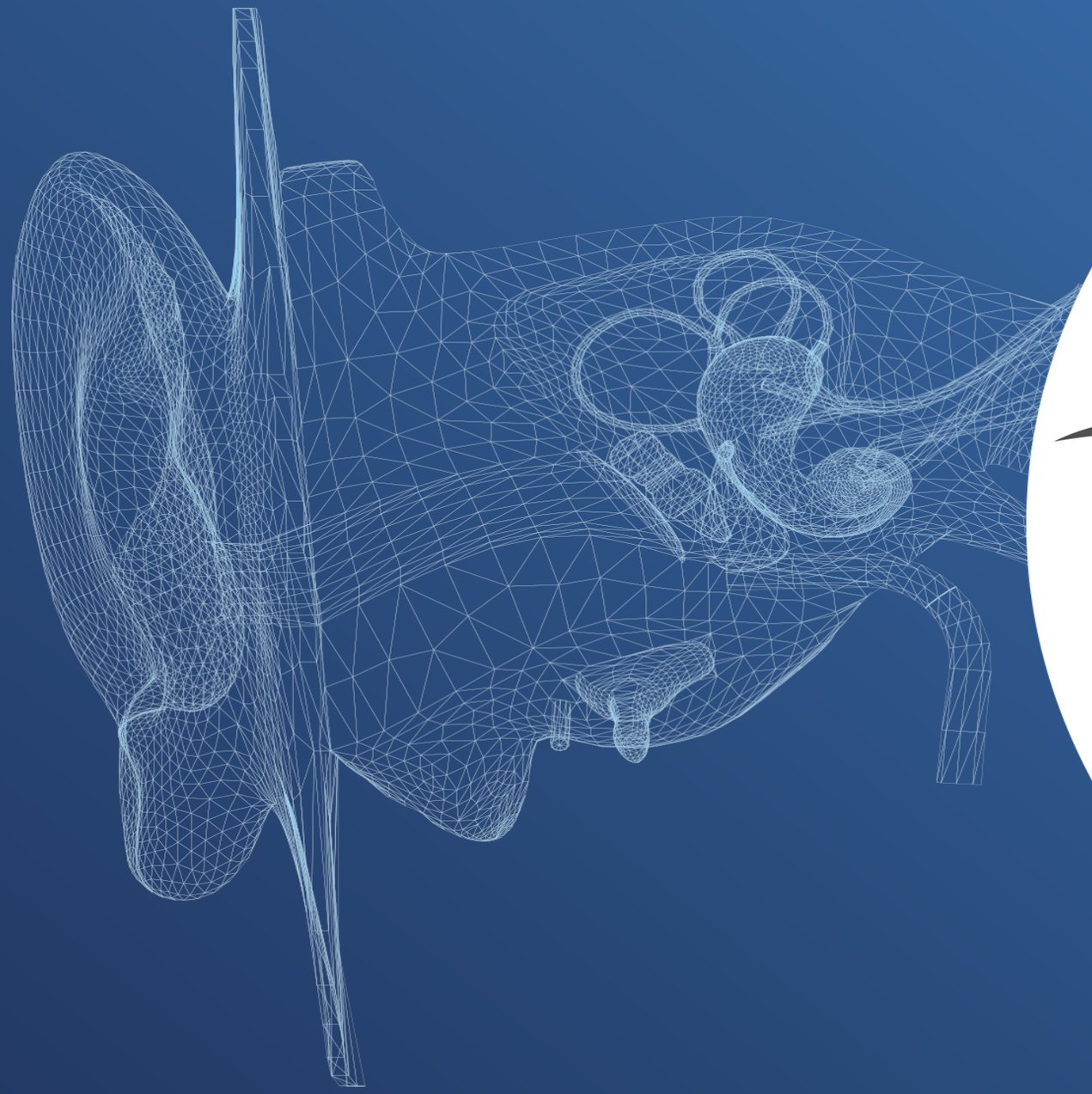

Sensorion

Assessment of an Adeno Associated Vector-Based Gene Therapy (GJB2-GT) for the Non-Syndromic Deafness 1 (DFNB1) in Cynomolgus Monkeys

Laurent Désiré, PhD

ARO 2024

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Sensorion's Gene Therapy Programs Target Rare Auditory Diseases

FIRST PROGRAMS RESULTING FROM THE INSTITUT PASTEUR COLLABORATION

OTOFERLIN DEFICIENCY

- Patients with mutations in OTOF suffer from severe to profound sensorineural prelingual non-syndromic hearing loss
- Otoferlin deficiency could be responsible for up to 8% of all cases of congenital hearing loss
- Prevalence ~20,000 in the USA + EU
- Incidence ~1,100 per year in USA + EU
- EU and US ODD, US RPDD
- Clinical Trial Application Filed (UK MHRA & Europe)

GJB2-RELATED HEARING LOSS

Three forms of hearing loss are associated with *GJB2* gene mutations:

- Congenital[7]
- Progressive childhood onset[8]
- Early onset of severe presbycusis[9]

- Prevalence of congenital and childhood onset forms are estimated to be **~210,000** patients as around 50% of autosomal recessive non syndromic hearing loss cases are thought to be from *GJB2* mutations[10, 11]
- Patients between 30- and 69-years old thought to be affected by a monogenic form of presbycusis due to *GJB2* mutations[11]

Sources: Akil et al. 2019 (link), Orphanet (link), NIH (link), company estimates based on publicly available population data, Chardan 2020 report, Bryan, Garnier & Co 2019 report, Institut Pasteur, Zhu Y, et al (2015), Boucher S, et al (2020), Tsukada K, et al (2020)

Children are usually **diagnosed during routine newborn screening** and current SoC is cochlear implantation prior to language acquisition

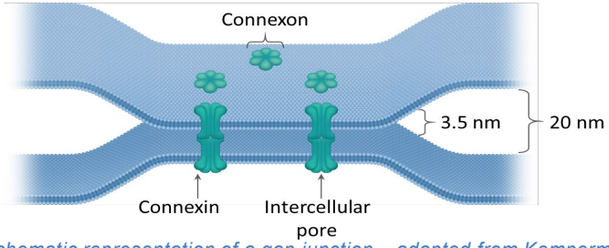
GENE THERAPY HAS A LIFE-CHANGING POTENTIAL FOR THESE AUDITORY DISEASES

Connexin 26: a Gap-junction Protein Encoded by *GJB2* Gene and Responsible for Tissue Homeostasis

Mutations in the Gene Lead to Deafness

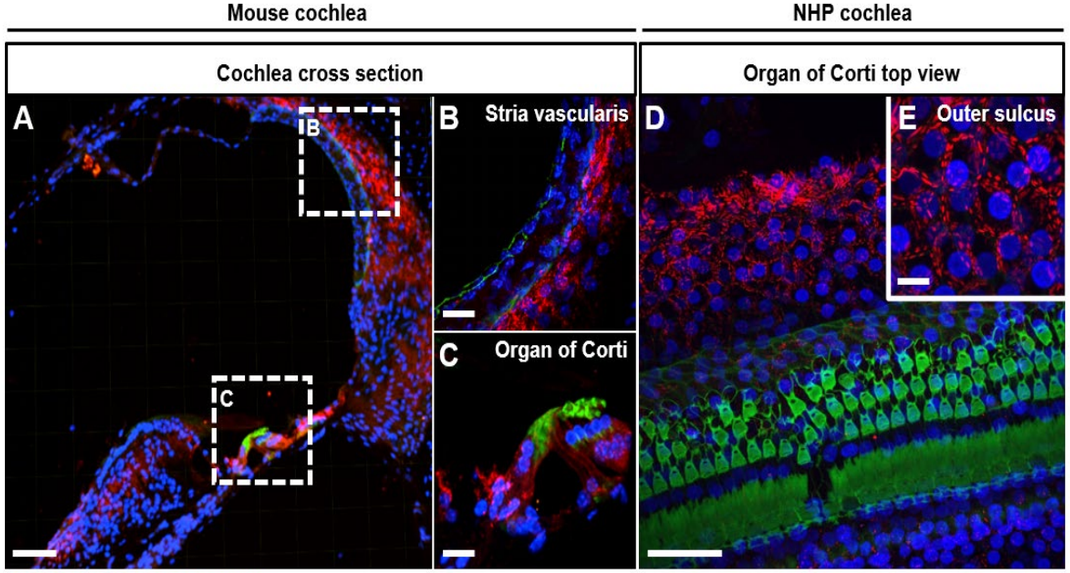
Background

- *GJB2* is the gene encoding for the Connexin 26 protein; one of 20 known connexins
- Cx26 and Cx30 proteins are the dominating connexins in the cochela; heteromeric or heterotypic hexamers forming Gap Junctions
- Gap Junctions are key for the intercellular exchange of molecules (miRNA, glucose, ions, etc.) hence responsible for tissue homeostasis
- More than 100 recessive mutations origin Cx26 truncation / deletion leading to non-syndromic hearing loss and deafness, most are addressable via gene replacement
- Severity of hearing loss correlates with degree of loss of GJB2 function



Schematic representation of a gap junction – adapted from Kemperman, Hoefsloot and Cremers J R Soc Med 2002;95; 171-177

