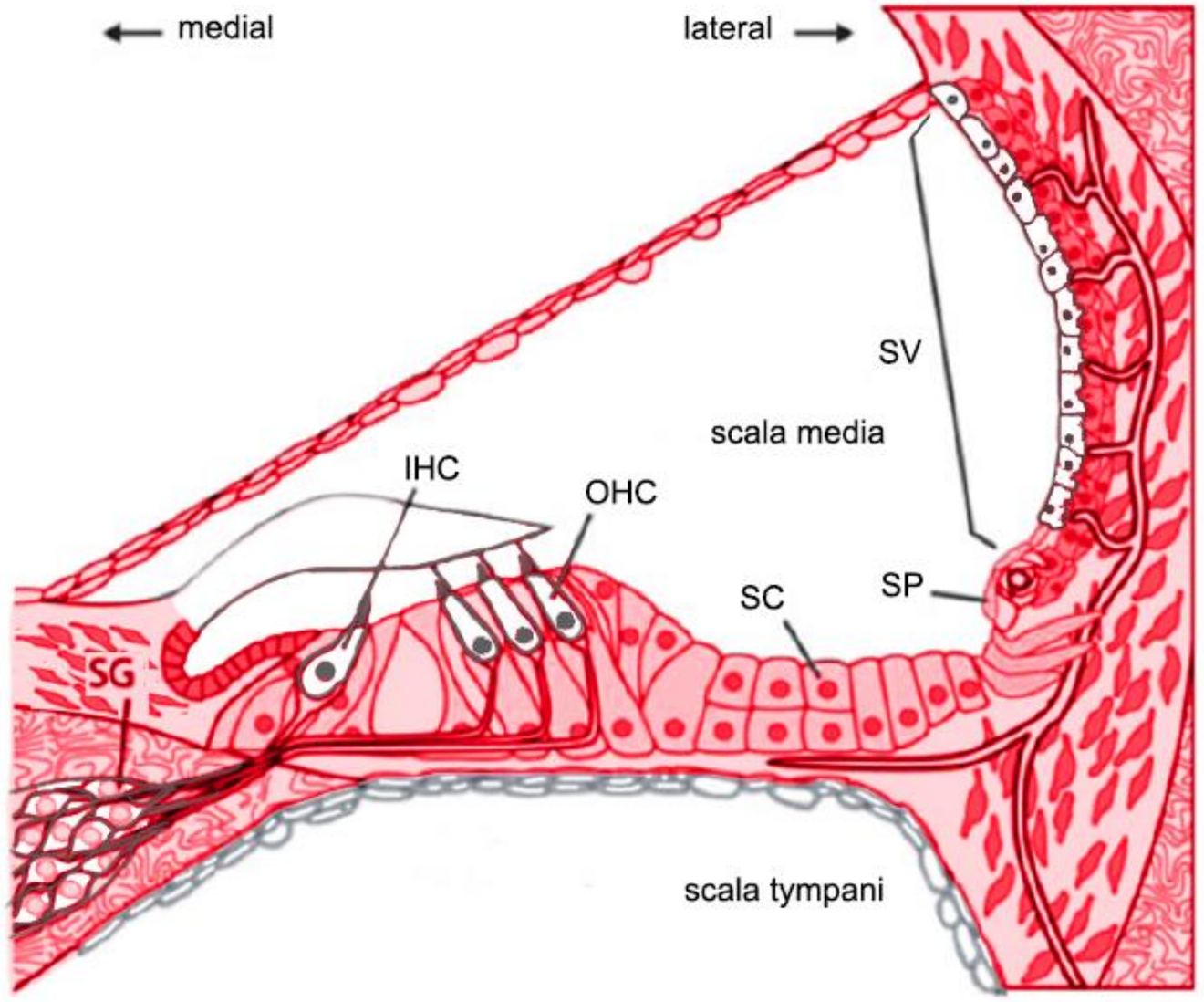
TR: truncating variant
miss: missense variant

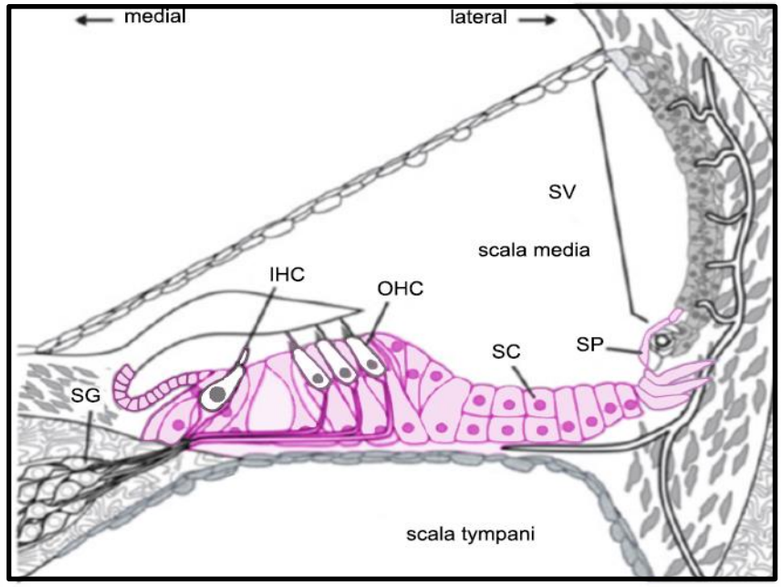
HEARING LOSS PROGRESSION WITH AGE IN GJB2 TR/TR



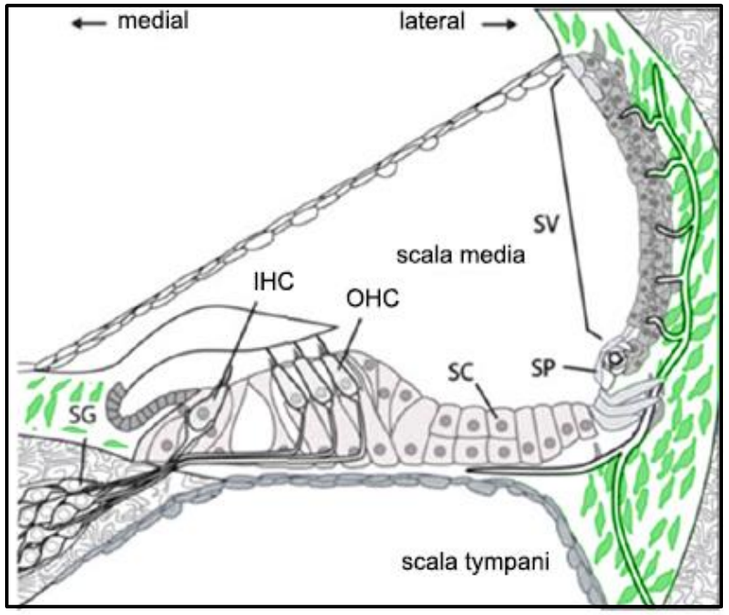
Carson et al., 2023, JAMA Otolaryngol Head Neck Surg

Connexin 26 Expression in Mouse Cochlea

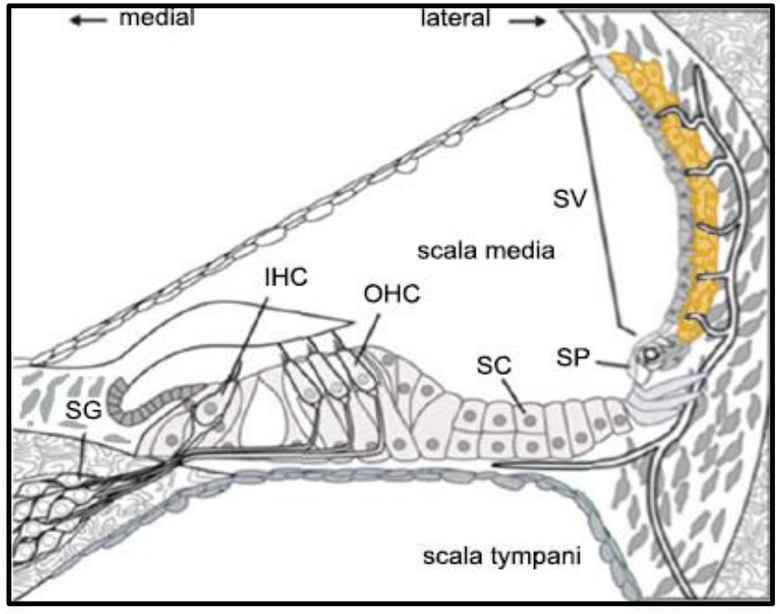




Neuroepithelial Cx26 network

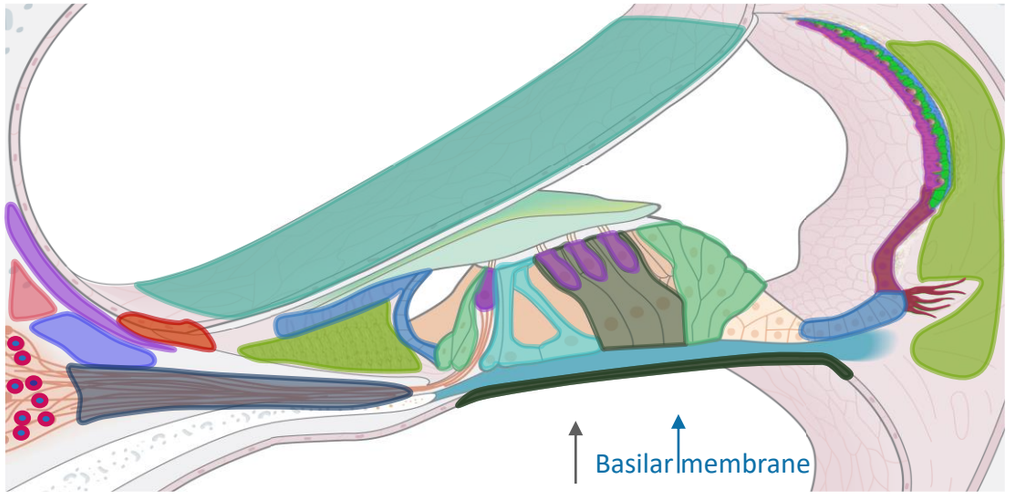


Fibrocyte Cx26 network

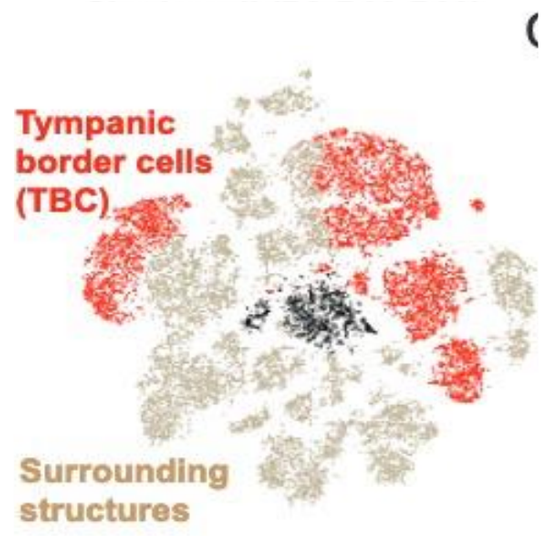


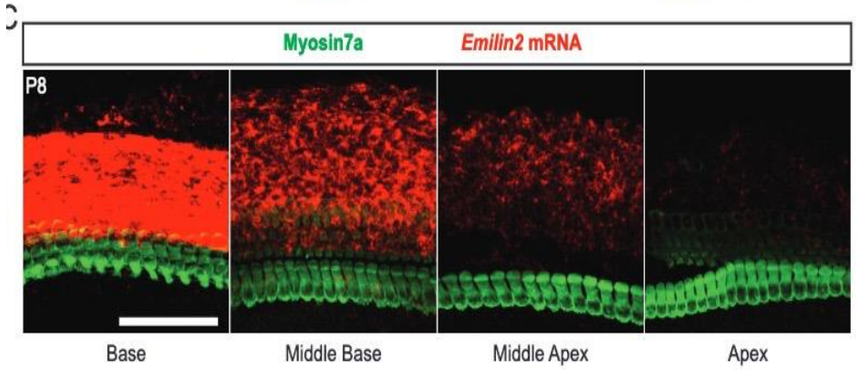
Stria vascularis Cx26 network

Identification of Cochlear Cell Types: Transcriptomic Profiling and RNAscope Analysis



