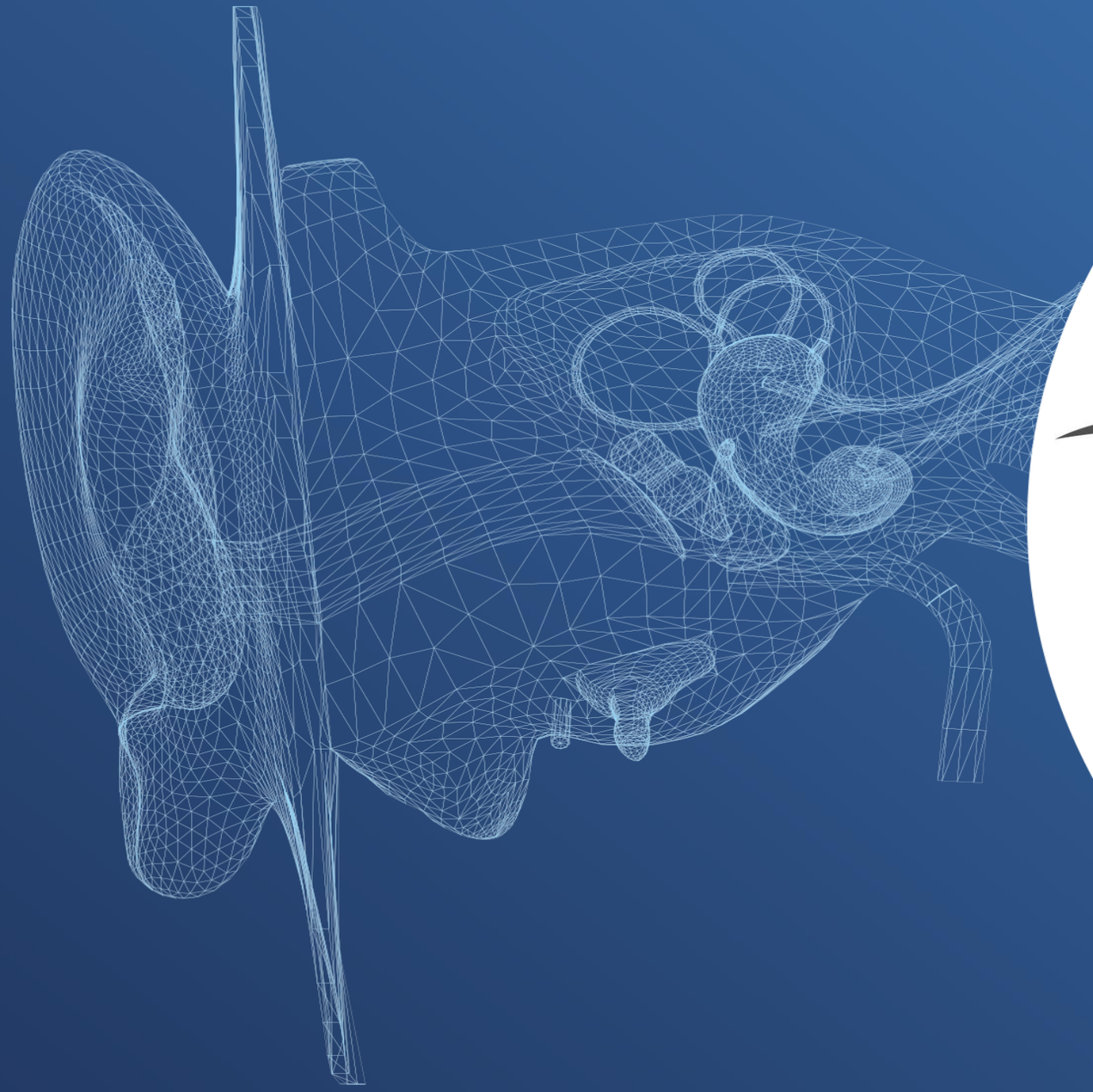


Sensorion

28TH OCTOBER 2021

SENS-401 CIO: ADDRESSING A HIGH UNMET MEDICAL NEED

DISCLAIMER

As a reminder, during today‘s webinar, we will make forward looking statements based on our current expectations. Our actual results may differ materially from such statement

Q&A

Today there will also be an opportunity to ask questions. Please wait until the end

PRESENTATION & REPLAY

The presentation will be available on Sensorion‘s website and a replay will be available later today

TODAY'S AGENDA

Introduction
Nawal Ouzren, Chief Executive Officer of Sensorion

Overview on hearing loss caused by cisplatin-induced ototoxicity, epidemiology, current treatments landscape and unmet medical needs in adults
Nicole C. Schmitt, M.D., FACS, Head and Neck surgical oncologist and scientist at Emory University in Atlanta

Sensorion: Development of SENS-401 in cisplatin-induced ototoxicity
Geraldine Honnet, Chief Medical Officer of Sensorion

PIPELINE: BUILDING AN ATTRACTIVE PIPELINE IN THE HEARING SPACE

	Product	Indication	Discovery	In vivo PoC	Pre-clinical	Phase 1	Phase 2	Phase 3	Next milestones (estimated timelines)
TREAT	SENS-401	Sudden sensorineural hearing loss							Topline data release January 2022
PREVENT	SENS-401	Cisplatin induced ototoxicity							Clinical trial design submission H2 2021
PREVENT	SENS-401	Hearing preservation after cochlear implantation					Cochlear™		Clinical trial design submission H2 2021
PREVENT	SENS-401	Aminoglycoside induced ototoxicity							
RESTORE	OTOF-GT*	Otoferlin deficiency							Clinical Trial Application in H1 2023
RESTORE	Usher-GT*	Usher syndrome Type 1							Confirmatory In-vivo PoC
RESTORE	GJB2-GT*	GJB2-related early presbycusis							Candidate selection
RESTORE	GJB2-GT*	Pediatric progressive GJB2-related hearing loss							Candidate selection
RESTORE	GJB2-GT*	Congenital GJB2-related hearing loss							Candidate selection

