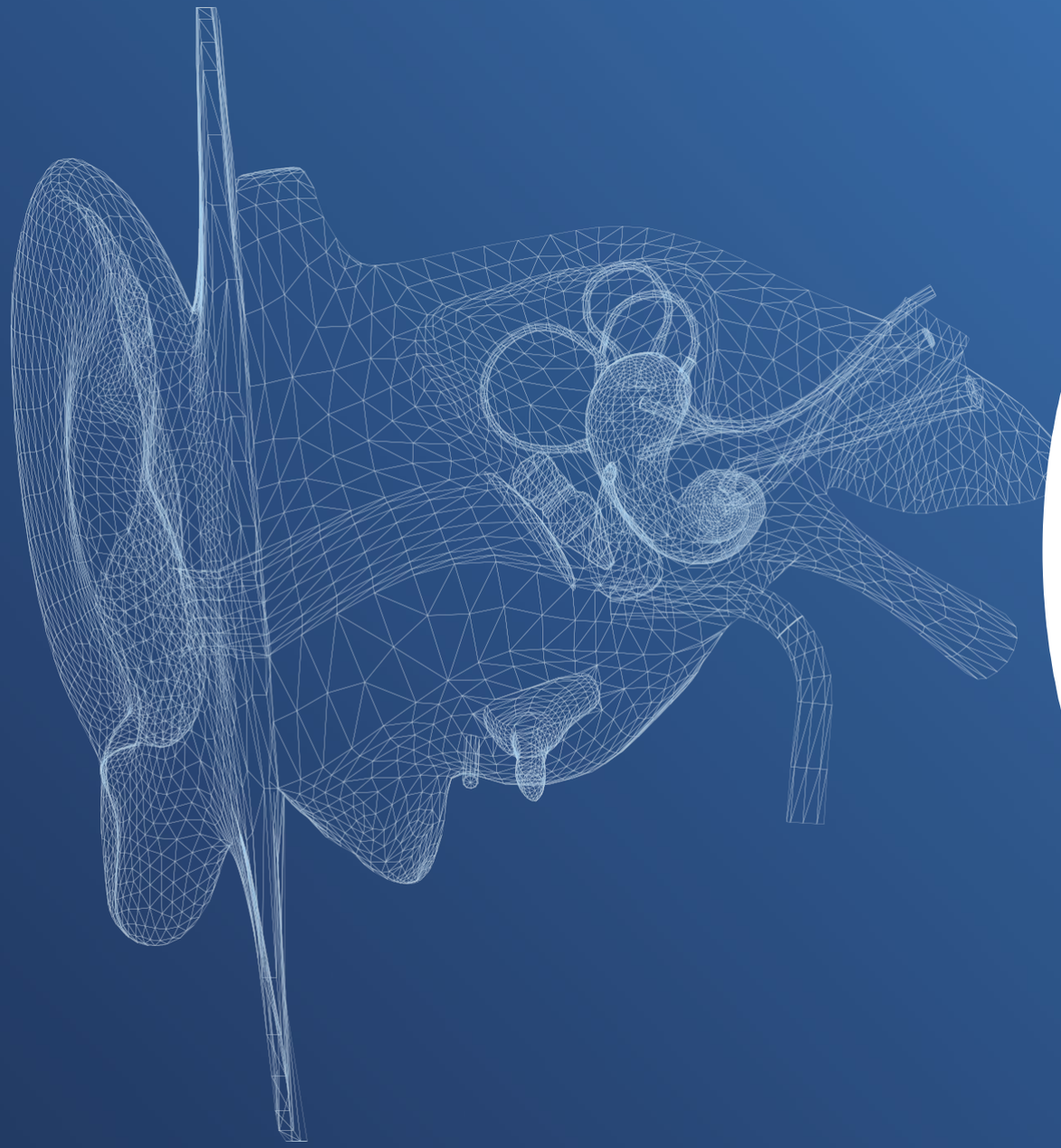

Sensorion

SENS-501 Gene Therapy for Autosomal Recessive Non-Syndromic Deafness 9 (DFNB9)

Laurent DESIRE, 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[10, 11]

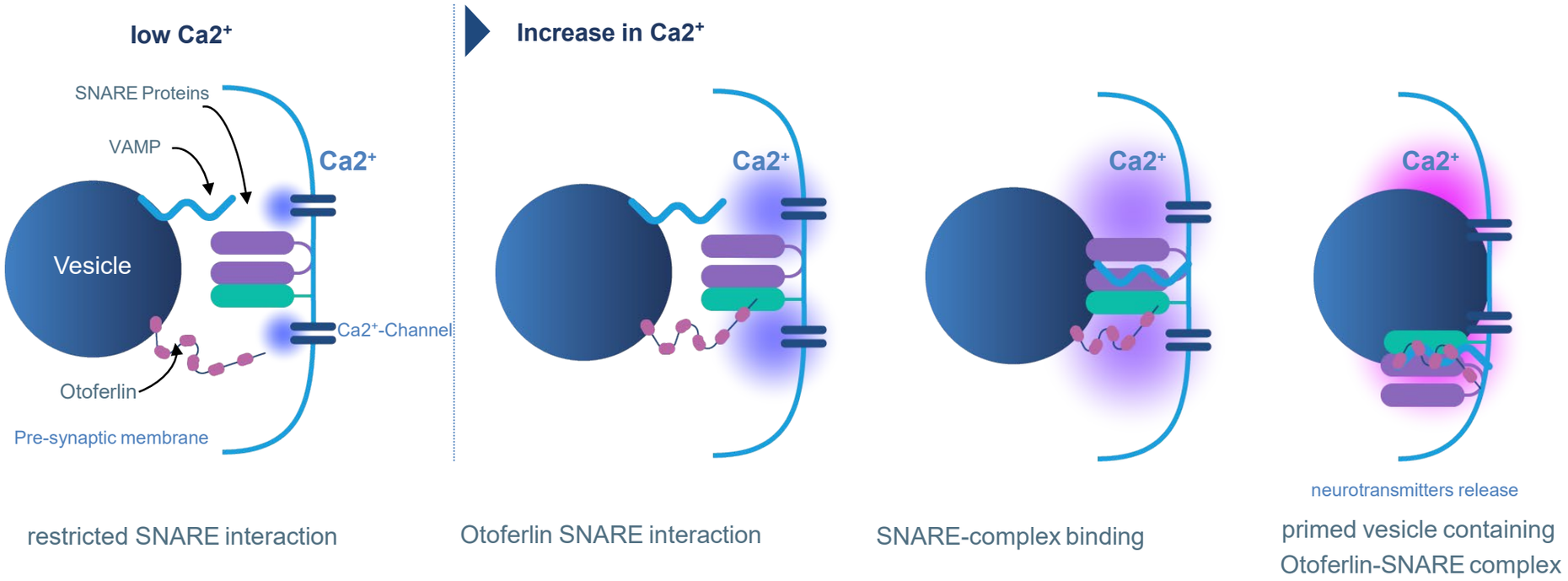
- **~100,000** patients between 30- and 69-years old thought to be affected by a monogenic form of presbycusis due to *GJB2* mutations[11]