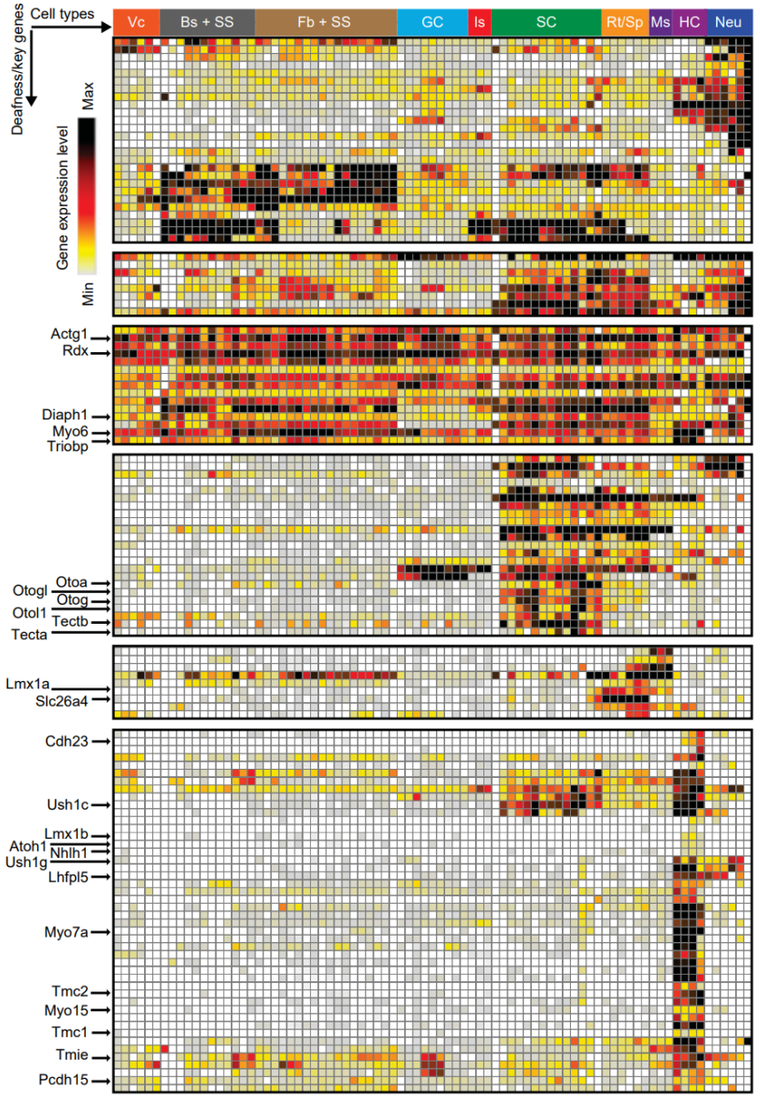
Tympanic border cells





Jean P. Wong V. ….Petit C* & Michalski N* *submitted*

Clustering of Genes Key to Cochlear Development and Function to their Temporal and Spatial Patterns of Expression



Jean P. Wong V. ….Petit C* & Michalski N*
submitted


Auditory therapies innovation lab
Asadollah AGHAIE
Crystel BONNET
Anne-Valérie HERITIER
Andrea LELLI
Nawel MEKDAD
Solène ROUX
Amrit SINGH-ESTIVALET
Virginie WONG JUN TAI
Muriel SUDRES
Christine PETIT
Plasticity of central auditory circuits
Philippe JEAN
Sabrina MECHAUSSIER
Nicolas MICHALSKI
Cochlear development and therapeutic perspectives
Hassan OMAIS
Raphaël ETOURNAY

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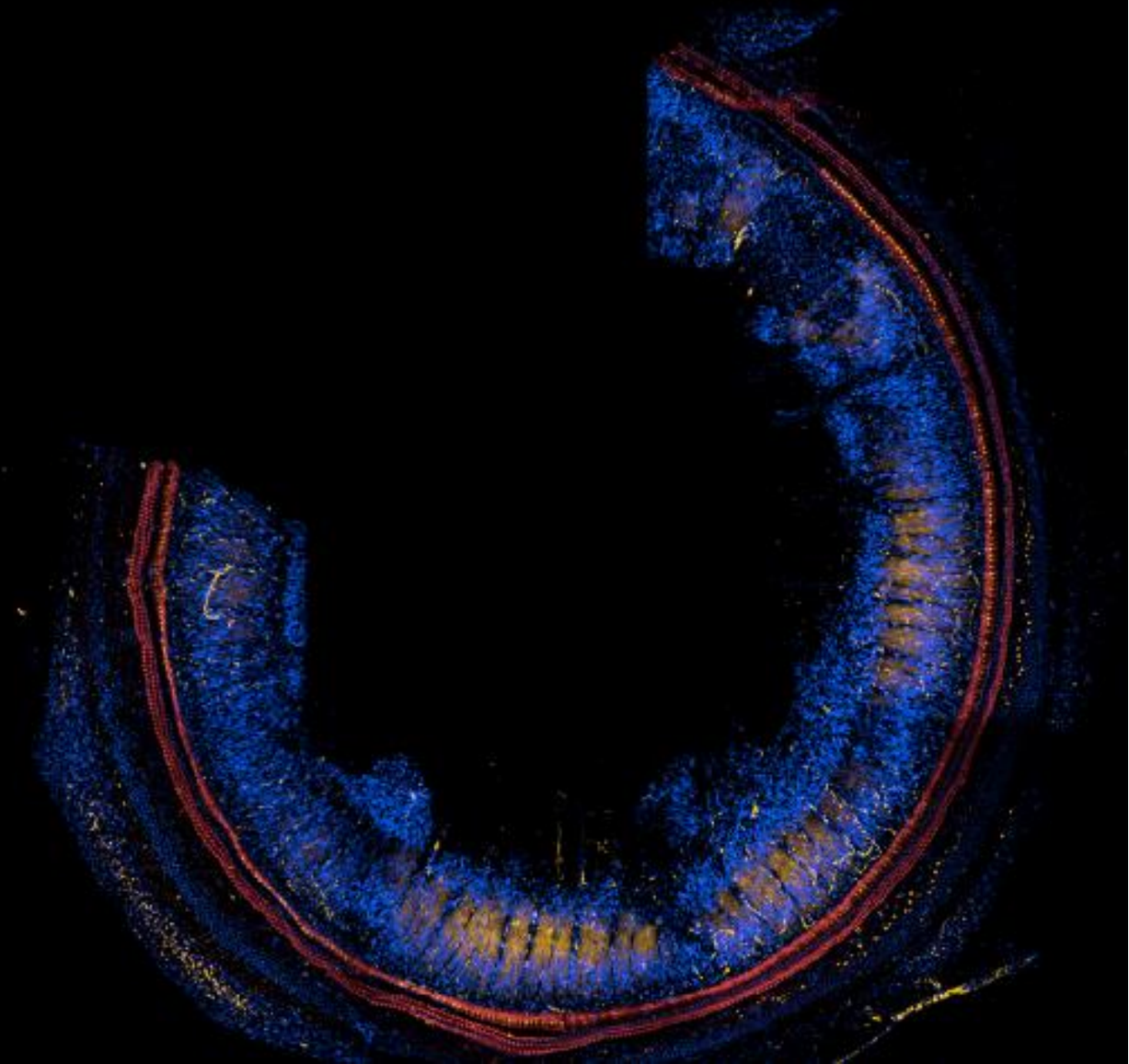
GJB2-GT PROGRAM
DATA TO DRIVE NEXT STEPS

Dr. Laurent Désiré
Head of Preclinical Development
Sensorion

April 6, 2023



We Aim To Develop Best-in Class and First-in Class Gene Therapy

CRITERIA	SENSORION
AAV capsid selected for high-level of target cells specificity	✓
GT product showing high-level of target cells transduction	✓
Limited off-target tissue biodistribution	✓
Surgical approach developed and mastered by ENT surgeons	✓
Natural History Study preparing execution of the clinical trial	✓
Regular engagement with regulatory agencies	✓

We Estimate That GJB2 Related Hearing Loss Affects More Than 300,000 Patients in the US, EU and Japan

We have identified 3 forms of hearing loss associated with GJB2 gene mutations (Connexin 26).

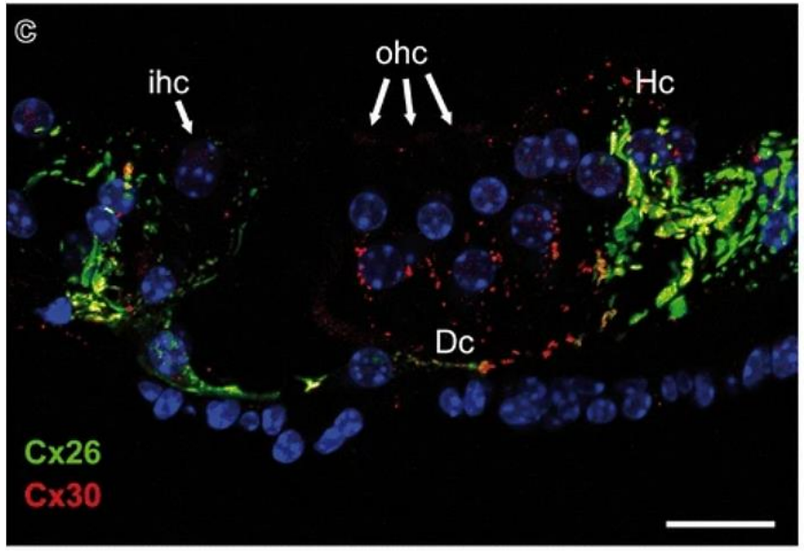
Prevalence of Congenital and Childhood onset forms estimated to be around 200k patients and around **50% of autosomal recessive non syndromic hearing loss cases are thought to result from GJB2 mutations.**

CONGENITAL	• Congenital hearing loss due to GJB2 mutations is typically severe to profound • ~80% of hearing loss cases due to GJB2 mutations in children are thought to be congenital.
CHILDHOOD ONSET	• Estimates are that ~20% of cases feature a late onset (during childhood) progression of hearing loss. • The onset becomes more severe around 6 years old and continues.
ADULT EARLY ONSET OF PRESBYCUSIS	• ~100k patients between 30- and 69-years old thought to be affected by a monogenic form of presbycusis due to GJB2 mutations.