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

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

CISPLATIN OTOTOXICITY: RECOGNIZING THE PROBLEM AND SEARCHING FOR SOLUTIONS

Nicole C. Schmitt, MD

Associate Professor of Otolaryngology

Co-Director for Translational Research,

Head and Neck Program

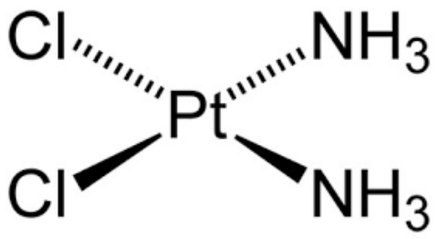
EMORY WINSHIP CANCER INSTITUTE
National Cancer Institute-Designated Comprehensive Cancer Center

NCI Designated Comprehensive Cancer Center

CISPLATIN CHEMOTHERAPY

Discovered by accident in 1965 by Rosenberg at Michigan

- Inhibited E Coli division
- Then it worked in a mouse sarcoma model



How does it work?

- Radiosensitizer
- DNA damage (inter- and intrastrand crosslinks)
- Inflammation

CLINICAL INDICATIONS FOR CISPLATIN

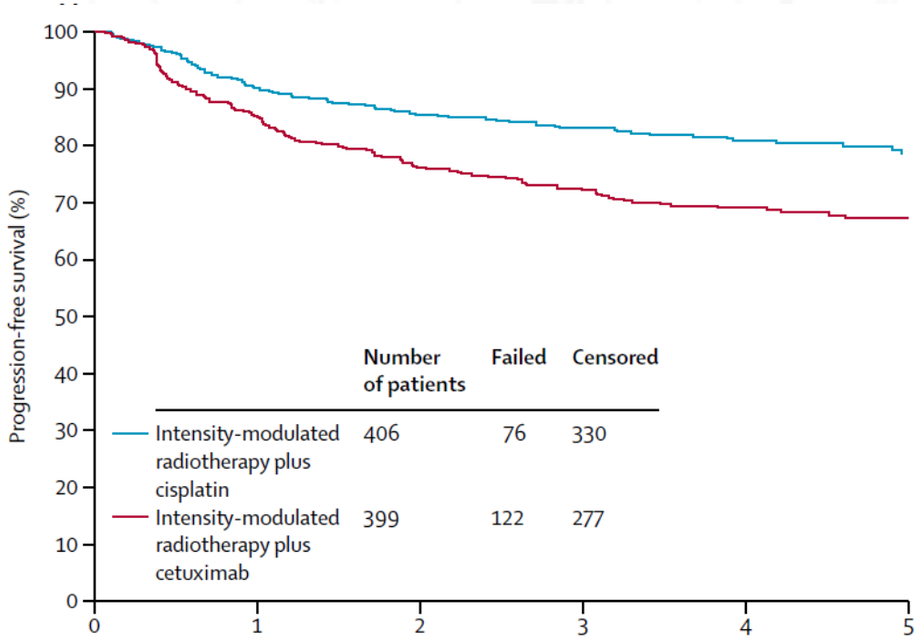
- Currently used for 30 different types of cancer in adults and children

Adrenocortical carcinoma
Anal carcinoma
Bladder cancer
Brain metastases
Breast cancer, triple-negative
Cervical cancer
Endometrial cancer
Esophageal cancer
Gastric cancer
Gestational trophoblastic neoplasia
Head and neck cancer
Hodkin lymphoma
Maignany pleural mesothelioma
Multiple myeloma
Neuroendocrine carcinoma
Non-Hodgin lymphoma
Non small cell lung cancer
Osteosarcoma
Ovarian cancer
Pancreatic cancer
Primary CNS lymphoma
Prostate cancer
Small cell lung cancer
Testicular cancer
Thymic carcinoma
Thymoma
Unknown Primary adenocarcinoma
Unknown primary squamous cell carcinoma

- Often used in combination with radiation or with other drugs (cytotoxic drugs, immunotherapy)
  - Used without other drugs for **head and neck***, cervical cancers

CISPLATIN IS HERE TO STAY (FOR NOW)

- Drugs that were designed to replace cisplatin have shown disappointing results
  - Carboplatin, oxaliplatin
  - Targeted therapies, e.g., cetuximab



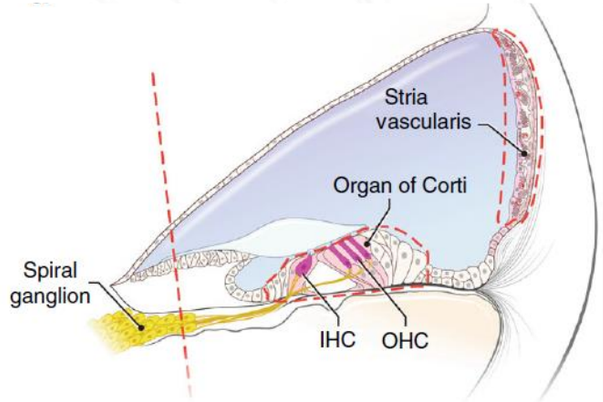
RTOG 1016

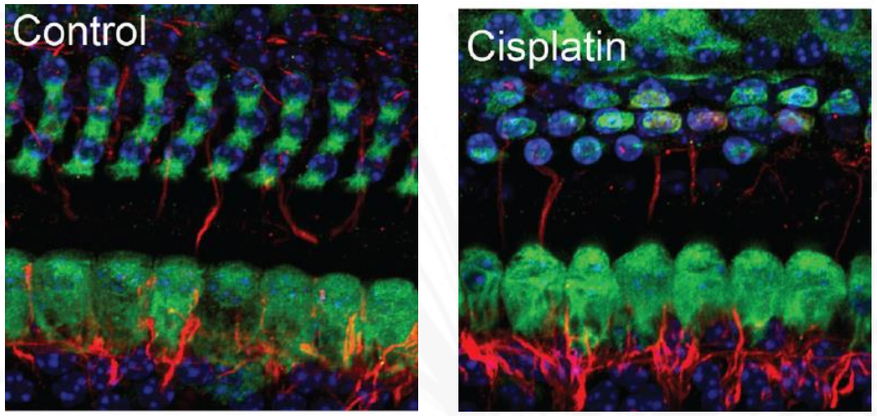
Gillison et al., *Lancet Oncology,* 2019

→ It is worth investing time and resources into preventive strategies.