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, Boucher et al. 2020 (link)

DELAYED DIAGNOSIS – NOT SUSPECTED AT FIRST SIGHT

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

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

Rationale for OTOF Mutation-associated Hearing Loss Gene Therapy

SENS-501 (OTOF-GT) to restore physiological hearing

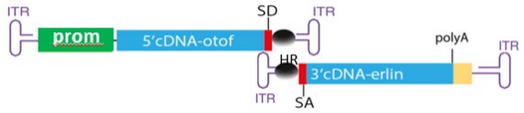
- Well understood biology and pathology of the otoferlin deficiency
- Full functionality of the remaining chain
- High specificity for the inner hair cells (IHCs), no off-target effect expected

- Pilot program demonstrating that GT is a relevant medical approach for the inner ear
- Establish understanding of GT in the inner ear by the Regulators and the 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 eligibilty for voucher in the US

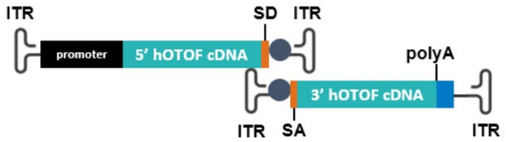
Current strategies for OTOF gene therapies

Dual AAV - Different serotypes and promoters[1-5]

Sensorion
AAV8

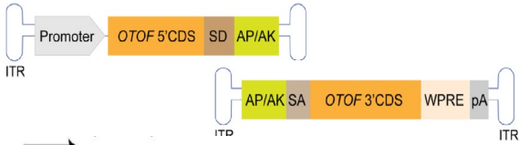


AKOUOS
ANC80

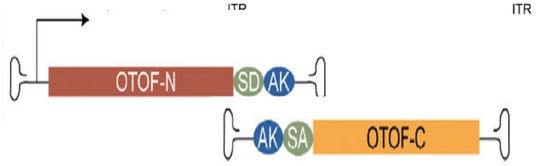


Decibel THERAPEUTICS™
AAV1

Shanghai Refreshgene Therapeutics
AAV1

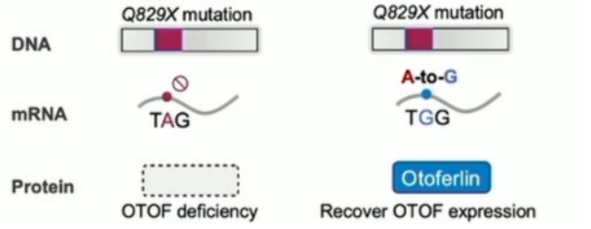


Suzhou Otovia Therapeutics
AAV



Dual AAV - Protein trans-splicing of N- and C-terminal otoferlin[6]

RNA Base conversion (correction of Q829X stop mutation)[7]



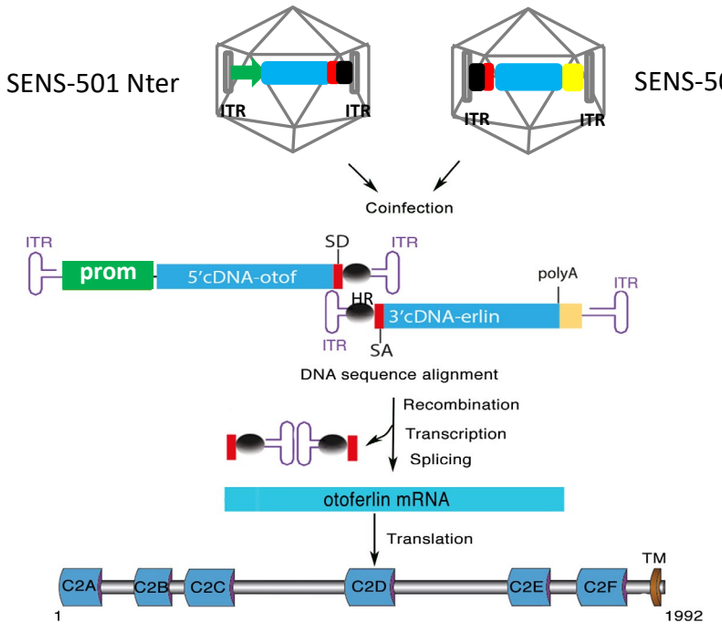
[1] Sensorion (link), [2] Akouos (link), [3] Decibel (link), [4] Mol Ther Methods Clin Dev 2023/Lancet 2024, [5] Adv Sci (Weinh). 2024, [6] Hum Genet 2023, [7] Mol Ther 2023