GJB2 Plays a Critical Role in Inner Ear

GJB2 IS THE GENE ENCODING FOR THE CONNEXIN 26 PROTEIN

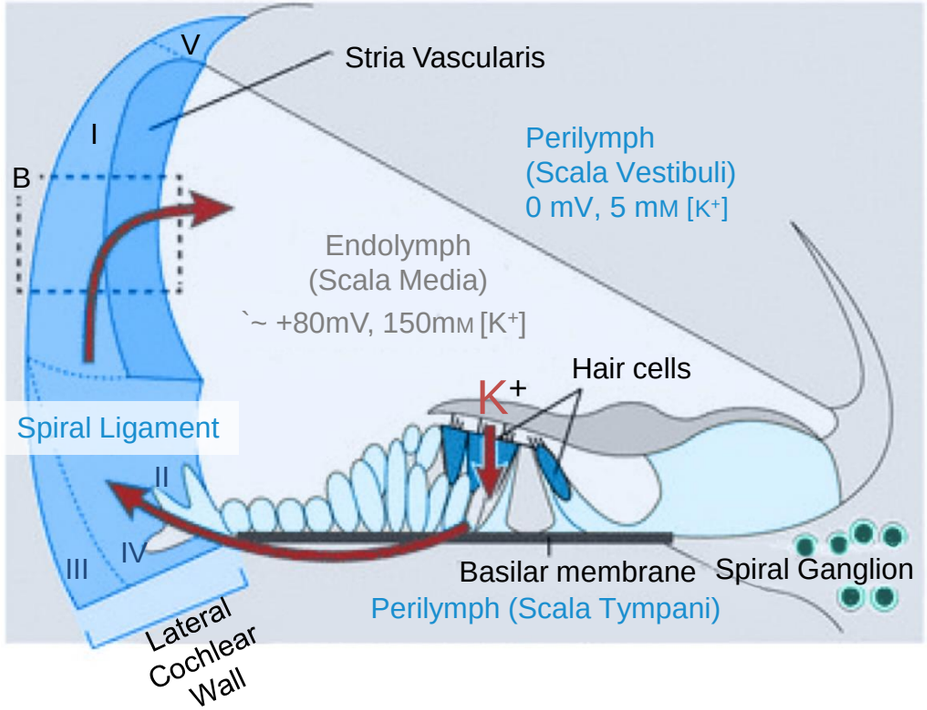
GJB2 IS NOT NATURALLY EXPRESSED IN HAIR CELLS BUT IS EXPRESSED IN SUPPORTING CELLS



Source: Ahmad S, Chen S, Sun J, Lin X (2003) Connexins 26 and 30 are co-assembled to form gap junctions in the cochlea of mice. Biochem Biophys Res Commun 307:362–368

IHC: inner hair cells, OHC: outer hair cells, DC: deiter cells, HC: hensen cells

CONNEXIN 26 PROTEIN IS INVOLVED IN THE K+ HOMEOSTASIS

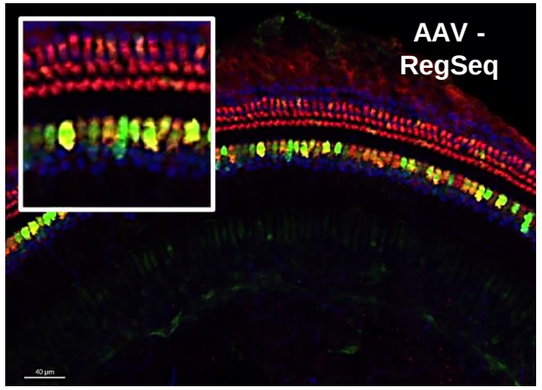


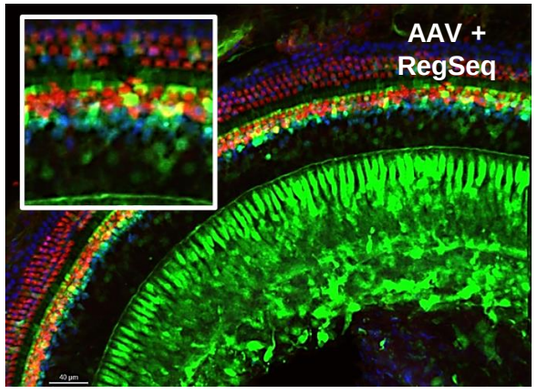
Source: The mechanism underlying maintenance of the endocochlear potential by the K+ transport system in fibrocytes of the inner ear.

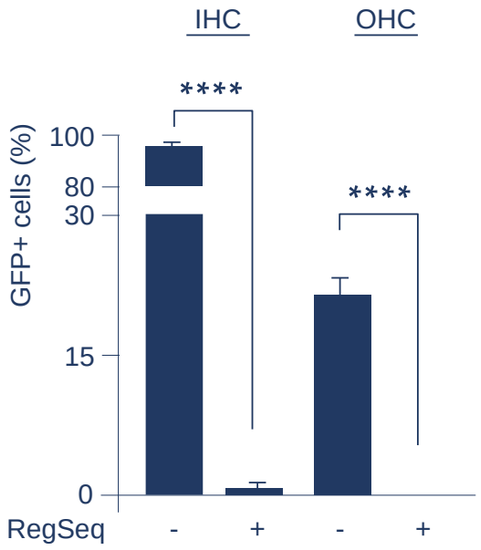
Physiol. 2013 Sep 15; 591(Pt 18): 4459–4472.

Our Lead Candidate Is Designed to Ensure Broad Coverage of Relevant Cochlear Cells While Detargeting Hair Cells

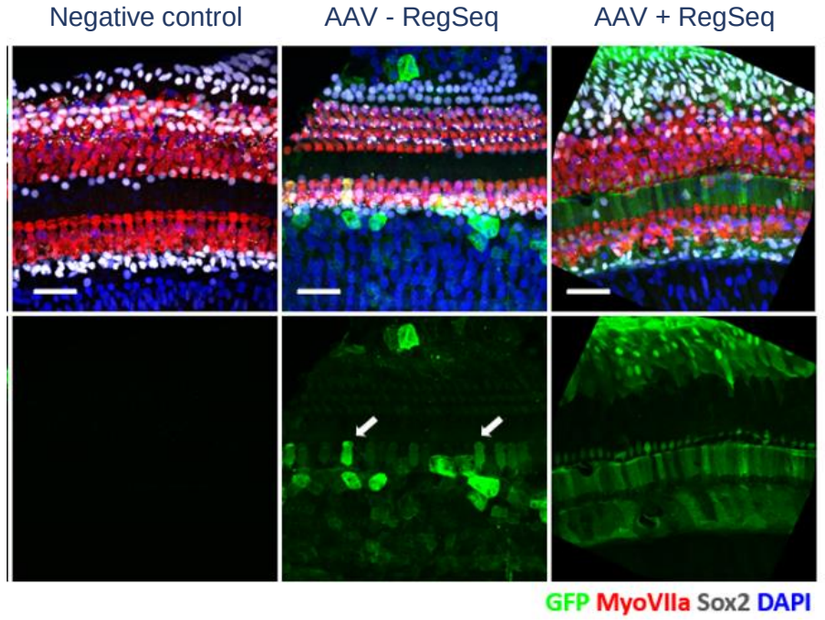
WT MOUSE







WT NON-HUMAN PRIMATE

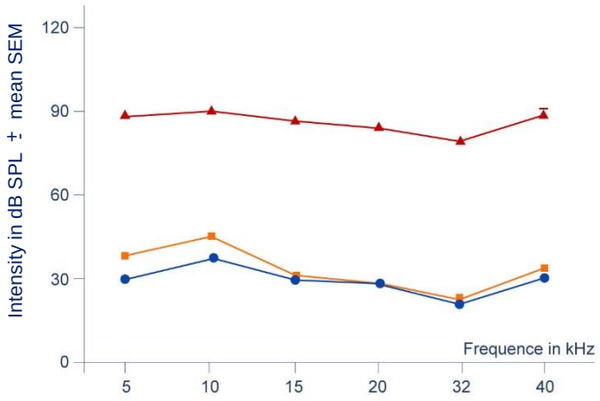


Our Lead Candidate Prevents Hearing Loss in Relevant Mouse Model

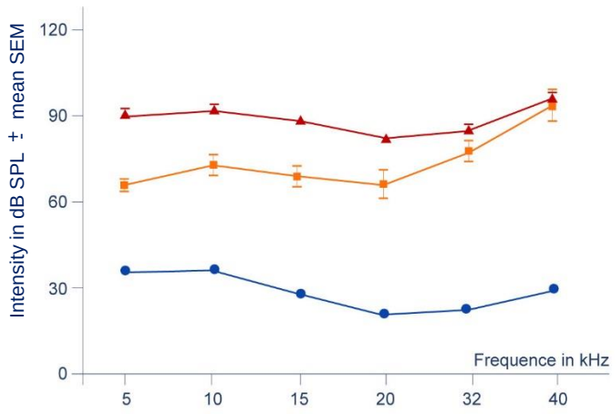
PROOF OF CONCEPT IN PROGRESSIVE MOUSE MODEL

Conditional knock-out mouse model leading to 2 phenotypes

ABR threshold - 1 month after birth

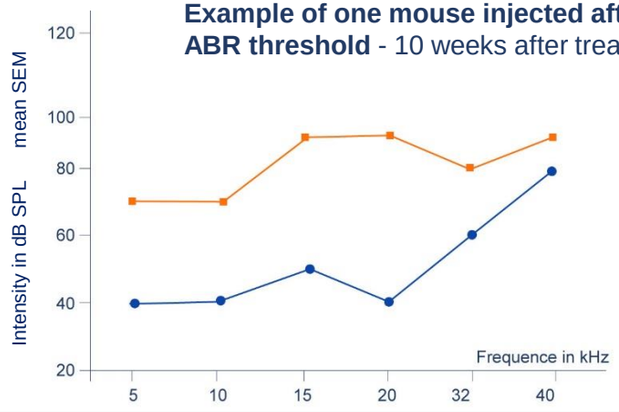


ABR threshold - 6 months after birth



Control mice Congenital-like Profound *Cx26* ↓↓↓ Progressive*Cx26* ↓

Example of one mouse injected after hearing onset
ABR threshold - 10 weeks after treatment



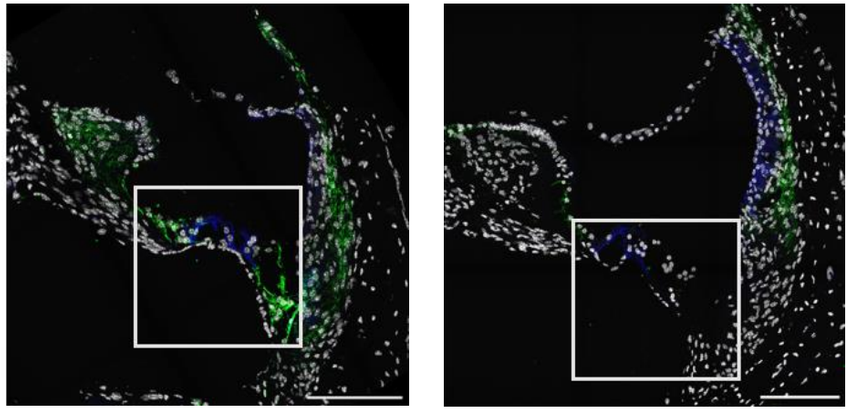
Non injected ear

Lead candidate injected ear

HEARING LOSS PREVENTION CORRELATES WITH CONNEXIN 26 EXPRESSION

Example of one mouse injected after hearing onset
Connexin 26 expression in the cochlea
- 10 weeks after treatment

Lead candidate injected ear Non injected ear



Left: Green staining demonstrates efficient Cx26 re-expression in target cells, which are otherwise depleted (right) in Cx26 in the GJB2 deficient model

ABR: Auditory Brainstem Response

Our Lead Candidate Is Moving Into IND/CTA Enabling Studies

CRITERIA	LEAD CANDIDATE
AAV capsid selected for high-level of target cells specificity	✓
GT product showing high-level of target cells transduction	✓
Limited off-target tissue biodistribution	→
Surgical approach developed and mastered by ENT surgeons	✓
Natural History Study preparing execution of the clinical trial	→
Regular engagement with regulatory agencies	→