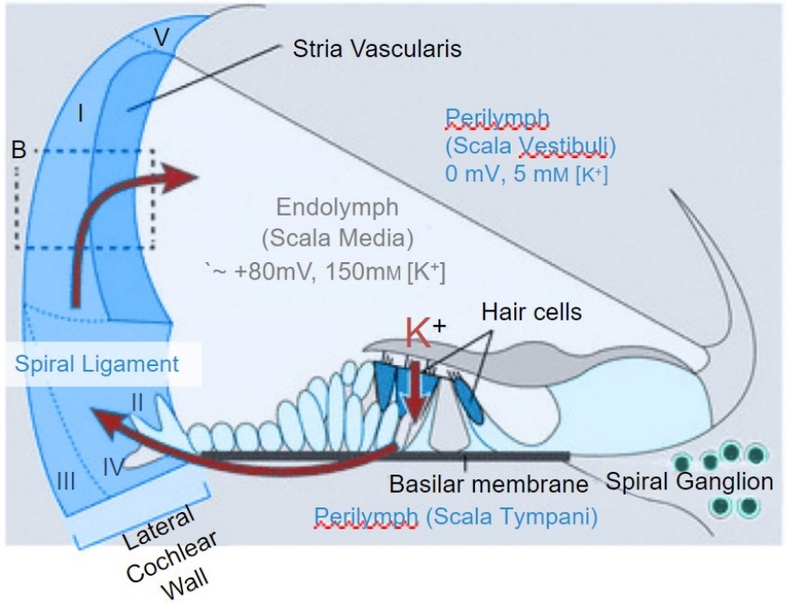
Gjb2 expression in the cochlea



- Supporting cells of the organ of Corti
- Fibrocytes of the spiral limbus and the lateral wall
- Intermediate and basal cells of the stria vascularis
- Not expressed in hair cells

Goals of *GJB2* Gene Therapy

Cx26 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.

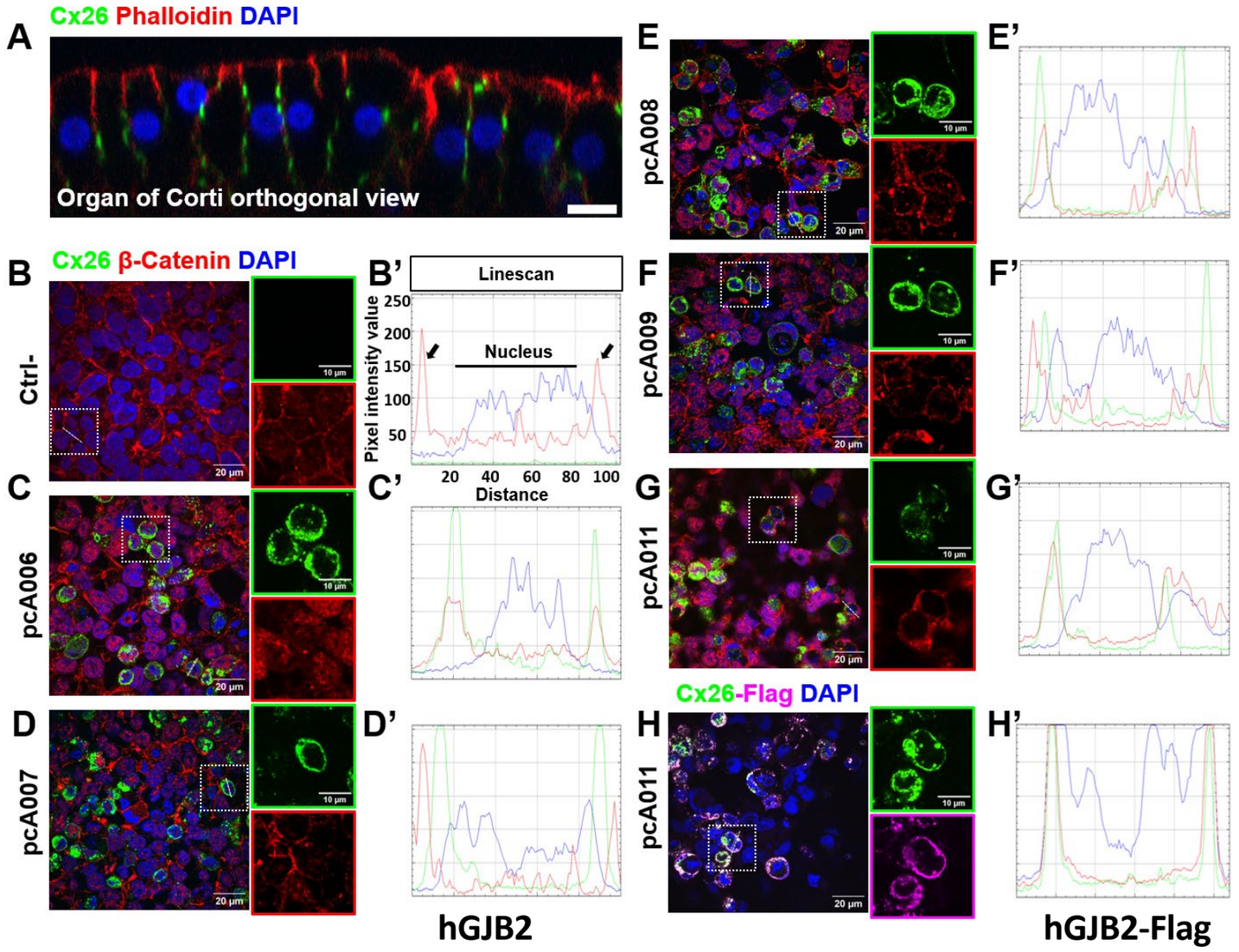
- GJB2 mutations induce loss of Cx26, disrupting K+ homeostasis and endocochlear potential
- The aim of GJB2-GT is to
  - Restore gap junctions in the cochlea
  - Restore hair cell function and prevent their degeneration
  - Restore hearing thresholds
- GJB2 cDNA length is 681 bp and is compatible with the use of a single AAV