Development Strategy

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 ENTs surgeons	✓
Natural History Study preparing execution of the clinical trial	✓
Regular engagement with regulatory agencies	✓

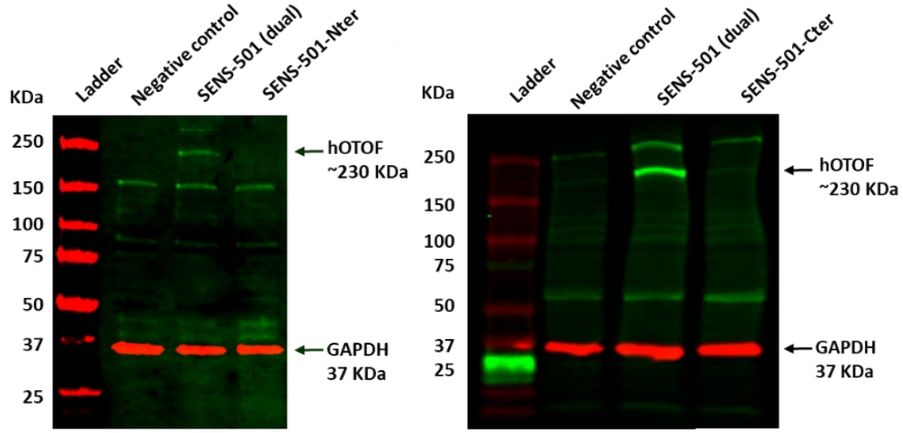
SENS-501 Is a Dual AAV8 Containing The Coding Sequence Of Human Otoferlin, Allowing Expression Of Full-length Otoferlin

Schematic hybrid dual AAV8



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

In vitro expression of full length Otoferlin protein

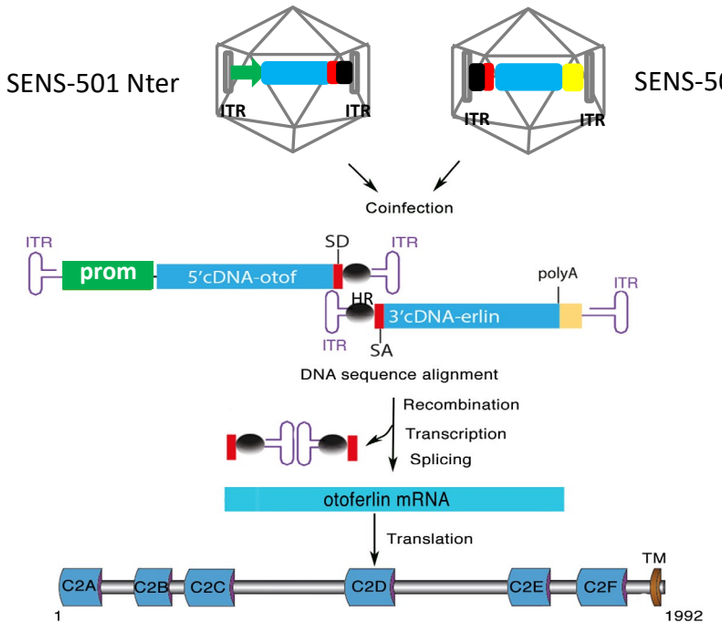


- Highly efficient recombination (e.g. full length mRNA)
- Efficient splicing (e.g. full length hOTOF protein expression)
- Ratio 1:1 selected for in vivo studies
- No Otoferlin protein expression with single vectors (confirmed by Mass Spectometry)

bp: base pair, kDa: kilo Dalton, MK : ladder

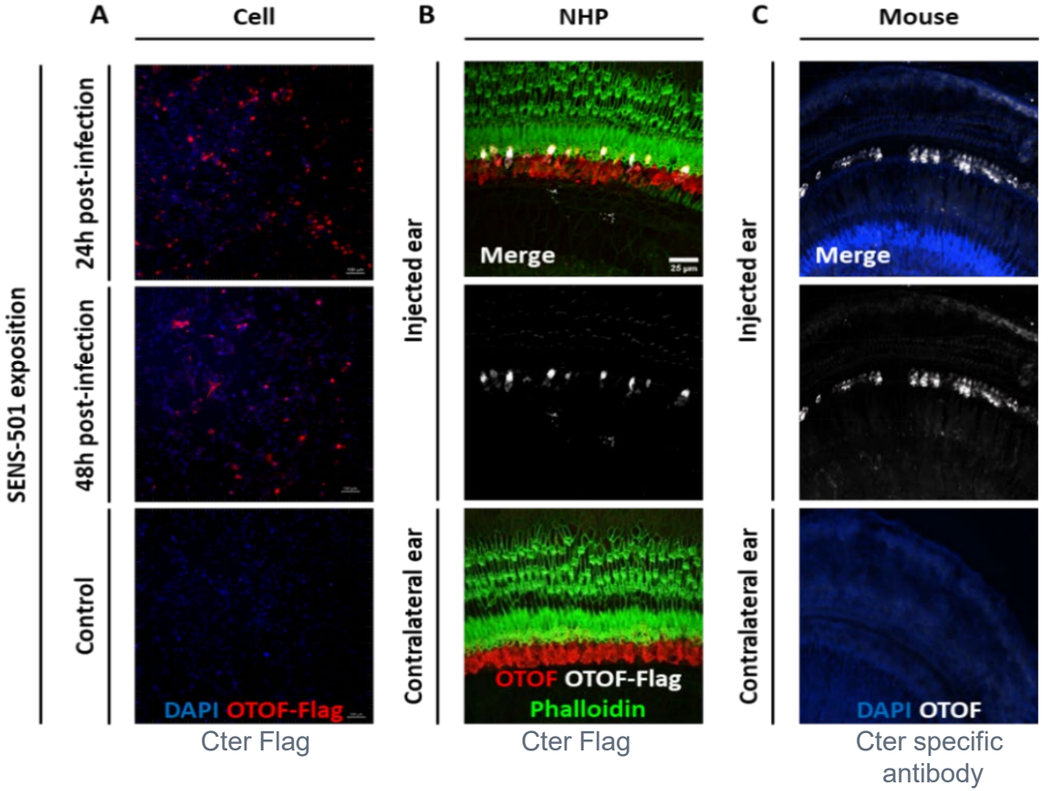
SENS-501 Is a Dual AAV8 Containing The Coding Sequence Of Human Otoferlin, Allowing Expression Of Full-length Otoferlin