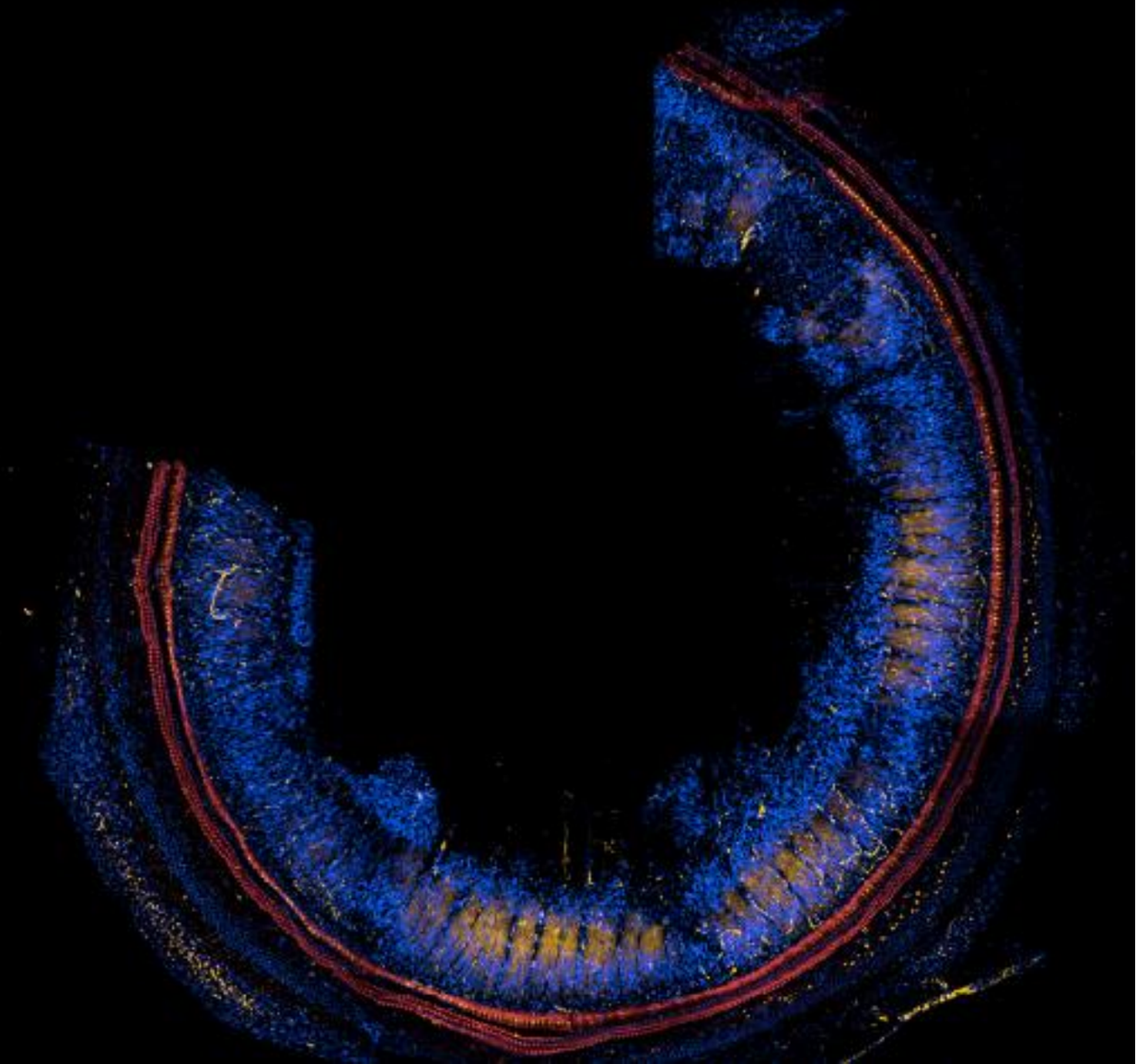
Sensorion

GJB2-GT PROGRAM

NATURAL HISTORY STUDIES TO PREPARE EXECUTION OF CLINICAL TRIALS

Dr. Géraldine Honnet
Chief Medical Officer
Sensorion

April 6, 2023



We are Running Two Studies to Better Understand the Profile of Early Onset Presbycusis (EOP) Patients and to Design the GT Trials

EOP AUDIOLOGIC PROFILE STUDY - AUDIOGENAGE

- Collaboration with the Institut Pasteur/CERIAH
- Performing a battery of tests to identify the most discriminating test to characterize the hearing of genetic form of EOP compared to a control group matched in age
- Enrollment ongoing

→ Genetic screening

→ Identification of the best audiological tests to measure endpoints

EOP NATURAL HISTORY STUDY - SONG

- Collaboration with Sonova
- Longitudinal prospective study of the Natural History of Early Onset Form of Presbycusis caused by mutations in GJB2 Gene in adult subjects

→ Genetic screening

→ Disease progression characterization

→ Endpoint and visit definition

Identification of patients and relatives potentially eligible to the future GT trial

GENE THERAPY CLINICAL TRIAL

AUDIOGENAGE - EOP Audiologic Profile Study

Study description

Qualification of audiological tests for the accurate diagnosis and follow-up of age-related hearing loss

Sponsor: The Institut Pasteur (NCT05312983)

Population

- Participants over the age of 40 with hearing loss about 20 years ahead of schedule for their age (n=500)
- Normal hearing participants for their age (control, n=200)

Aim

- Establish the **specificity** and **sensitivity** of the battery of audiological tests in participants with EOP after identification of pathogenic variants by sequencing the participants

Evaluation

- Audiological and vestibular tests
- Neurocognitive self-questionnaire
- Blood sampling

SONG - EOP Natural history study

Study description

Longitudinal prospective study of the Natural History of Early Onset Form of Presbycusis caused by mutations in *GJB2* Gene in adult subjects

Sponsor: Sensorion

Population

- Participants with no cochlear implant at baseline, aged from 30 to 55 years at selection, with a diagnosis of early onset of presbycusis, with genotyping results showing mutations in *GJB2* gene
- Approximately 2000 participants with no cochlear implant at baseline will be screened
- Amongst them, upon genotyping results, 100 will be proposed to enter the Natural History study

Aim

- Confirm the prevalence of the *GJB2* mutations/collect additional genetic data in the presbycusis population
- Follow up the evolution of the natural course of the disease

Evaluation

- Audiological tests and Speech Intelligibility test
- QoL/Social impact tests
- Neurocognitive questionnaire
- Biobank constitution

We are Running One Study to Better Understand the Profile of Congenital and Progressive Forms of Hearing Loss Related to *GJB2* Mutation in Children

Otoconex

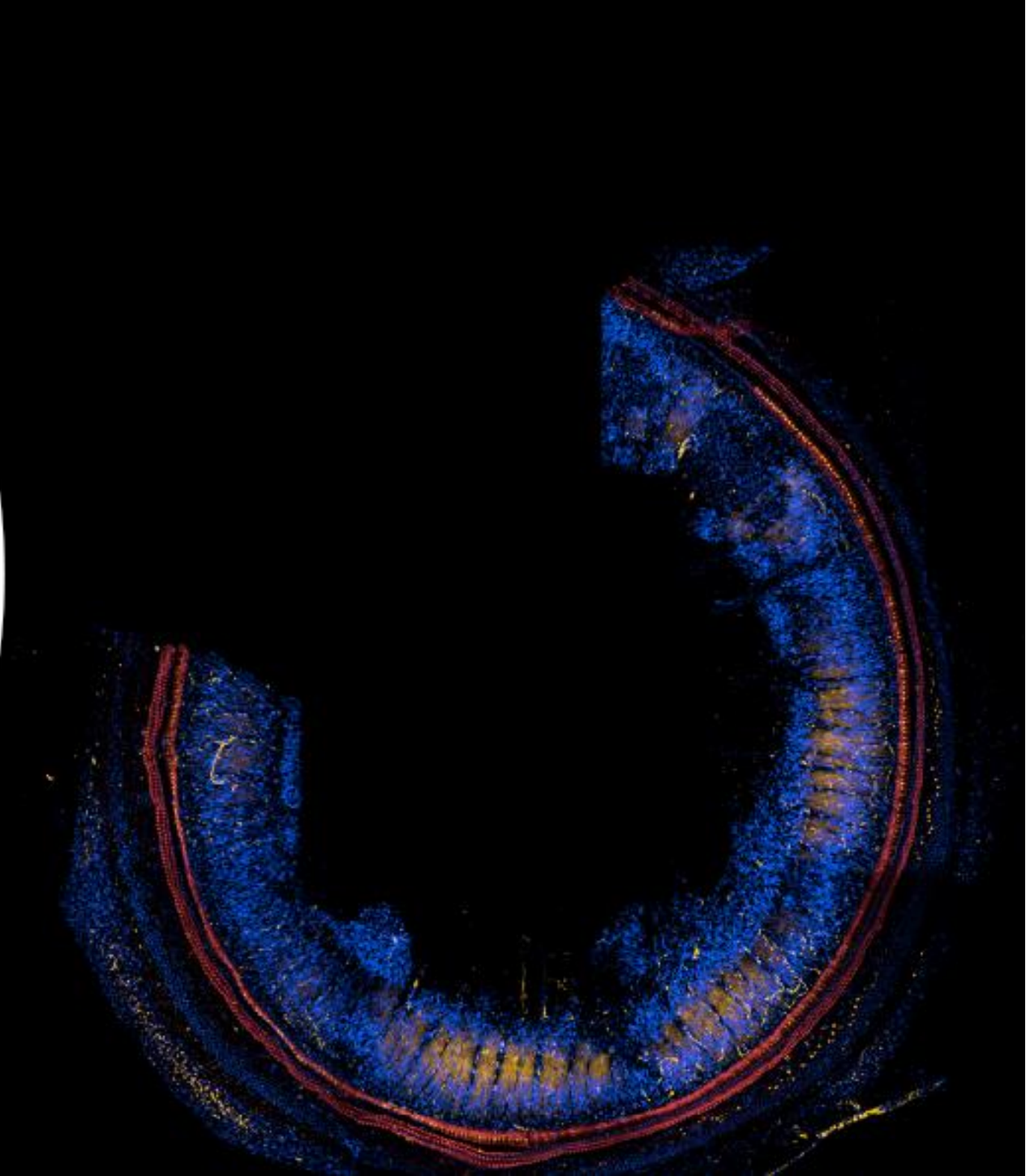
Longitudinal study of the natural history of otoferlin and connexin 26 related deafness in children up to 10 years

Sensorion

OTOFERLIN DEFICIENCY: APPROACHES TOWARDS HEARING RESTORATION

Pr. Natalie Loundon
Director of the Cochlear Implant and Audiology Unit
Necker Hospital

April 6, 2023



Auditory Neuropathy Spectrum Disorder

ANSD clinical aspects

5-10% Sensorineural Hearing loss

- Mild to profound hearing loss (Pure Tone Audiometry, PTA)
- Poor speech intelligibility rate
- Desynchronized Auditory Brainstem Response (ABR)
- Normal Otoacoustic Emissions (OAEs)

Standard of care

- Hearing aids
- Cochlear implantation

ANSD various origins

Brain

- Preterm, Hyperbilirubinemia, Mitochondrial

Nerve

- Hereditary sensory-motor neuropathy
- Later onset (10-15 yo)
- Abnormal cochlear nerve

Synapse

Otoferlin (DFNB9) OTOF

- **Non-syndromic recessive ANSD**
- Prevalence: **~28,000** in USA + EU + Japan (8,000)
- Incidence: ~**1,080** per year in USA + EU + Japan