GT-GJB2 Initial Criteria for Development

CRITERIA	LEAD CANDIDATE
Natural and synthetic AAV capsid libraries screening for broad coverage of target cells	
Expression cassette design for high-level of target cells transduction	
Avoiding off-target expression (i.e. hair cells) : promoter and regulatory sequences design	
Limited off-target tissue biodistribution	
Surgical approach developed and mastered by ENT surgeons	

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

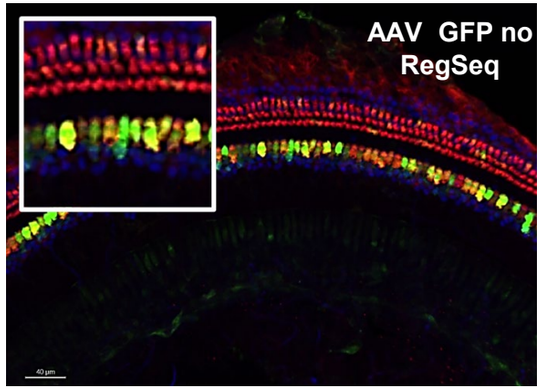
In Vitro Evaluation

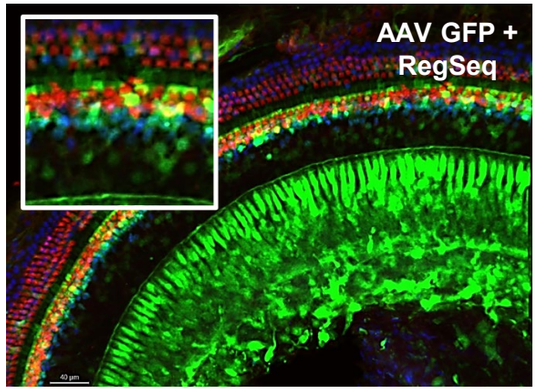


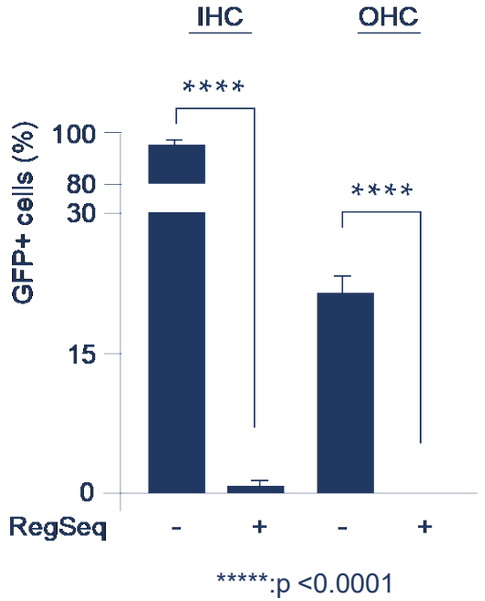
- Cx26 is addressed at the plasma membrane
- Addition of a Flag tag does not impact localization
- Next step is demonstration of functional gap junctions

Our Lead Candidate Demonstrates Broad Coverage of Relevant Cochlear Cells While Detargeting Hair Cells