Schematic hybrid dual AAV8



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

In vivo expression of full length Otoferlin protein



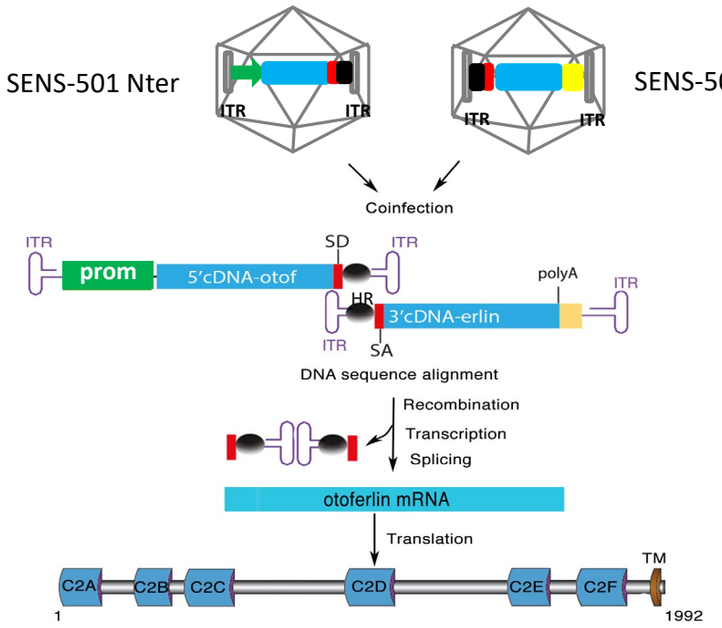
- Recombination and Otoferlin protein expression in 3 models

NHP: OTOF-Flag (tag sequence fused in frame with the Cter Otoferlin)

Mouse: SENS-501 injected in Otof -/- mutant mice; Cter specific antibody

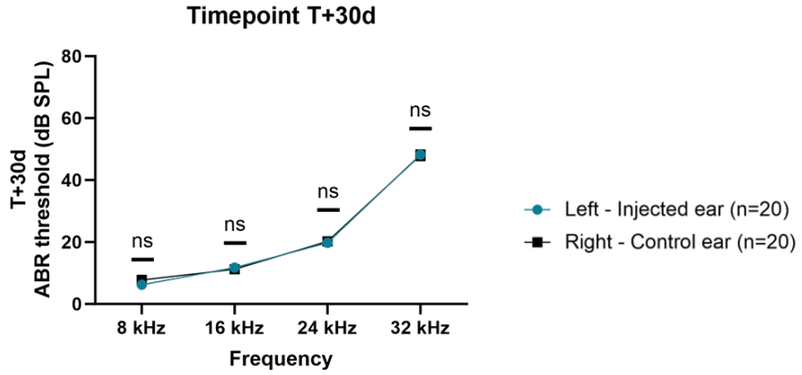
SENS-501 Is a Dual AAV8 Containing The Coding Sequence Of Human Otoferlin, Allowing Expression Of Full-length Otoferlin

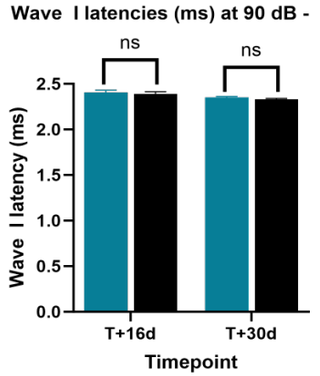
Schematic hybrid dual AAV8

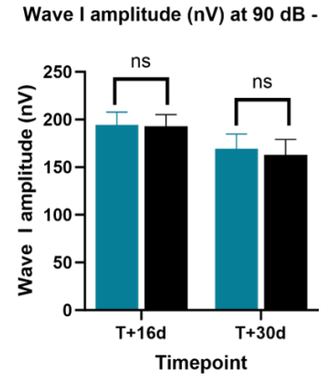


ITR: Inverted Terminal Repeat; SD/SA: Splicing Donor/Acceptor sequence, HR: Homology Region

No deleterious impact on cochlear histology and ABR at high dose in WT mice







SENS-501 Efficacy is Supported by multiple *In Vivo* Studies Conducted in a Translational Model of Otoferlin Deficiency