DFNB9: Good Candidate for Gene Therapy Treatment

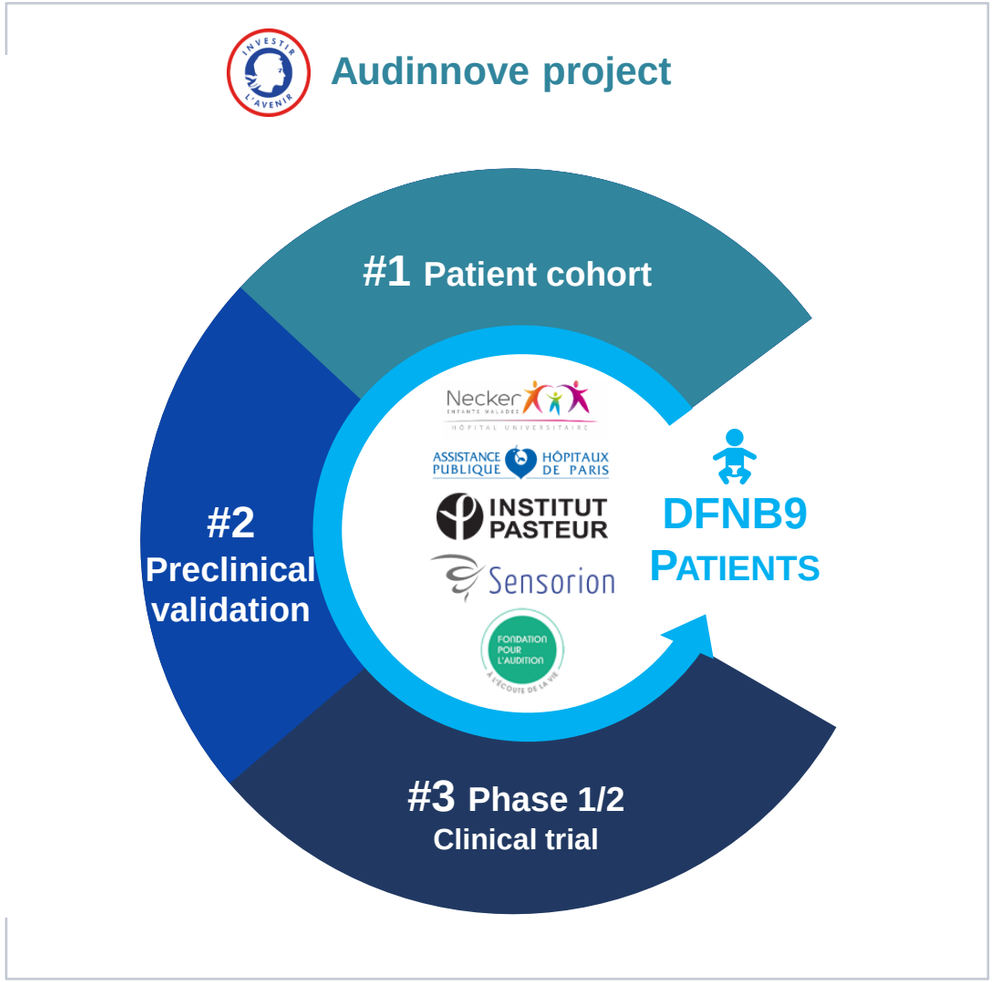
- Mostly severe to profound hearing loss
- Recessive mutations in *OTOF* encoding otoferlin
- Deep understanding of the pathophysiology
- Defective inner hair cell synapse
- Preserved inner ear structures
- Mouse model

PNAS

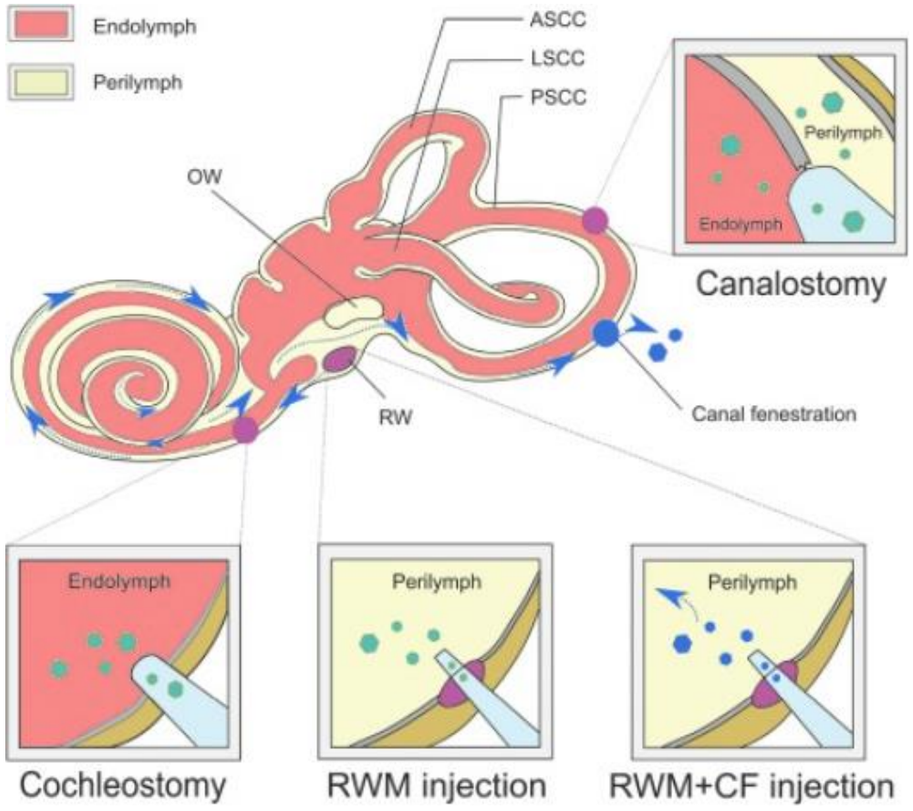
Dual AAV-mediated gene therapy restores hearing in a DFNB9 mouse model

Omar Akil[a], Frank Dyka[b], Charlotte Calvet[c,d,e], Alice Emptoz[c,d,e], Ghizlene Lahlou[c,d,e], Sylvie Nouaille[c,d,e], Jacques Boutet de Monvel[c,d,e], Jean-Pierre Hardelin[c,d,e], William W. Hauswirth[b], Paul Avan[f], Christine Petit[c,d,e,g,1], Saaid Safieddine[c,d,e,h,1], and Lawrence R. Lustig[i]

[a]Department of Otolaryngology–Head and Neck Surgery, University of California, San Francisco, CA; [b]Department of Ophthalmology, College of Medicine, University of Florida, Gainesville, FL 32610; [c]Genetics and Physiology of Hearing Laboratory, Institut Pasteur, 75015 Paris, France; [d]Inserm Unité Mixte de Recherche en Santé 1120, Institut National de la Santé et de la Recherche Médicale, 75015 Paris, France; [e]Complexité du Vivant, Sorbonne Universités, F-75005 Paris, France; [f]Laboratoire de Biophysique Sensorielle, Faculté de Médecine, Centre Jean Perrin, Université d'Auvergne, 63000 Clermont-Ferrand, France; [g]Collège de France, 7505 Paris, France; [h]Centre National de la Recherche Scientifique, 75794 Paris, France; and [i]Department of Otolaryngology–Head and Neck Surgery, Columbia University Medical Center and New York Presbyterian Hospital, New York, NY 10032



Gene Therapy in the Inner Ear: Surgical Approach



Omichi *et al*., Hum Mol Genet., 2019

The inner ear is a good target for gene therapy

- Routine surgical access
- Isolated organ limiting off-target effects

Developing specific tools for an efficient injection:

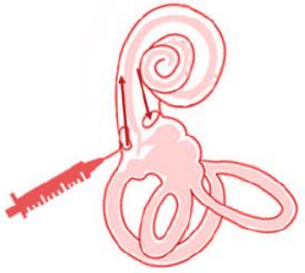
- Minimally invasive
- Reproduceable among surgeons across the world
- Round Window Membrane
- Fixed volume and controlled delivery rate

Proprietary injection system developed

We have Developed a Dedicated Surgical Approach for Gene Therapy Administration

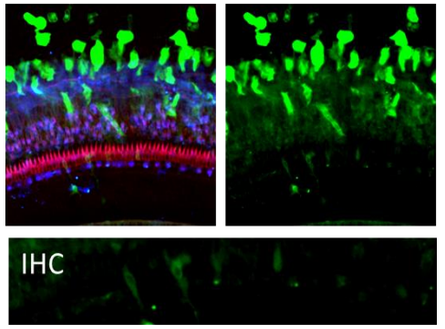
Non-Human Primates injected through the round window membrane (RWI) with or without stapedotomy (stap)

1 FENESTRATION
(Round window membrane)

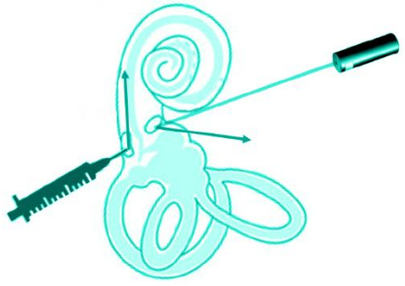


Used for cochlear implant

- Overpressure
- Limited volume
- Backflow
- Irregular transduction rate

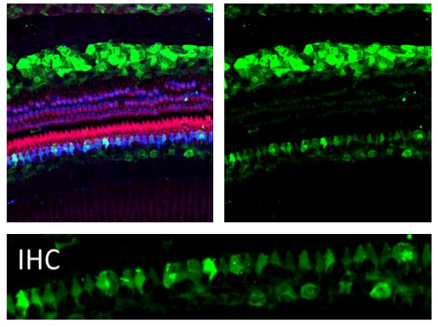


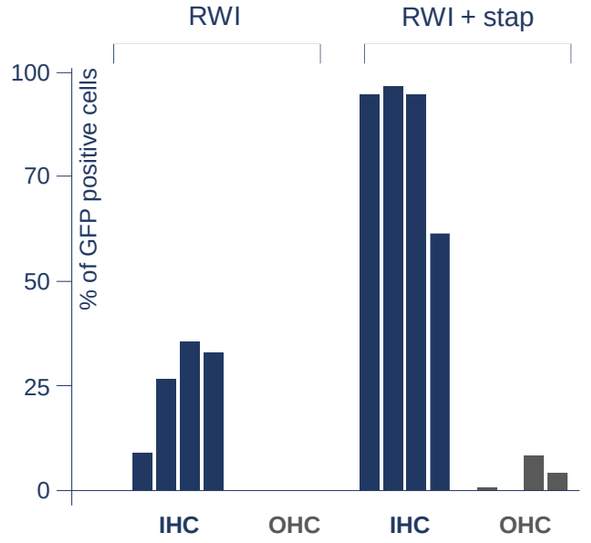
2 FENESTRATIONS
(Round window membrane + oval window)



Combining 2 common surgical technics: cochlear implant and stapedotomy

- No overpressure
- No backflow
- Homogenous and efficient transduction rate





Data indicate cell counting in 4 regions from the apex (left) to the base (right)
I/OHC: Inner/Outer Hair Cells

Assessing the Prevalence of DFNB9 Among Patients with ANSD

Audinnove project

Audioferlin

Evaluation of a Cohort of Congenital Deep Deafness Patients and/or With Auditory Neuropathy, Looking for DFNB9

Sponsor: Necker Hospital

Main objectives:

- To assess the prevalence of otoferlin related deafness among children with auditory neuropathy and/or severe to profound bilateral congenital deafness
- To genotype all new diagnosed patients with ANSD
- To identify best candidates for future gene therapy study

Design:

- Cohort 1: Infants < 3Y with bilateral severe to profound HL
- Cohort 2: Children < 16Y with auditory neuropathy
- Cohort 3: Patients < 25Y with Otoferlin mutations
- Enrollment ongoing

Assessing the Natural History of DFNB9

Otoconex

Longitudinal study of the natural history of otoferlin (and connexin 26) related deafness
Sponsor: Sensorion