CISPLATIN OTOTOXICITY

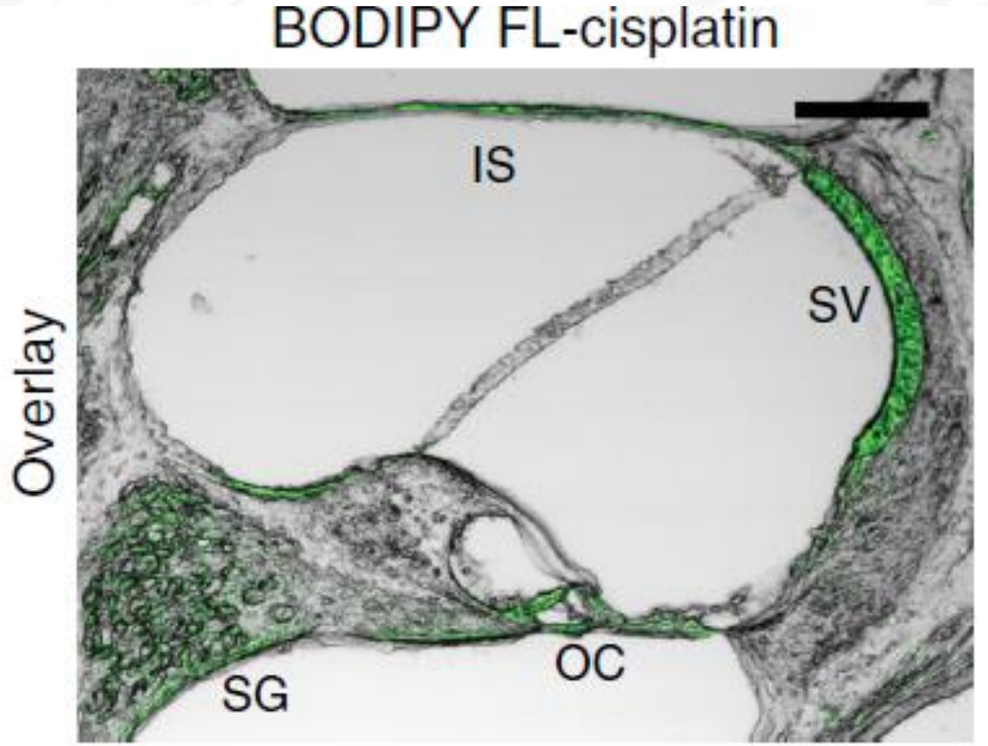
Involves damage to outer hair cells, spiral ganglion neurons, and the stria vascularis





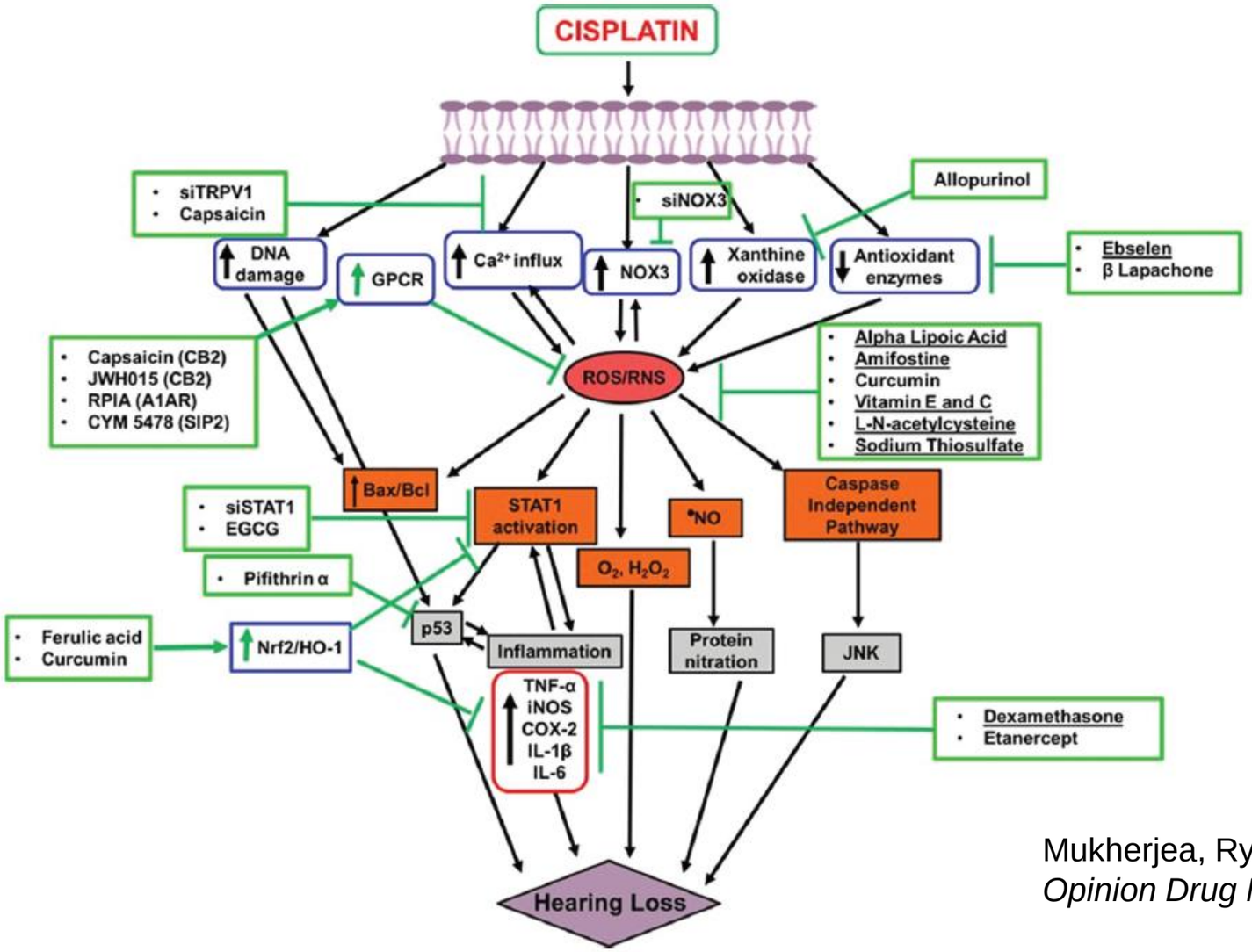
Schmitt and Rubel, *Otolaryngol Head Neck Surg, 2013*