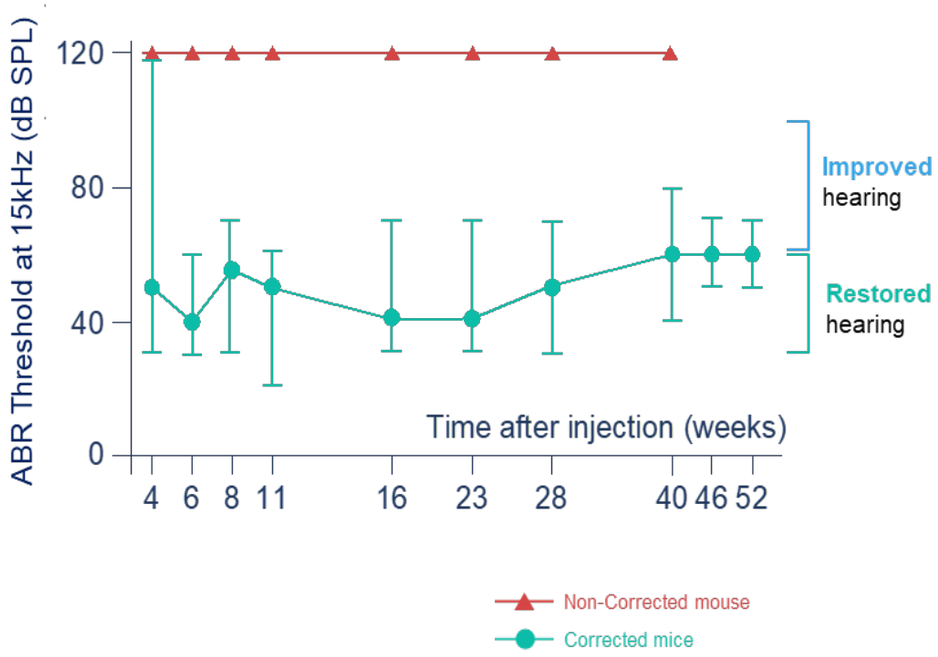
Dual vector	Treatment OTOF -/- mice[1]	Duration	Main results[2]
AAV8 – **murine OTOF**	Before hearing onset (P10)	1 year	• Stable & long-term restoration as early as 4w post injection • No adverse events observed
AAV8 – **murine OTOF** AAV8 – **human OTOF**	After hearing onset (P17-p25)	6 months	• Stable & long-term restoration as early as 4w post injection confirmed in mature mice • No adverse events observed
SENS-501	After hearing onset (P17-P25)	10 months	• Stable & long-term restoration as early as 4w post injection • No adverse events observed • Dose response • Behavioral test (startle reflex) confirms hearing restoration

[1]: Akil et al., PNAS 2019; [2]: Olivier et al. ASGCT 2023 link

SENS-501 Leads To Long-term Hearing Recovery In OTOF-/- Mice

Long-term hearing restoration

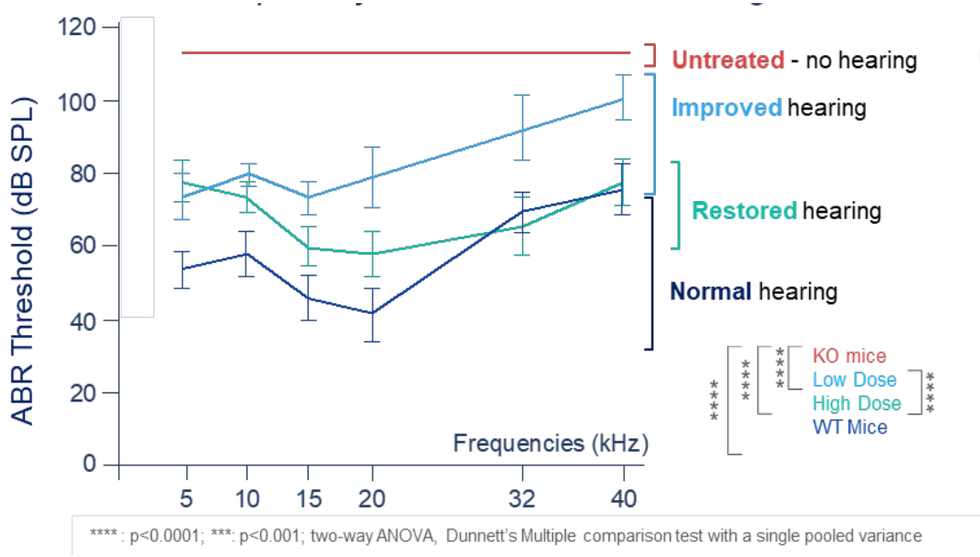
AAV-mOTOF injected in mice before hearing onset

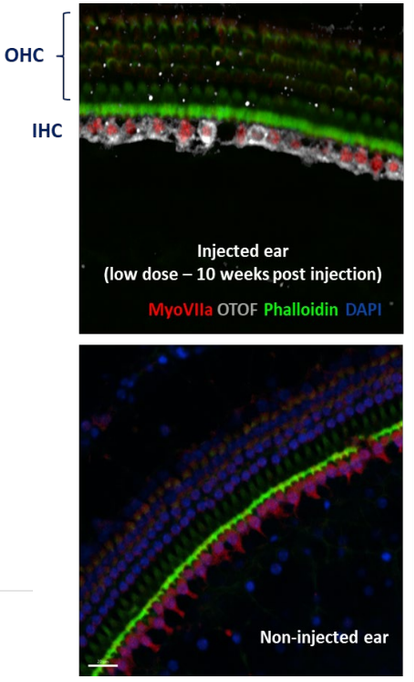


- Durable hearing restoration in Otof-/- mice by dual AAV-OTOF directly delivered to the inner ear up to one year post-injection

Hearing restoration correlates with de novo OTOF expression

SENS-501 injected in mice after hearing onset





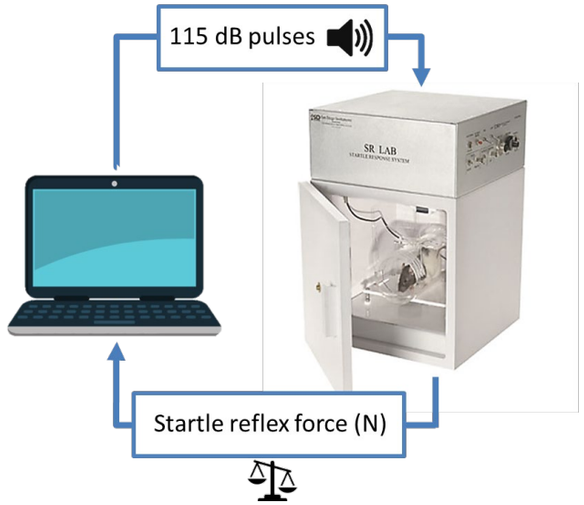
O/IHC: Outer/Inner Hair Cells

- Long term (up to 10 months) efficacy in Otof-/- mice
- Dose studies allowed to define minimal active dose (MABEL)
- Selective Otoferlin expression in Inner Hair Cells with normal subcellular localisation
- No expression in contralateral ear