Main objectives:

- To assess the natural course of OTOF (and GJB2) related deafness
- To assess the quality of life after CI surgery (short-term and mid-term)
- To identify the relevant endpoints for future gene therapy study
- To identify best candidates for future gene therapy study

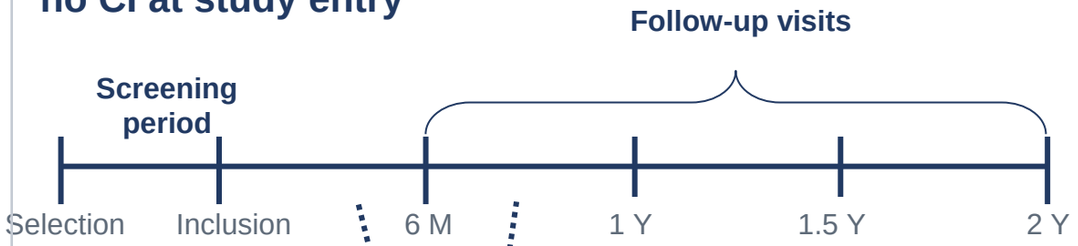
Design:

- Multicentric (10 centers), 5 EU countries including France
- Children ≤ 10yo with either a DFNB9 or GJB2 related moderate to profound sensorineural hearing loss
- Enrollment: ongoing

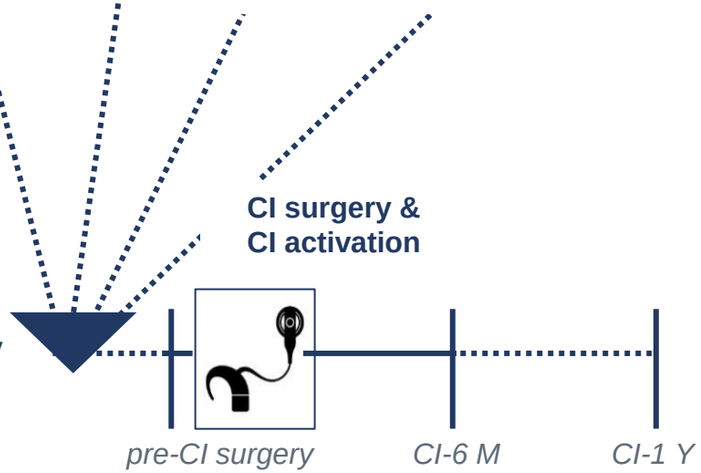
Longitudinal Study of the Natural History of Otoferlin and Connexin 26 Related Deafness in Children Up to 10 Years

COHORT 1: WITHOUT CI AT STUDY ENTRY

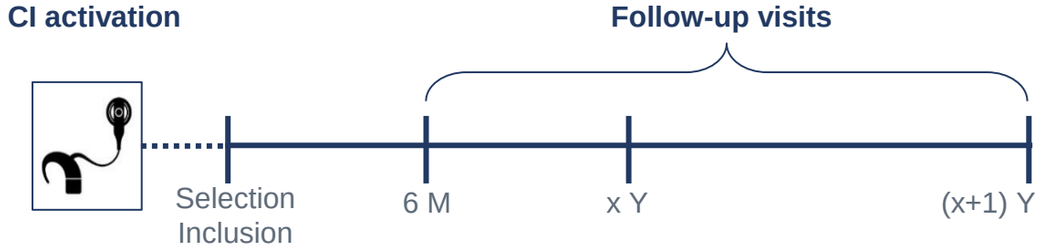
COHORT 1a: no CI at study entry



COHORT 1b: CI after study entry



COHORT 2: WITH CI AT STUDY ENTRY



Hearing tests:

PTA, ABR, OAE, Speech audiometry…

Questionnaires on:

Sound perception and intelligibility
QoL and burden of the disease

CI: Cochlear Implant; PTA: Pure Tone Audiometry, ABR: Auditory Brainstem Response, OAE:Otoacoustic Emission, QoL: Questionnaire of Life

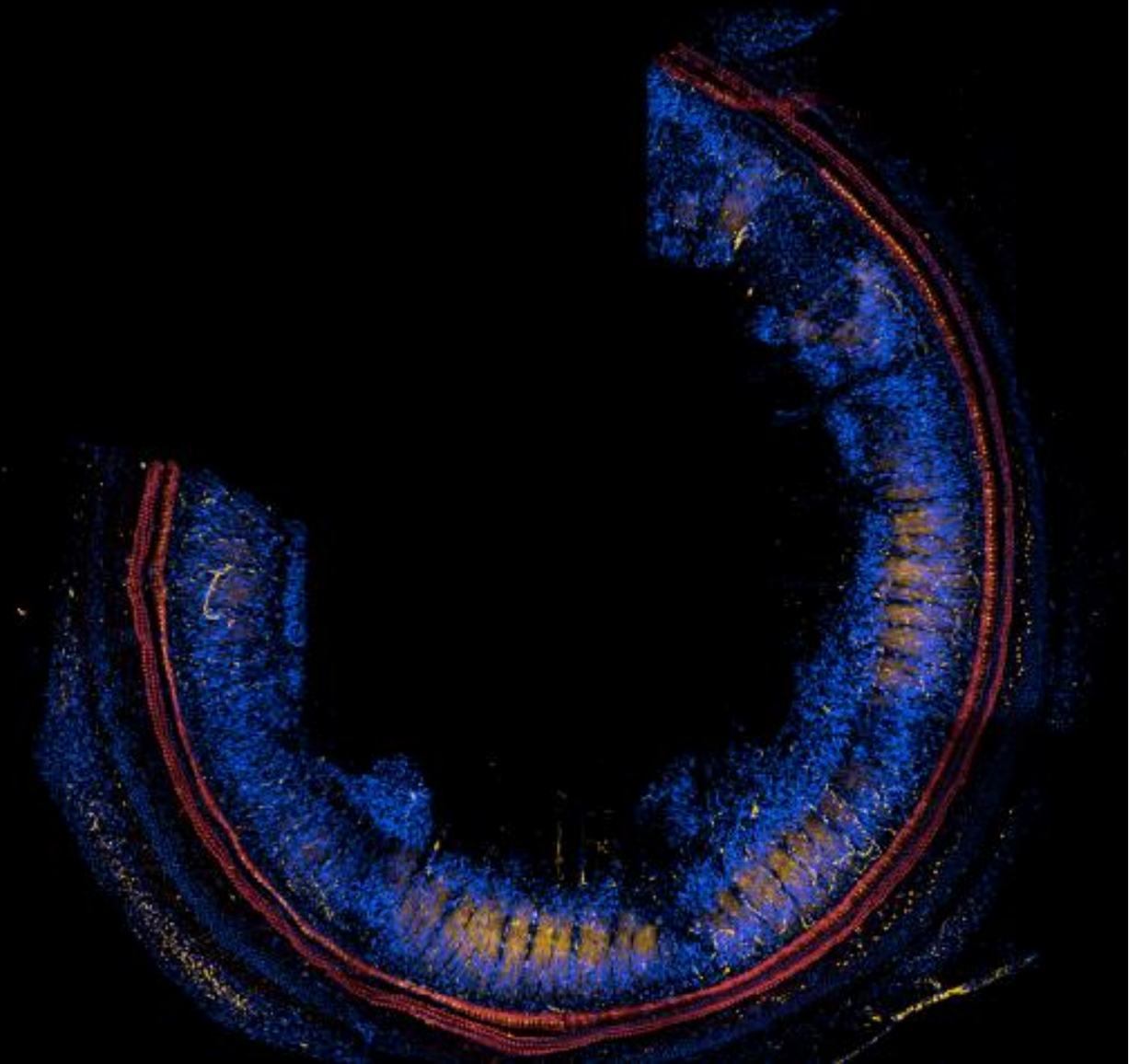
We are Excited to Get the Gene Therapy Trial Started!

Sensorion

OTOF-GT PROGRAM: SENS-501 SENSORION'S LEAD GENE THERAPY PROGRAM

Dr. Laurent Désiré
Head of Preclinical Development
Sensorion

April 6, 2023



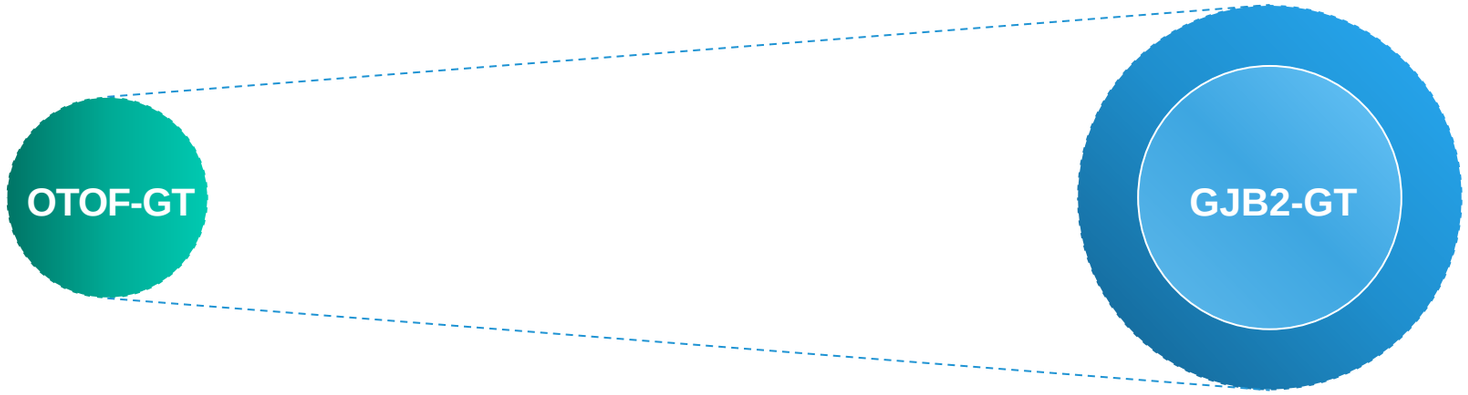
The Gene Therapy Pediatric Indications Have Blockbuster Sales Potential

OTOF-GT IS THE PERFECT PILOT PROGRAM

- Well understood biology and pathology of the otoferlin deficiency
- Full functionality of the remaining chain
- High specificity for the inner hair cells (IHCs), no off-target effect expected

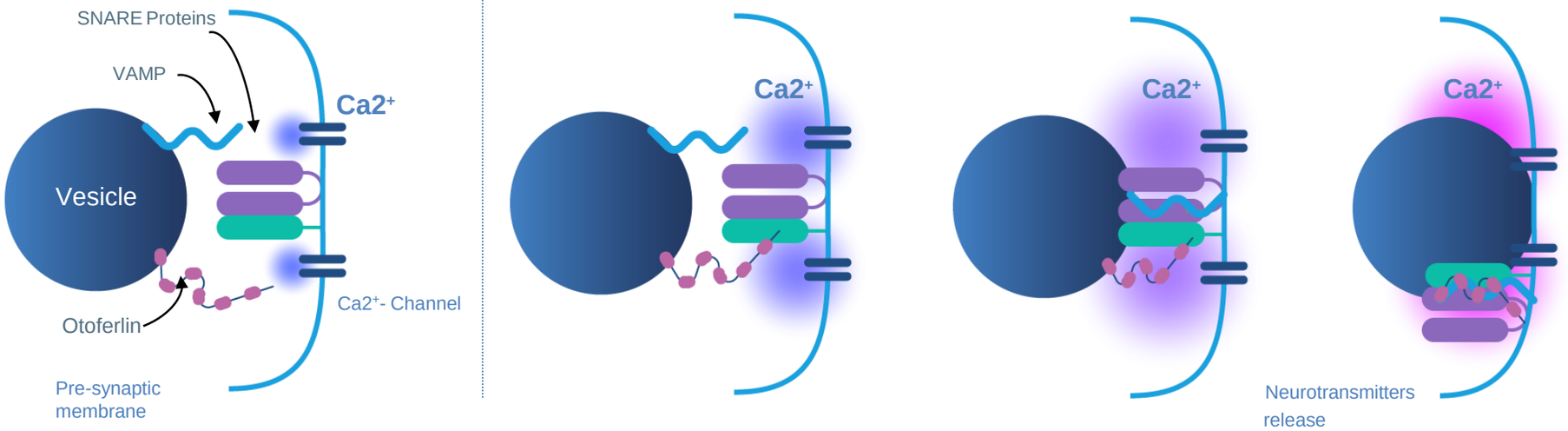
- OTOF-GT will be the pilot program demonstrating that GT is a relevant medical approach for the inner ear
- OTOF-GT will establish understanding of GT for the inner ear by KOLs, Regulators and Payers for future GT programs
- Medical plausibility and target population have been confirmed through:
  - Orphan Drug Designation in the US and EU
  - Rare Pediatric Disease Designation with eligibility for voucher in the US