WT mouse







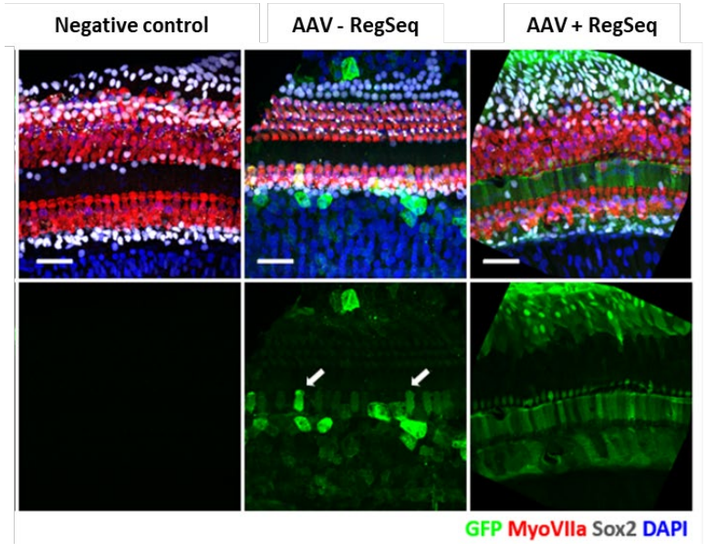
Non- human primate

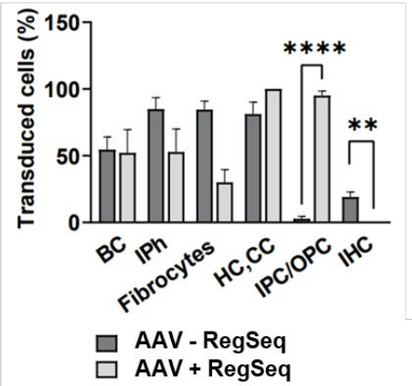
Combining 2 common surgical technics: cochlear implant and stapedotomy

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

Proprietary injection device developed to inject a defined volume at a controled flow rate

Cleared for clinical use

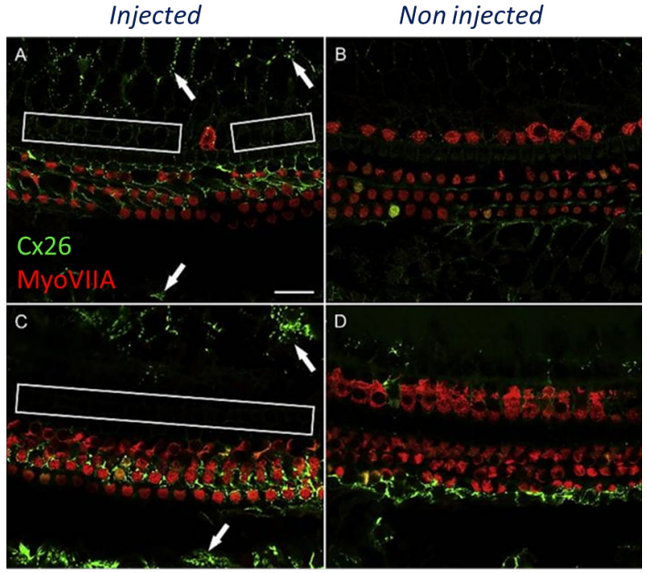


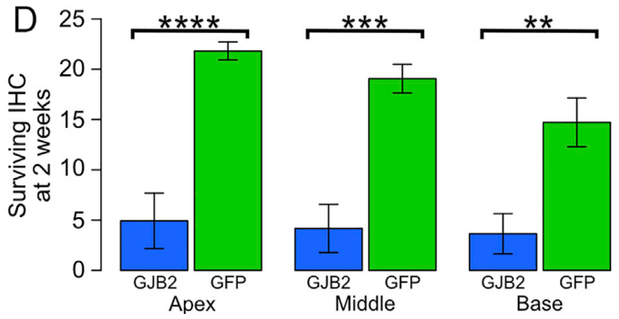


IHC: inner hair cells, BC: border cells, DC: Deiter cells, HC: Hensen cells, CC: Claudius cells, Iph inner phallengeal cells, IPC/OPC: inner/outer pilar cells

Evidence for Long-term Local Tolerability in Mice

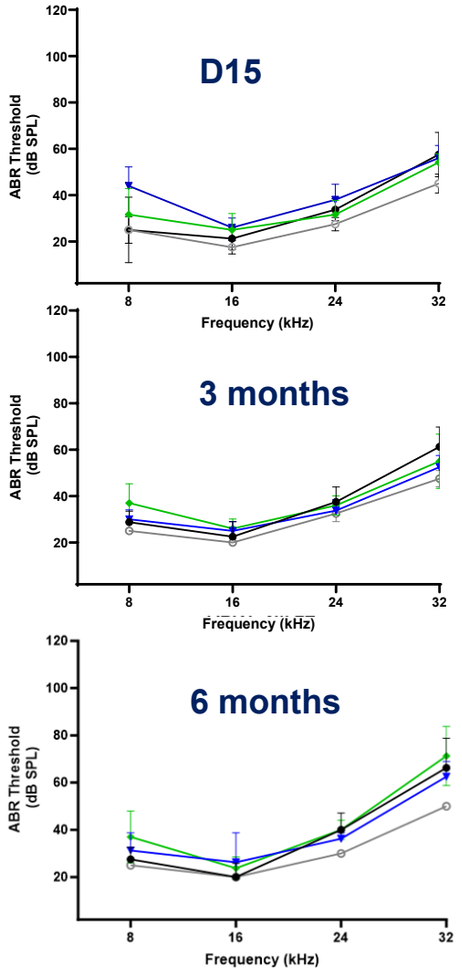
Example of ectopic Cx26 expression in HC and cell loss in WT mice





Guo et al. Mol Ther Methods Clin Dev. 2021 Oct 1;23:319-333.