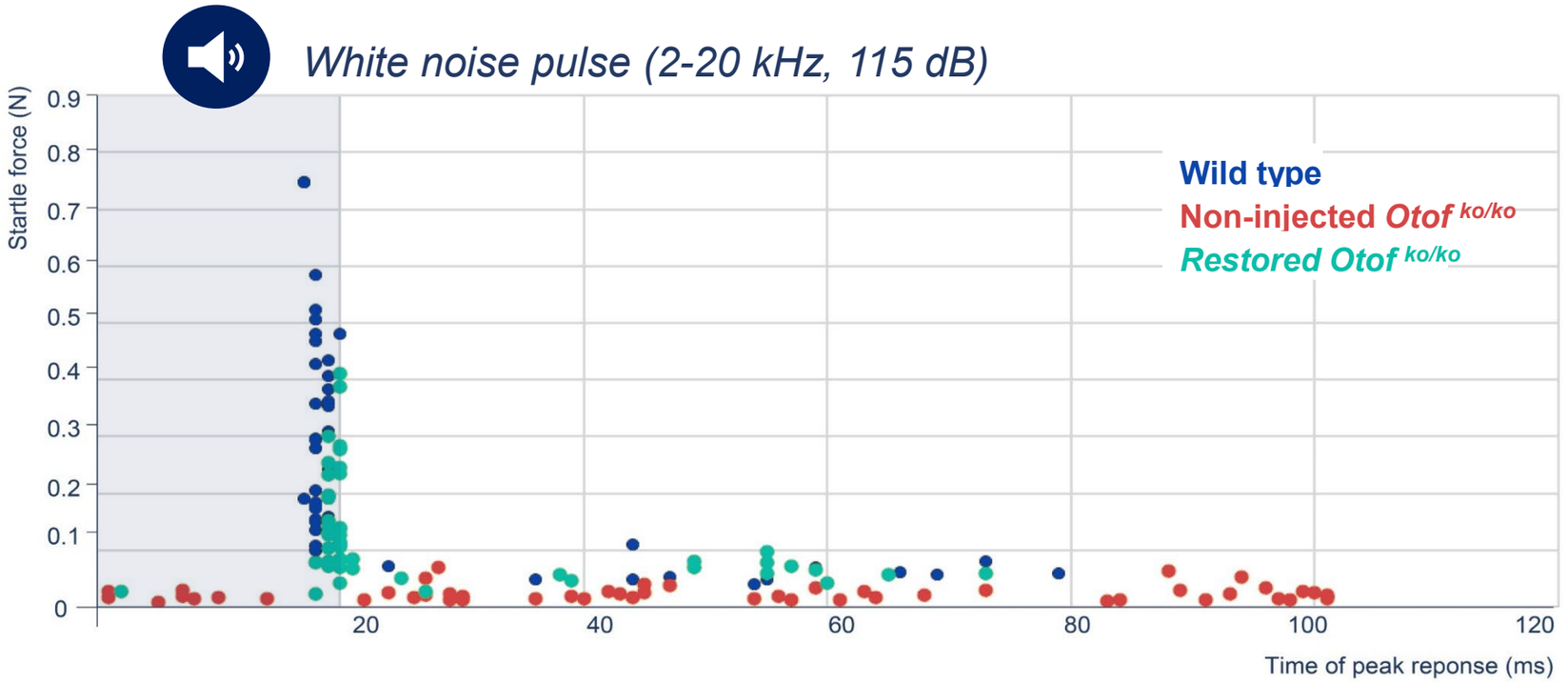
Olivier et al. ASGCT 2023 link

SENS-501 Leads To Restoration Of The Startle Reflex In OTOF-/- Mice

Startle platform



Behavior test based on hearing recovery implemented in P14 Otof-/- mice



- **Restoration of the startle reflex in Otof-/- mice**, efficient integration of the sound stimulus

Olivier et al. ASGCT 2023 link

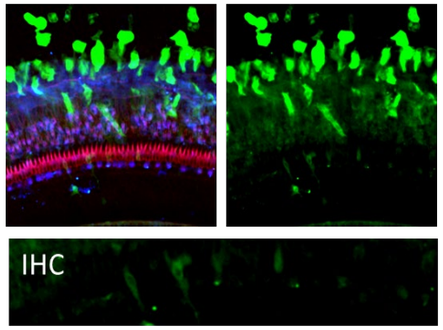
Dedicated Surgical Approach For Gene Therapy

Non-Human Primates injected through the round window membrane (RWI) with or without stapedotomy (stap) with AAV8 GFP