SALES POTENTIAL ILLUSTRATION



Sources: Sensorion, AT Kearney market research

OTOF Gene Encodes Otoferlin, A Key Ca2+ Sensor Protein



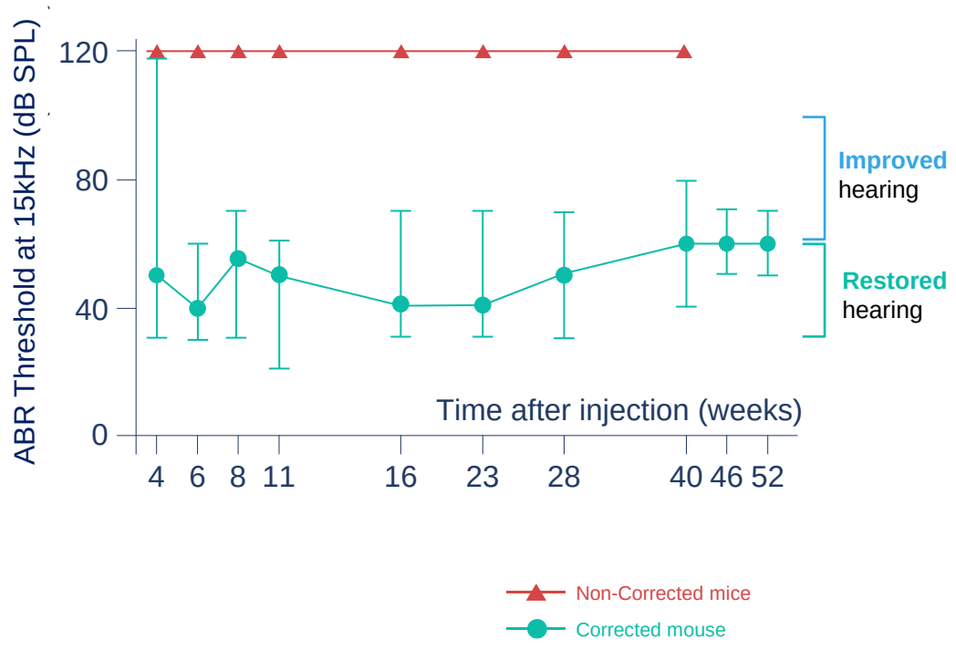
Model illustrating calcium regulation of otoferlin/SNARE interaction in the hair cell - Adapted from Ramakrishnan *et al.* 2014

OTOF is the gene coding for the otoferlin protein, a Ca2+ sensor for vesicle fusion and vesicle pool replenishment at auditory hair cell ribbon synapses.

SENS-501 Leads to Long-term Hearing Recovery in a Translational Model of Otoferlin Deficiency