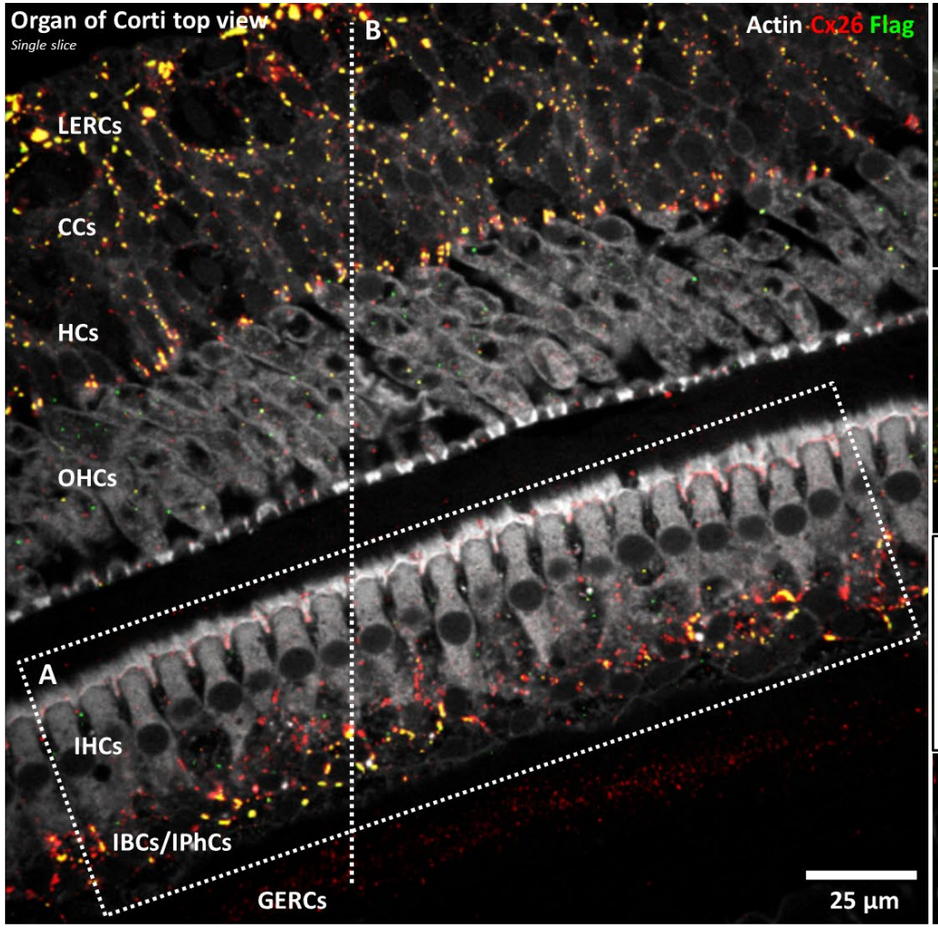
ABR thresholds in WT mice following GT-GJB2 injection