Accumulates in these areas of the organ of Corti



Breglio, Cunningham et al., *Nature Communications*, 2017

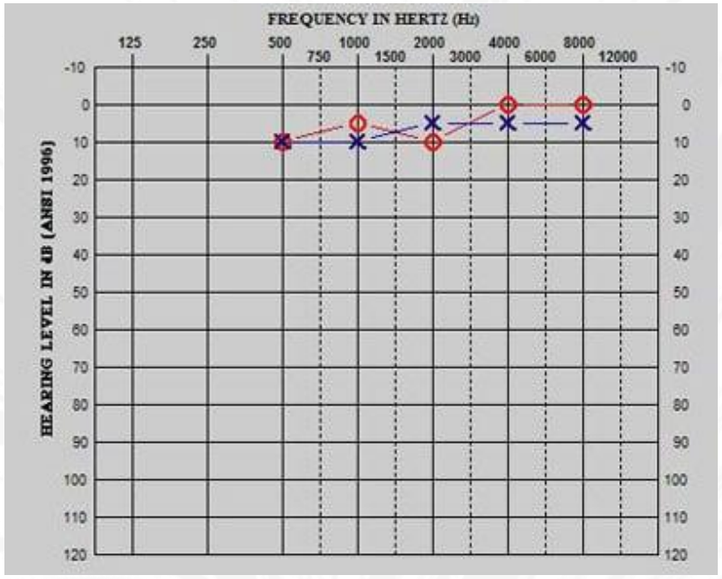
MOLECULAR MECHANISMS OF CISPLATIN OTOTOXICITY



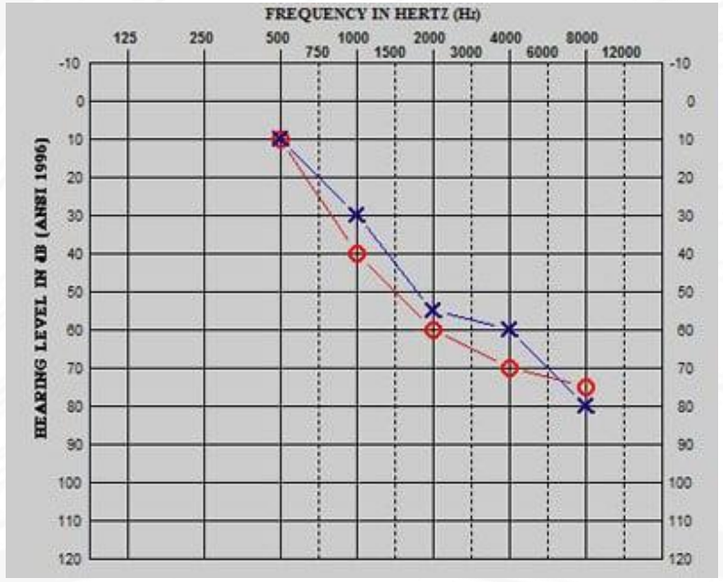
Mukherjea, Rybak, et al., *Expert Opinion Drug Metab Toxicol*, 2020

CLINICAL FEATURES OF CISPLATIN OTOTOXICITY

- High-frequency sensorineural hearing loss
  - Difficulty with speech discrimination in background noise
- Often accompanied by tinnitus
- Social isolation, frustration, depression