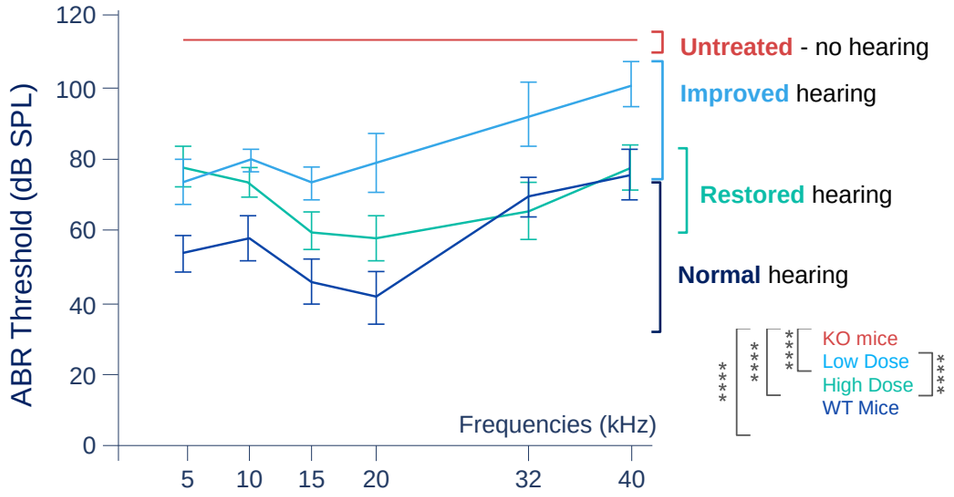
LONG-TERM HEARING RECOVERY

AAV-mOTOF injected in mice before hearing onset

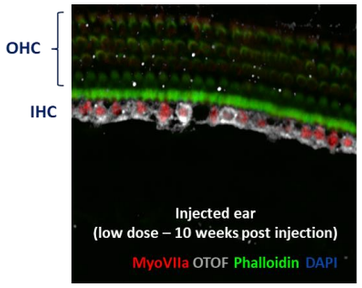


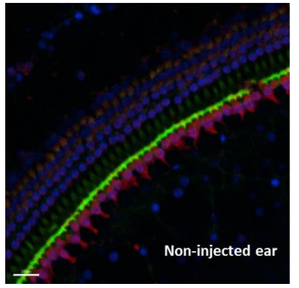
SENS-501 DOSE EFFECT

10 months post-injection in mice after hearing onset



**** : p<0.0001; ***: p<0.001; two-way ANOVA, Dunnett's Multiple comparison test with a single pooled variance

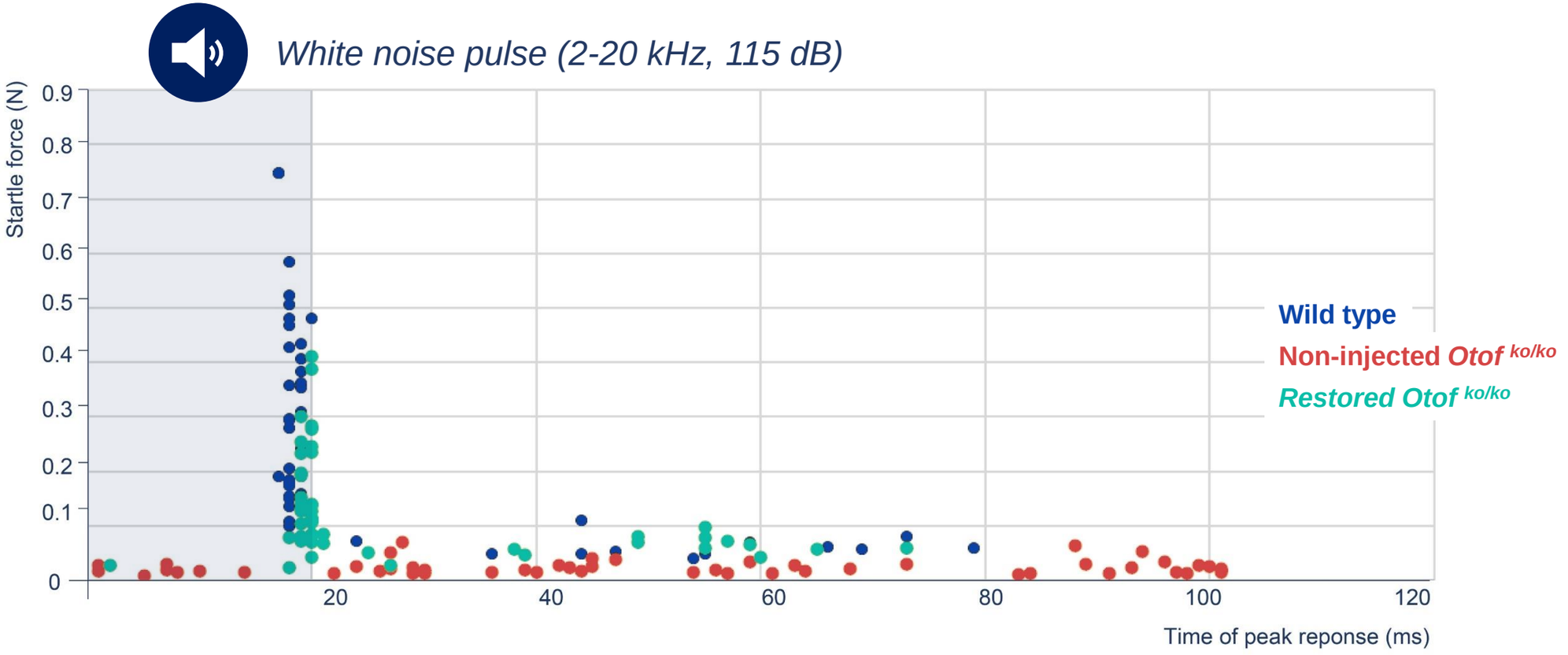




O/IHC: Outer/Inner Hair Cells

ABR: Auditory Brainstem Response

SENS-501 Leads to Restoration of Efficient Sound Processing in Behavioural Test



SENS-501 Plans CTA Submission by H1 2023

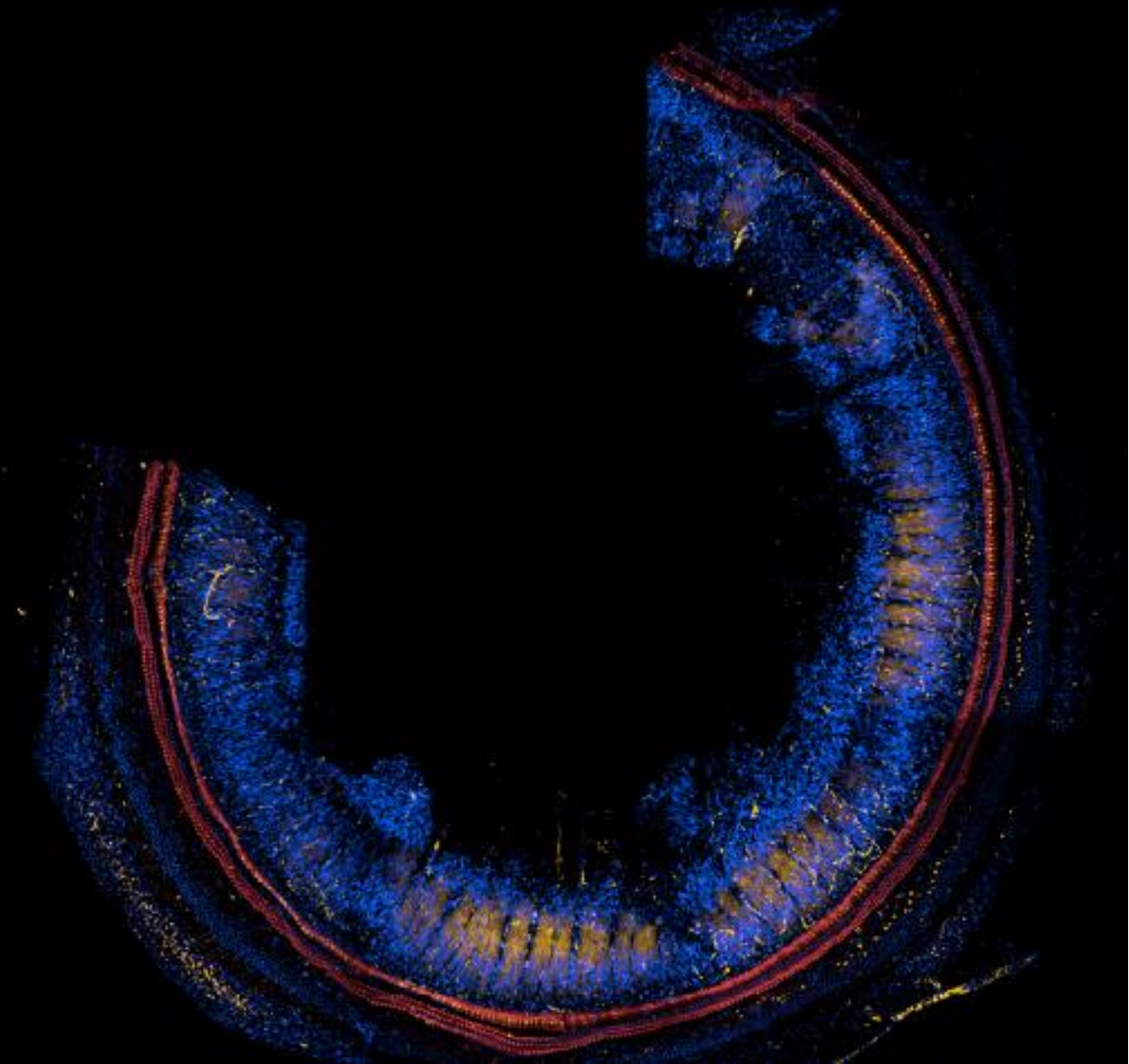
CRITERIA	SENS-501
AAV capsid selected for high-level of target cells specificity	✓
GT product showing high-level of target cells transduction	✓
Limited off-target tissue biodistribution	✓
Surgical approach developed and mastered by ENT surgeons	✓
Regular engagement with regulatory agencies	✓
Natural History Study preparing execution of the clinical trial	→
No findings – early biodistribution /safety /tolerability studies	✓
No correlation anti-AAV immunity and transduction efficacy	✓
GLP Tox studies under completion	→
Drug Product manufacturing under GMP conditions	✓

Sensorion

ENABLING RELIABLE GENE THERAPY MANUFACTURING AND ANALYTICAL CONTROL

Dr. Christine Le Bec
Head of GT CMC
Sensorion

April 6, 2023



We are Developing In-House CMC Capabilities

ADVANTAGES	SENSORION
AAV candidates supply for POC studies	✓
Early Process & Analytical development initiation	✓
Smooth and better control of the Tech Transfer to CDMOs	✓
Costs saving as process development is performed internally	✓
Reliable development timelines	✓

From Research to Clinical Process

2L to 50L scale

- Process Development
- Research material
- Process Definition - DoE at small scale for optimizing conditions
- Early CPPs identification

200L scale

- Process lock
- Tox batch
- Reference standard material
- Early specifications definition

200L scale

- Full scale GMP

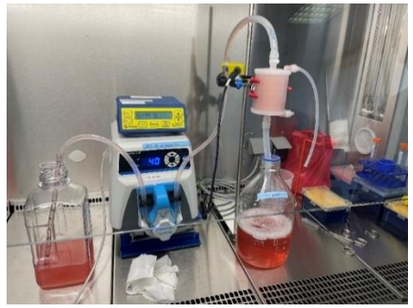
In-house **Transfer to CDMOs**

Derisking Early CMC Development Steps

Upstream Process platform

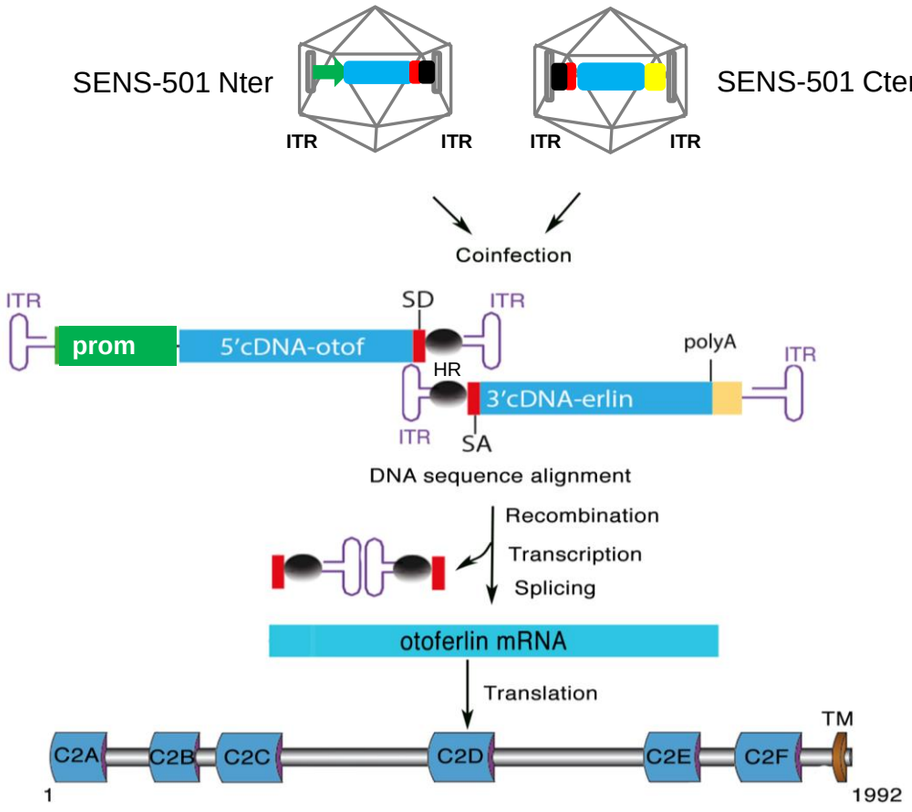
Downstream Process platform

Analytical development platform



We Have Completed the GMP SENS-501 Drug Product Manufacturing

SCHEMATIC HYBRID DUAL AAV



ITR: Inverted Terminal Repeat; SD/SA: Splicing Donor/Acceptor sequence, HR: Homology Region

- Tox batches manufactured
- GMP Drug Substances manufactured
- GMP Drug Product manufactured

We are Progressing Our GJB2-GT Lead Candidate in Manufacturing Process

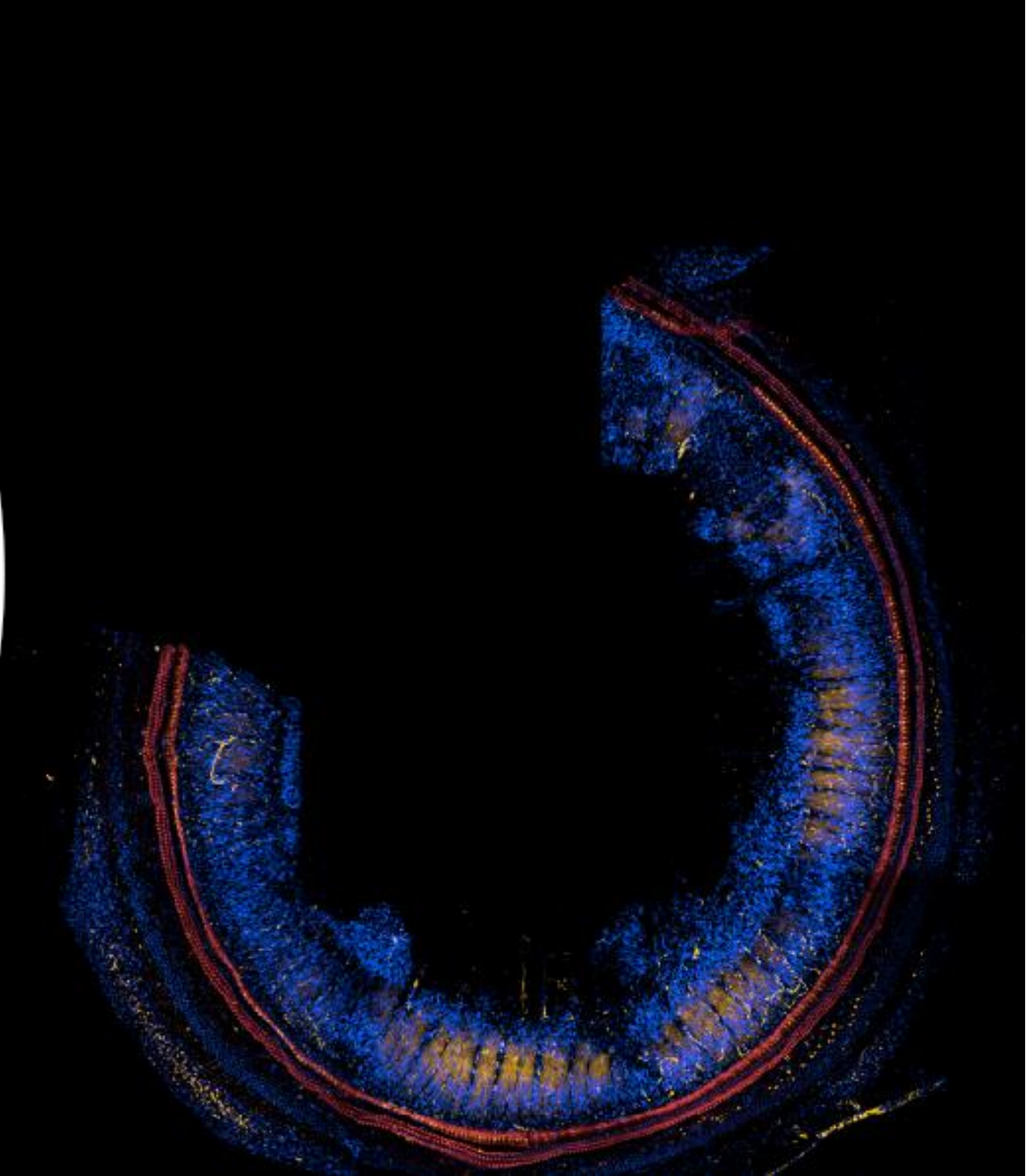
ADVANTAGES	GJB2-GT LEAD CANDIDATE
AAV candidates supply for POC studies	
Early Process & Analytical development initiation	
Smooth and better control of the Tech Transfer to CDMOs	
Costs saving as process development is performed internally	
Reliable development timelines	

Sensorion

Q&A SESSION CLOSURE

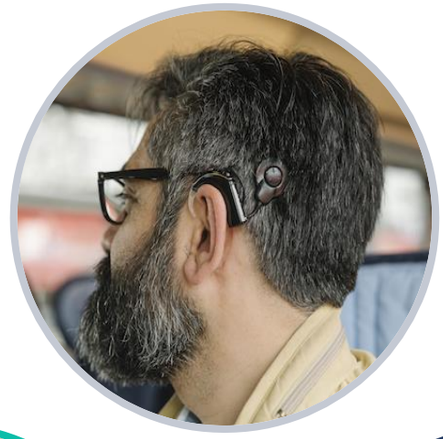
Nawal Ouzren
CEO, Sensorion

April 6, 2023



Transforming Lives, Connecting People

Our vision is to help people with inner ear hearing disorders to live life with unlimited connections





Sensorion

Sensorion Gene Therapy R&D Day

April 6, 2023

Institut de l'Audition
Institut Pasteur Center
Paris, France