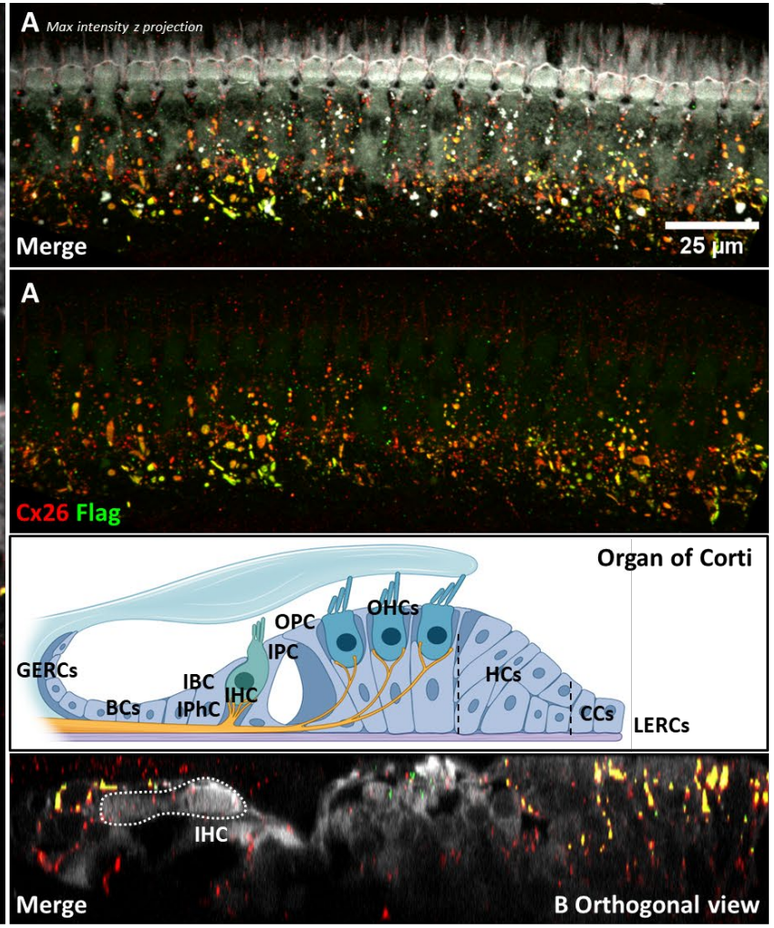


- GT-GJB2 FLAG
- GT-GJB2
- FVB mice - not injected
- FVB mice - vehicle

- No impact on ABR up to 6 months following GT-GJB2 injection
- Histology ongoing

Correct Cx26 Delivery In Support Cells Using GT-GJB2 Flag In NHP





Cell types	
Claudius cells (CC)	✓
Deiters cells (DC)	✓
Great epithelial ridge cells (GERCs)	✓
Hensen cells (HC)	✓
Inner border cells (IBC)	✓
Inner hair cells (IHC)	
Inner phalangeal cells (IPhC)	✓
Pillar cells (PC)	✓
Lateral epithelial ridge cells (LERCs)	✓
Outer hair cells (OHC)	
Claudius cells (CC)	✓
Stria Vascularis (SV)	✓

- Expanded knowledge of targeted cells populations in NHP
- No expression in HC confirmed
- No morphological defects observed 3 and 9 weeks after intracochlear administration

GT-GJB2 Exploratory Toxicity and Biodistribution Study in NHP

Study design

- N=4, M/F, juvenile at surgery
- 2 timepoints (1M, 3M)
- Same route of administration and injection device intended in human
- Conducted at an independent CRO under GLP-like status

Study results

- **GT-GJB2 is well tolerated** and did not induce any macroscopic/organ weight changes or local/systemic microscopic findings
- **Normal cochlear histology**
- ECG, clinical pathology, hematology and CRP : no findings
- **Biodistribution – 20 tissues**

qPCR analysis on several tissues

Tissues list	
Brain - Medulla	*Heart left ventricule*
Brain - Thalamus	*Kidney right*
Brain - Auditory nerve	*Ovaries / Testis*
Brain - Auditory cortex	*NL Mesenteric*
Brain - Cortex frontal	*Skeletal muscle*
Spinal cord cervical	*Liver lobe lateral*
Spinal cord Lombar	*Optical nerve*
Spinal cord thoracic	*Dorsal root lombar*
Spleen	*Brain cerebellum*
Lungs lobe apical	*LN parotid / cervical*

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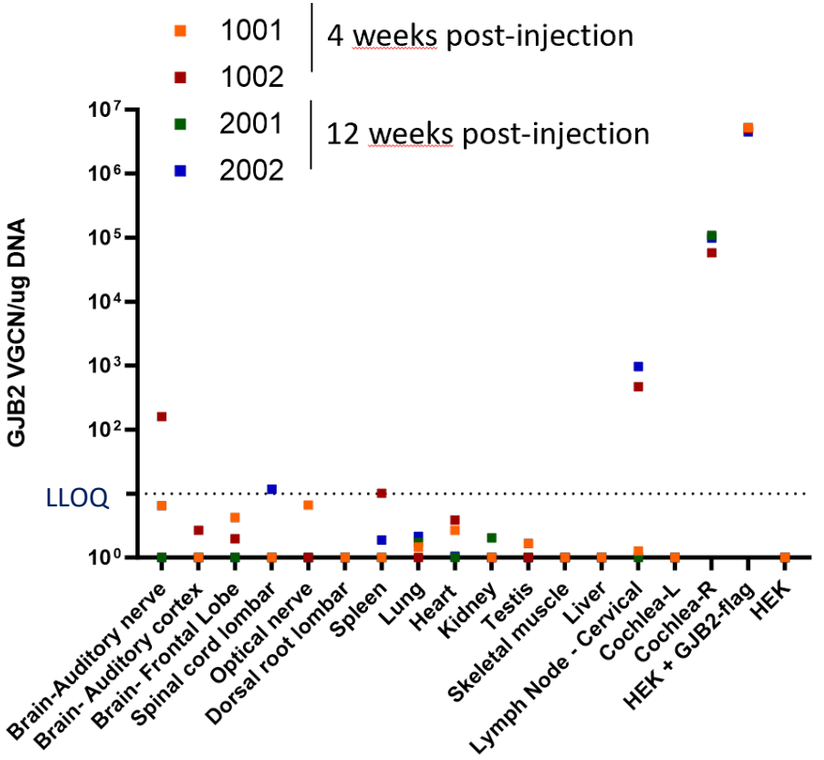
- ECG, clinical pathology, hematology and CRP : no findings
- **Biodistribution – 20 tissues**
  The vast majority of the vector remains in the injected ear, no dissemination was observed in gonads, main organs, DRG