Pretreatment audiogram of a child

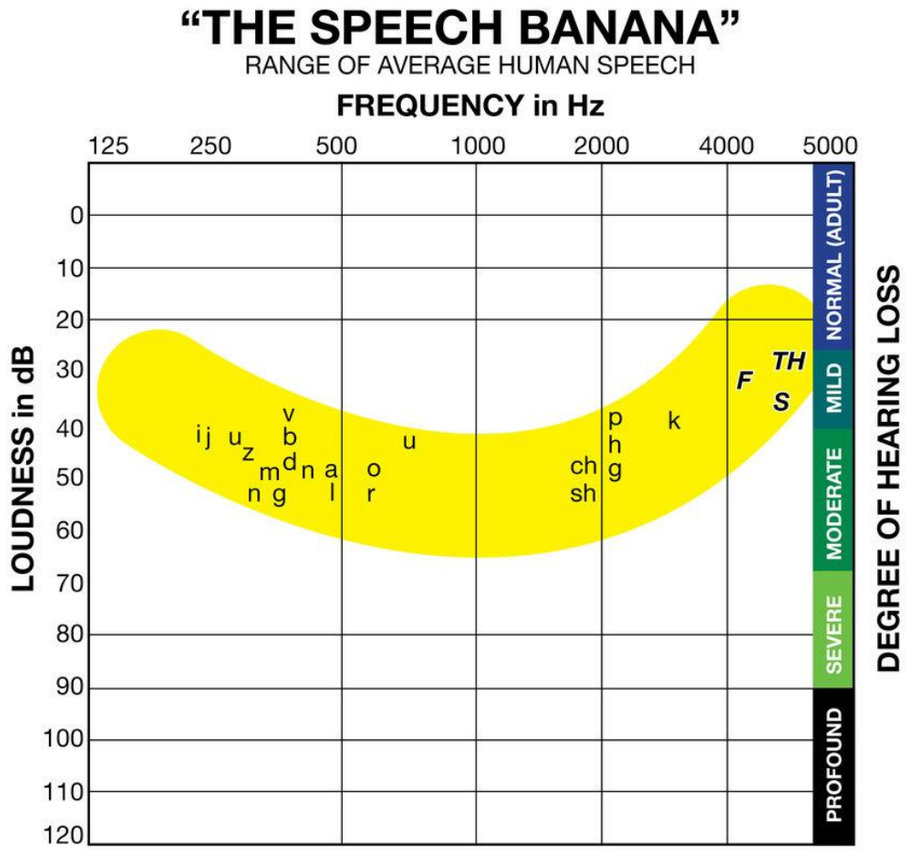


Audiogram after 2 cycles of cisplatin

American Speech and Hearing Association, Monitoring Ototoxicity in the Pediatric Oncology Population, ASHA website, June 2013

CLINICAL FEATURES OF CISPLATIN OTOTOXICITY

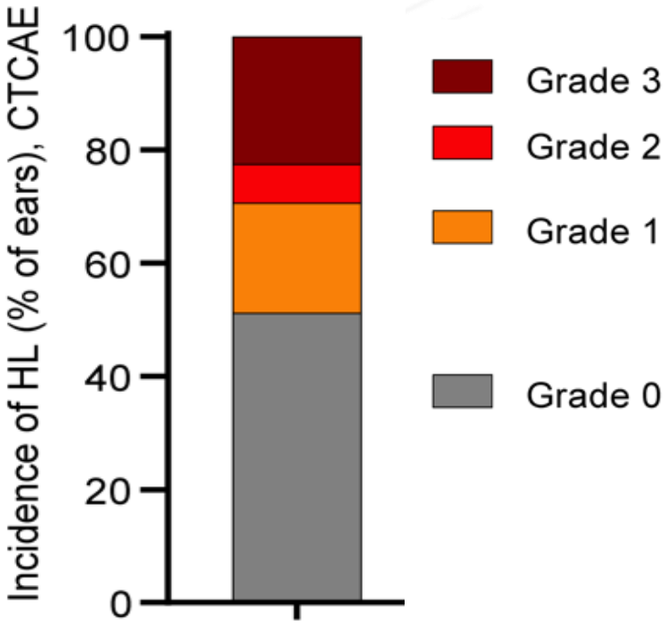
- High-frequency sensorineural hearing loss
  - Difficulty with speech discrimination in background noise
- Often accompanied by tinnitus
- Social isolation, frustration, depression
- Natural history: May worsen over time, spreading to lower frequencies (including speech frequencies)
  → <u>Permanent</u>



EPIDEMIOLOGY OF CISPLATIN OTOTOXICITY

Incidence and severity vary widely according to:

- Cancer type (and how that cancer is treated)
- Study (overall paucity of high-quality data)
- Grading system use
  - ASHA
  - TUNE
  - CTCAE
- For head and neck cancer, incidences from 17-88% have been reported
- *Hearing loss is worse/more frequent in patients with better hearing at baseline*



Fernandez et al., *JCI*, 2021

EPIDEMIOLOGY OF CISPLATIN OTOTOXICITY

Children are especially vulnerable

- Reports of severe, progressive hearing loss
- Interferes with speech development and learning
- *A major concern among survivors of pediatric cancer*

PREVENTIVE STRATEGIES- SUCCESSES AND LIMITATIONS

The ideal strategy for preventing cisplatin-induced hearing loss would accomplish 4 goals:

1) Decreased incidence

2) Decreased severity

3) Equal or Enhanced Anti-Tumor Activity of Cisplatin

4) Efficacy in adults and children

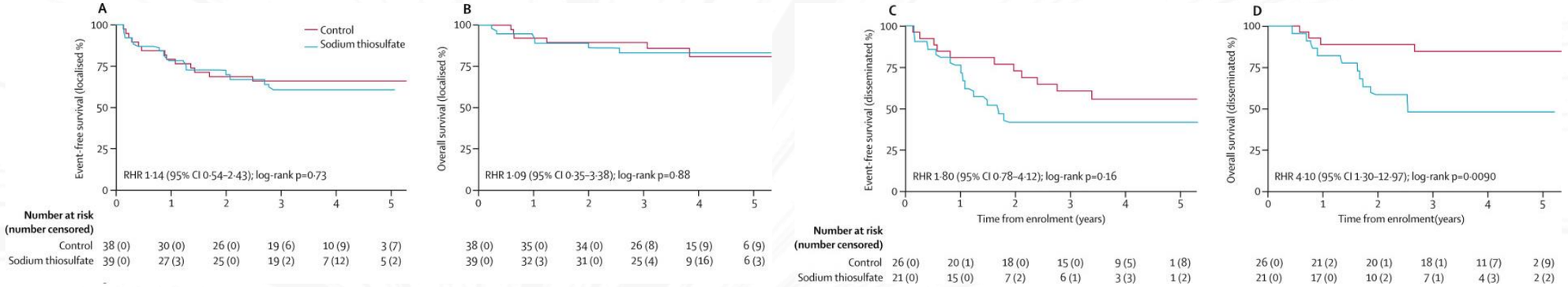
(severity often worse in children; but cisplatin-treated adults far outnumber children)

SODIUM THIOSULFATE

Some protection noted with intratympanic administration in adults

ACCL0431: Sodium thiosulfate to prevent cisplatin-induced hearing loss in children with cancer (Freyer et al., Lancet Oncology, 2016)

- 125 children treated with cisplatin for cancer randomized to observation vs. STS (IV, 6 hours after cisplatin)
- Hearing loss in 56.4% of control group vs. 28.6% with STS (OR of 0.32)