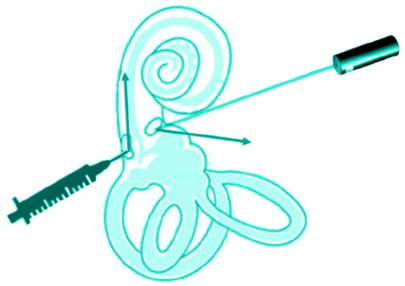
1 Fenestration

Used for cochlear implant

- Overpressure
- Limited volume
- Backflow
- Irregular transduction rate

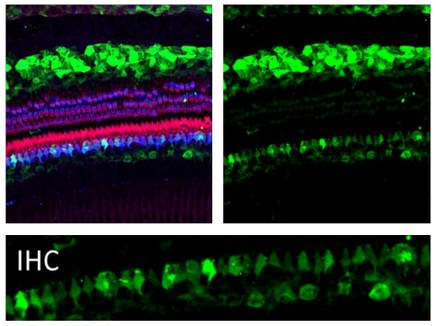


2 FENESTRATIONS
(Round window membrane + oval window)



Combining 2 common surgical technics: cochlear implant and stapedotomy

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



Surgical approach

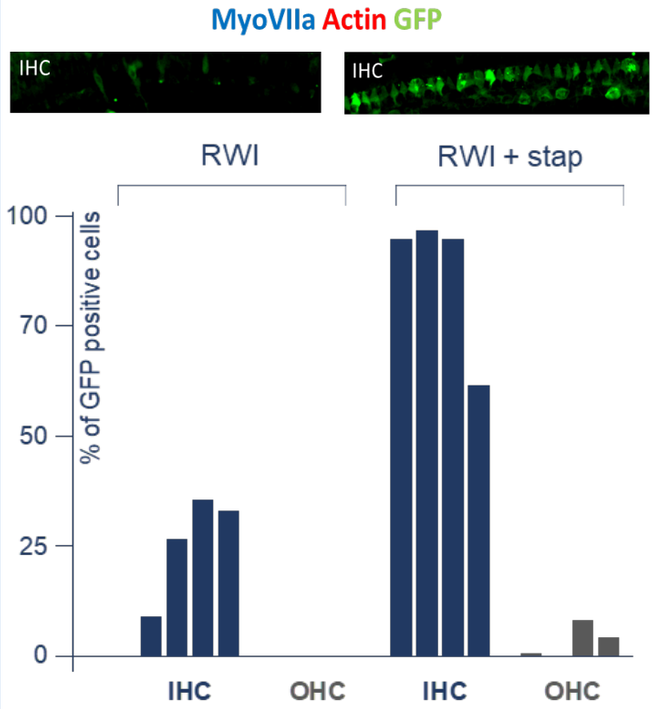
- Surgical procedure **mastered by ENTs surgeons**
- Optimized surgery uses **stapedotomy procedure** to maximize target cells exposure along the full length of the tonotopic axis
  - trans-canal approach
  - access to the canal through preauricular incision
- **Proprietary injection device developed** to inject a defined volume at a controled flow rate

See poster SU57

Dedicated Surgical Approach For Gene Therapy

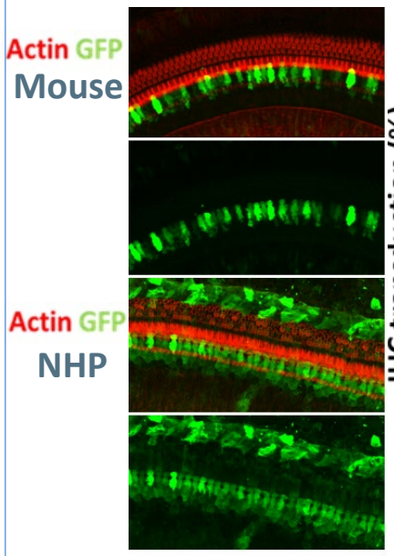
Non-Human Primates injected through the round window membrane (RWI) with or without stapedotomy (stap) with AAV8 GFP

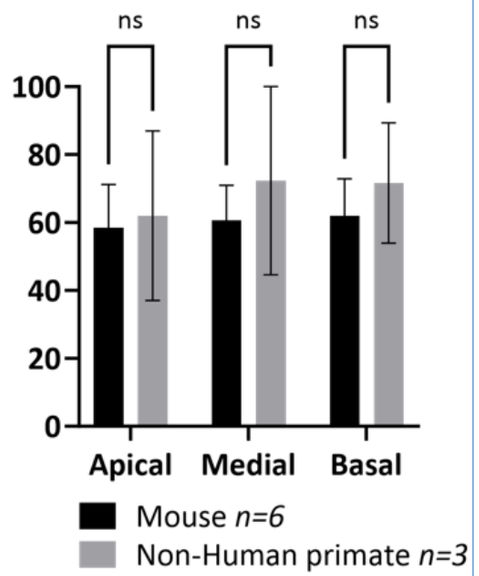
Efficient transduction in NHP from base to apex



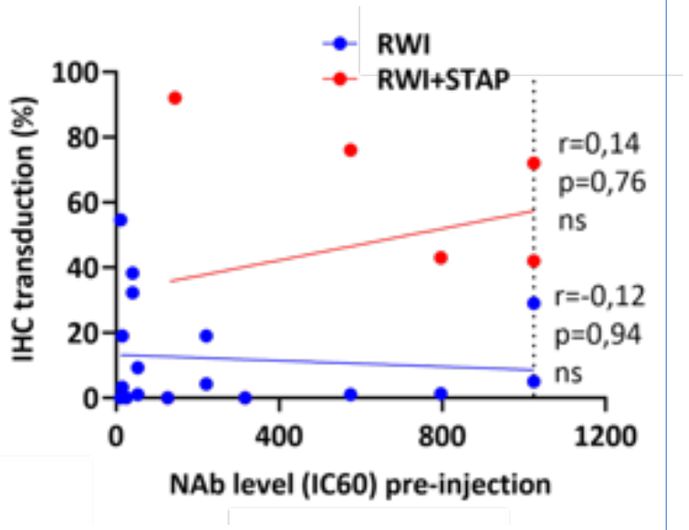
Cell counting from apex (left) to base (right)
I/OHC: Inner/Outer Hair Cells