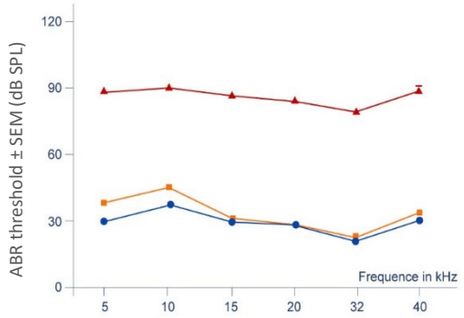


Efficacy in a Mouse Model of *GJB2* Deficiency

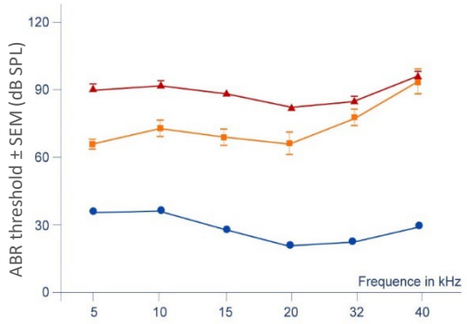
Proof Of Concept In Progressive Mouse Model

Conditional knock-out mouse model leading to 2 phenotypes

ABR threshold - 1 month after birth



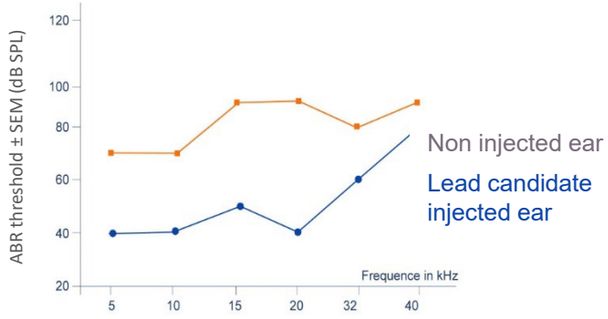
ABR threshold - 6 months after birth

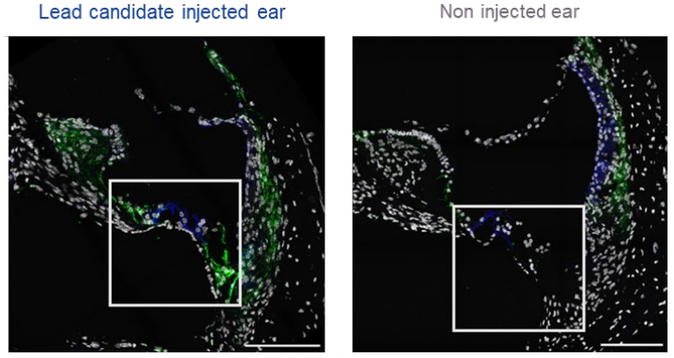


Control mice Congenital-like Profound *Cx26* ↓↓↓ Progressive*Cx26* ↓

- GJB2 deletion during or after development often results in hearing loss and cellular degeneration (HC, SC, SGN) in mice
- Severe observed cochlear phenotypes can preclude their use for gene replacement therapy
- New models are needed that can provide a window of opportunity for treatment

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





Cx26 *AcTub* *DAPI*

- Cell types that critically express Cx26
- Prevention of hearing loss is associated with re-expression of Cx26 in target cells
- Efficacy studies in GJB2 cKO mice are currently ongoing in large cohorts

From Sensorion R&D Day, 2023

Summary
GJB2-GT Is Moving Into IND/CTA Enabling Studies

CRITERIA	GT-GJB2
Broad coverage of cells naturally expressing Cx26, detargeting HC	✓
Well tolerated in mice and NHP	✓
Limited off-target tissue biodistribution	✓
Surgical approach developed and mastered by ENT surgeons	✓
Hearing rescue in mice models adressing the different intended populations	→
Preclinical IND/CTA enabling studies	→
International Natural History Studies to prepare execution of the clinical trial	→

European Natural History Study OTOCONEX ✓

Natural History Study in collaboration with Sonova ✓

Acknowledgements

Arnaud Giese
Rafik Boudra
Lise Barrot
Emilie Bousquet
Christine Le Bec
Audrey Broussy
Selma Dadak
Julie Duron Dos Reis
Laura Gallot
Anne-Gabrielle Harrus
Anne-Gabrielle Harrus
Pauline Liaudet
Guillaume Olivier
Anais Pages
Géraldine Petit
Sandra Pierredon
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Crystel Bonnet
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Amrit Estivalet
Andrea Lelli
Solène Roux
Virginie Wong Jun Tai
Muriel Sudres
Nicolas Michalski
Christine Petit

Jerome Nevoux
Ghizlene Lahlou

Natalie Loundon

THANK YOU

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