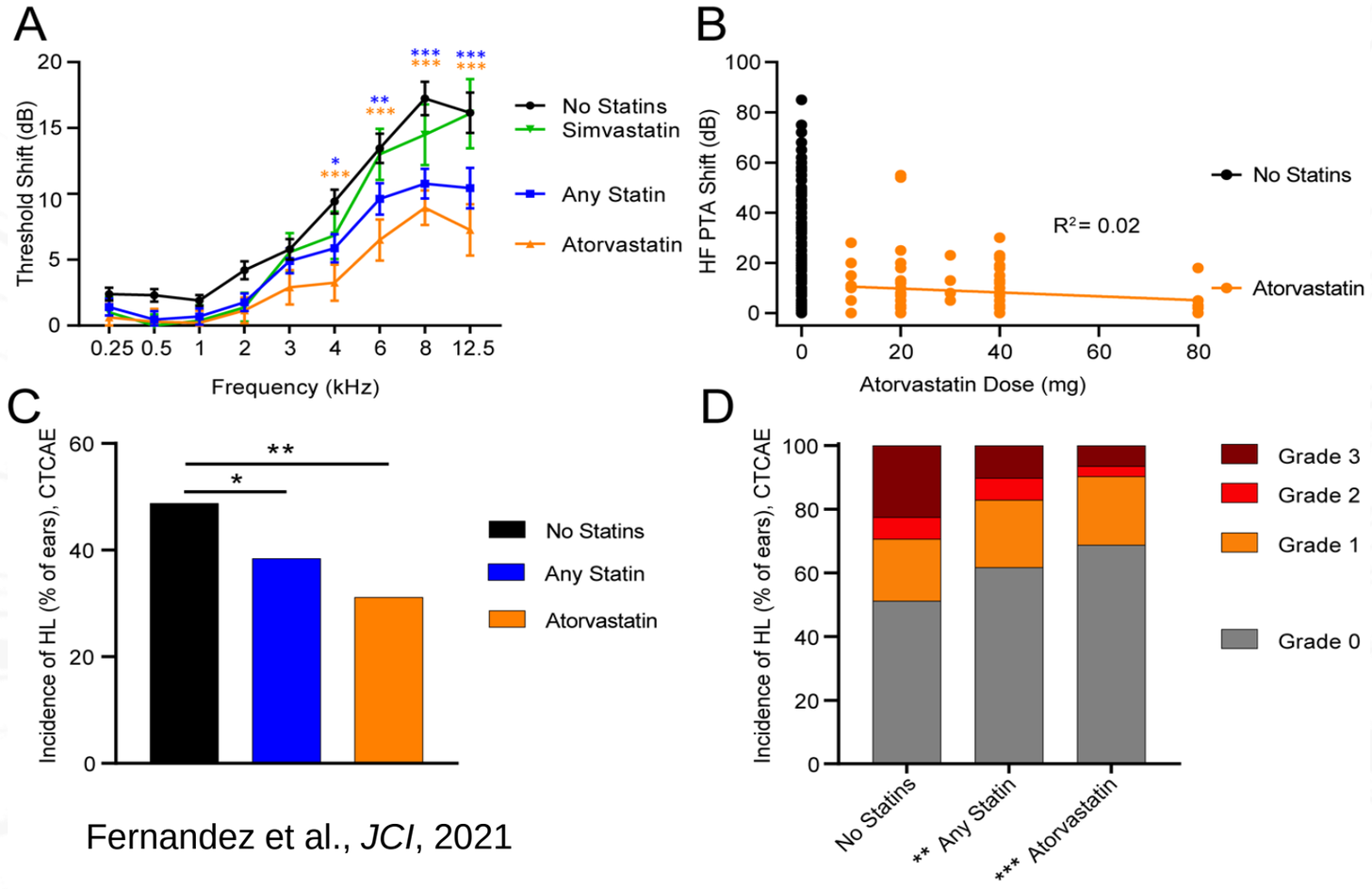
- Similar protection seen by Brock et al. (NEJM, 2018) in pediatric hepatoblastoma; no difference in survival, but patients with metastatic disease were excluded.

4 goals:

- ✓ Decreased incidence
- ✓ Decreased severity
- ❑ Equal/enhanced anti-tumor activity
- ❑ Efficacy in adults and children

ATORVASTATIN

Multi-center study of 277 head and neck cancer patients treated with cisplatin + radiation



Fernandez et al., *JCI*, 2021

4 goals:

- ✓ Decreased incidence
- ✓ Decreased severity
- ✓ Equal/enhanced anti-tumor activity
- ❑ Efficacy in adults and children

OTHER PREVENTIVE STRATEGIES

- N-acetylcysteine (animal studies and small clinical studies)
- Intratympanic dexamethasone (small but impressive clinical study in Israel)
- Vitamin E
- **SENS-401**

CONCLUSIONS

Further research and more candidates needed to achieve our 4 goals:

1) Decreased incidence – *We can do better*

2) Decreased severity – *We can do better*

3) Equal or Enhanced Anti-Tumor Activity of Cisplatin – *Rarely studied*

4) Efficacy in adults and children – *No agent to date thoroughly studied in both adults and kids*

Other Future Directions:

Genetic susceptibility studies

ACKNOWLEDGEMENTS

Katharine Fernandez, PhD, AUD

Lisa L. Cunningham, PhD

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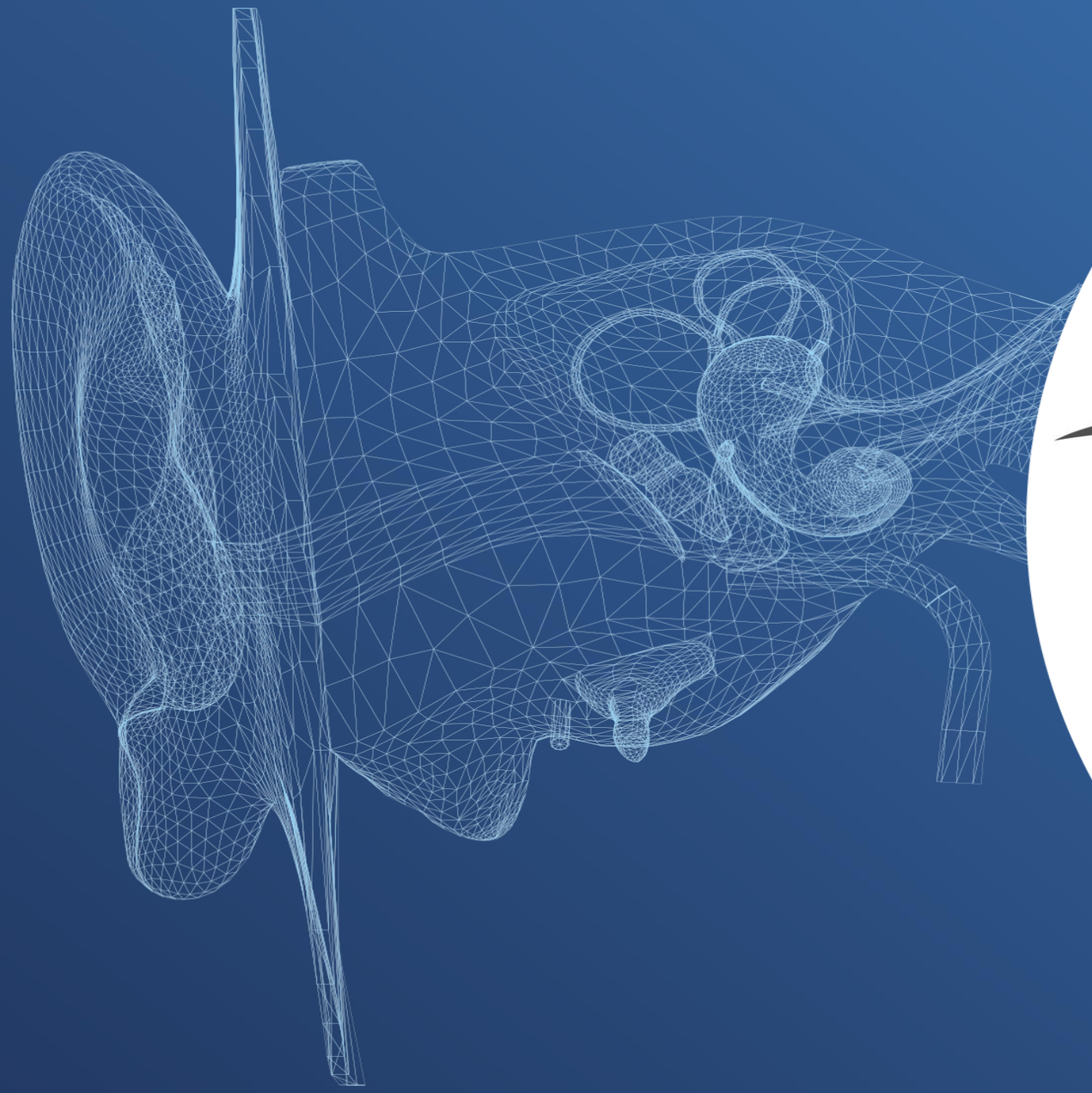


Sensorion

Focus on SENS-401 CIO program

28TH OCTOBER 2021

Hearing Loss: An under-recognized side effect of cisplatin cancer treatment

- Medical needs and market size
- SENS-401 preclinical in vivo and in vitro results:
  - Prevention of Cisplatin-Induced Ototoxicity (CIO) in animal model
  - Interaction studies between SENS-401 and cisplatin
- SENS-401 clinical development: Ph IIa study design (Notoxis study)

Cisplatin-Induced Ototoxicity (CIO)

Incidence

Between 350 to 450 per 100,000 people (~500,000 patients in 2017 in G7 countries)[1]