Comparable transducibility mouse vs NHP





No impact of anti-AAV8 immunity on transgene expression in NHP



3-month GLP Toxicology and Biodistribution Studies In NHP

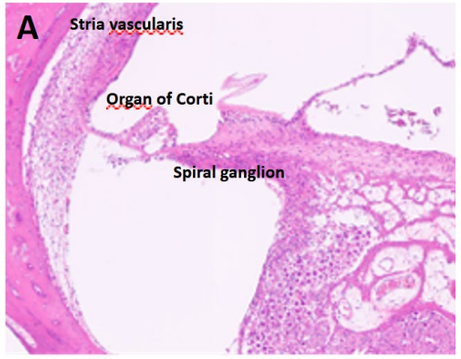
Study design

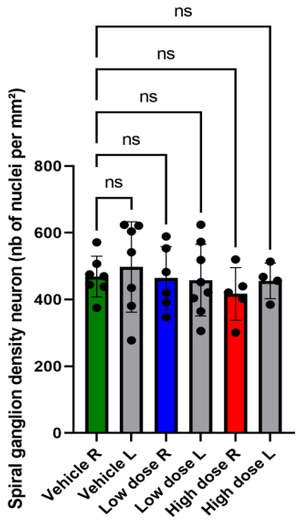
- **2 doses, vehicle group**
- **M/F, n=3/sex/group**
- **Juvenile at surgery**
- **Same route of administration and injection device intended in human**
- **Tested doses provide high safety margin vs intended clinical dose**

Toxicology

- **SENS-501 is well tolerated** and did not induce any macroscopic/organ weight changes or local/systemic microscopic findings
- **ECG, clinical pathology, hematology and CRP**: no SENS-501 related findings
- Immune response occurs in serum in the expected timeframe, is modest in occurence and magnitude, and is not accompanied with any findings

No local findings in the inner ear or vestibular system, the auditory nerve and the spiral ganglion





3-month GLP Toxicology and Biodistribution Studies In NHP

Study design

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- **Tested doses provide high safety margin vs intended clinical dose**

Biodistribution and shedding

- **The vast majority of the vectors remains in the injected ear, no dissemination** was observed in gonads, main organs and brain
  - Outside the inner ear, SENS-501 was quantified in cervical and parotid lymph nodes
  - Presence of vector DNA was not associated with any microscopic histological findings
- **Shedding: Limited persistence in fluids, vector persistence decreased over time**
  - Blood on Day 4,
  - Urine, feces, nasal swabs, saliva, tears on Day 16

SENS-501 Preclinical Development Status

- A 3-month single dose toxicology study aiming to assess toxicology, biodistribution, local tolerance and immunogenicity of intracochlear administration of SENS-501 in NHP (study SENS1100-TX-413).

- A 6-month single dose toxicology study aiming to assess toxicology, biodistribution, local tolerance and immunogenicity of intracochlear administration of SENS-501 in NHP (study SENS1100-TX-438).

- A 6-month single dose toxicology study aiming to assess toxicology, biodistribution and local tolerance of IV administration of SENS-501 in mice (study SENS1100-TX-414).

Overall, SENS-501 is well tolerated and did not induce any macroscopic/organ weight changes or local/systemic microscopic findings at the end of the observation.

Preclinical package allowed CTA filing in UK, EU in 2022

Phase 1/2 Audiogene Study (SENS-501) Approved in France
First Patient Communication Anticipated in H2 2024

Audiogene, a Phase 1/2 clinical trial in children aged 6 to 31 months to assess safety, tolerability, and efficacy of SENS-501 following unilateral injection into the cochlea

Audiogene Study Design

Pediatric patients, aged 6 to 31 months at the time of the injection
- Targeting the first years of life to maximize chances of acquiring speech and language

Single intra-cochlear unilateral injection

Dose escalation
- Primary endpoint: safety, tolerability

Dose expansion
- Primary endpoint: ABR (Auditory Brainstem Response)

Otoferlin “Audinnove” Consortium and ongoing Natural History Studies Provide Privileged Access To Patients And Surgeons

Audinnove consortium received Hospital-University Research (RHU) prize:

- The consortium is eligible to receive up to €9.7m to develop a Gene Therapy program addressing otoferlin deficiency
- Audioferlin: Natural History Study: clinical evaluation and selection of patients
- Database compilation with genotypic and phenotypic characterization of children with congenital hearing loss
- Phase 1/2 Gene Therapy study (financing up to 1st patient in the clinical study)

Audinnove consortium is key to the understanding of the epidemiology and to build awareness of the emerging gene therapies

Necker-Enfants Malades Hospital

- The first dedicated pediatric hospital in the world

The Reference Center for Genetic Deafness at Necker coordinates the French and European genetic deafness networks

Audinnove is financed by the French State, via the National Research Agency through the “Investing for the future” program (ref: ANR-18-RHUS-0007)

OTOCONEX: Natural History Study running across Europe to support identification of DFNB9 patients for Audiogene

- Multicentric (10 centers), 5 EU countries

AUDINNOVE CONSORTIUM MEMBERS

Sensorion

INSTITUT PASTEUR

Necker ENFANTS MALADES HÔPITAL UNIVERSITAIRE

FONDATION POUR L'AUDITION À L'ÉCOUTE DE LA VIE

SENS-501 (OTOF) Gene Therapy Program Status – Progressing

- Preclinical package completed ✓
- Injection device system development completed ✓
- GMP Drug product manufactured ✓
- CTA Approval in France ✓
- European Natural History Study OTOCONEX ✓
- First Patient Communication H2 2024 →

Acknowledgements

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Selma Dadak
Laura Gallot
Géraldine Petit

Christine Le Bec
Emilie Bousquet
Geraldine Honnet
Lionel Hofsepian
Laetitia Zara
Valerie Salentey
Ophelie Poujade
Yacobina-Laure Mbanga

Jerome Nevoux
Ghizlene Lahlou
Marie-José Lecomte
Saaid Safieddine
Baptiste Plion
Christine Petit

Natalie Loundon

Check-out our posters
SU56, SU57, S61