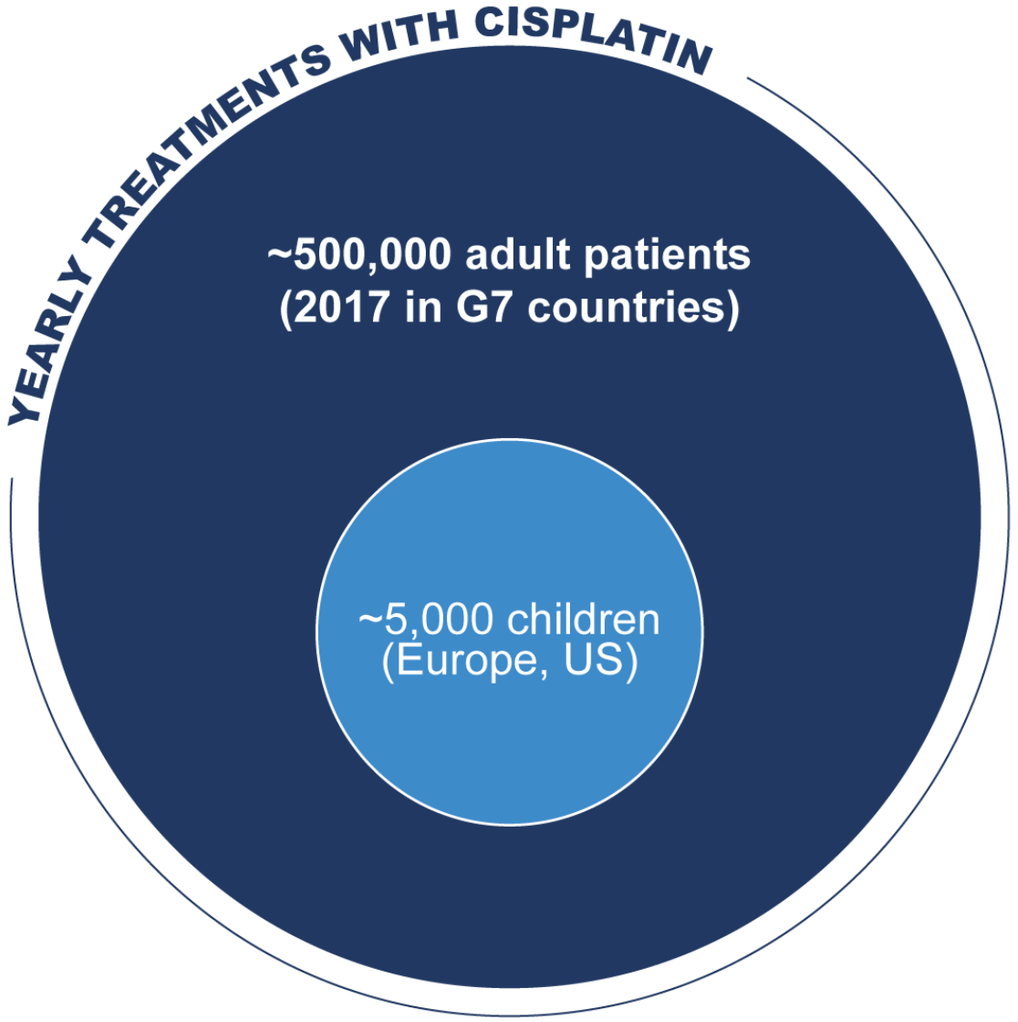
Unmet medical needs

- CIO leads to permanent inner ear problems in 50-60% of cases[2]
- These complications significantly impact patients' quality of life due to:
  - Hearing loss, tinnitus and dizziness impacting daily life activities
  - Problems in language acquisition and learning for pediatric patients
  - Difficulties in communicating, social isolation, cognitive decline
- Potential treatments must not interfere with chemotherapy efficacy

[1] *Company estimates based on publicly available data (in the US, Japan, Germany, France, the UK, Italy and Spain)*

[2] *Estimates varied from 10 to 95% depending on studied population, dose of cisplatin, audiometric tests or Hearing Loss definition*

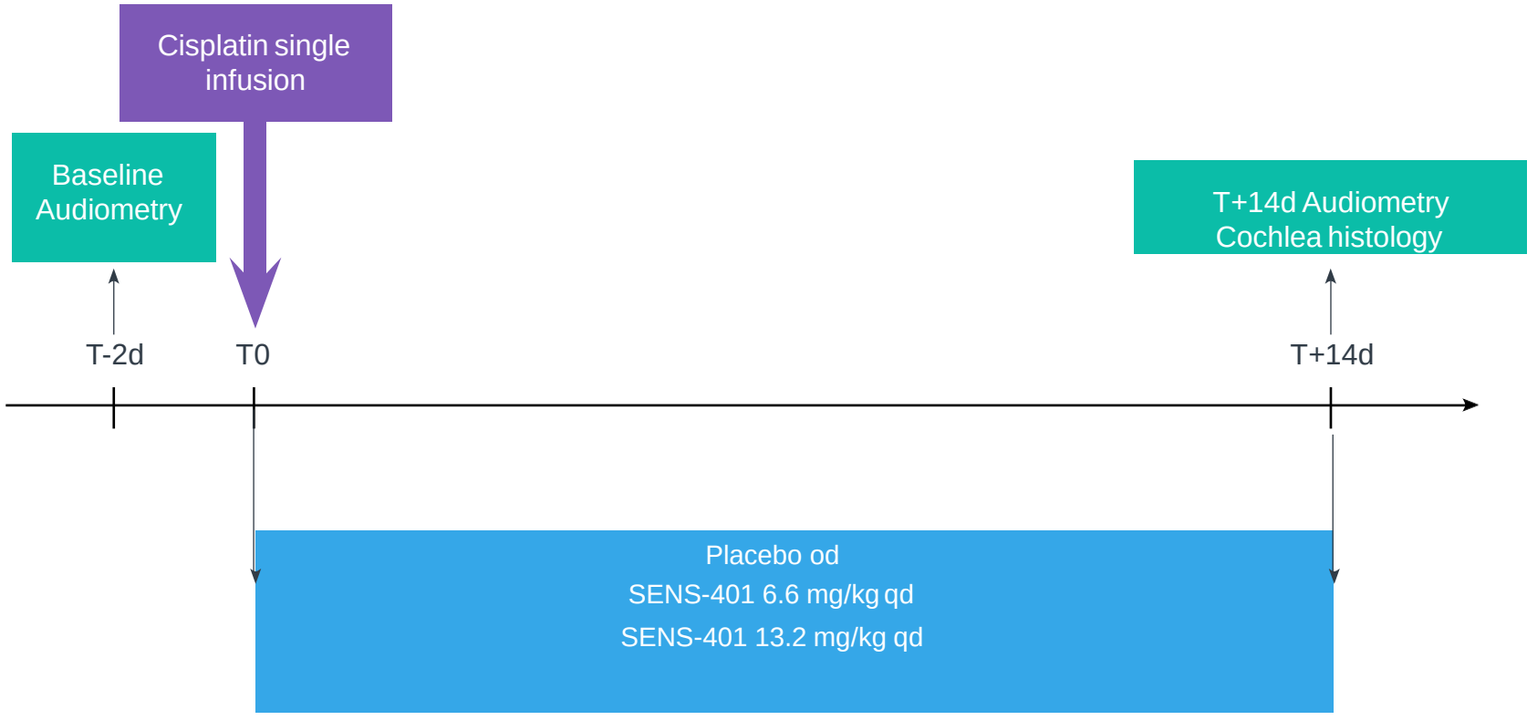
Large unmet medical need and untapped market opportunity



- 350 to 450 per 100,000 patients suffering from hearing loss
- No satisfactory preventive treatment
- No treatments approved by the FDA and EMA
- Hearing aids or cochlear implants are proposed to adults and children with severe cisplatin-induced ototoxicity

We developed a Cisplatin-Induced Ototoxicity (CIO) model to assess the otoprotective potential of SENS-401

- Female Wistar rats, 7 weeks old
- Audiometry at baseline, and after 14 days of treatment
- Cisplatin single infusion on D0
- SENS-401 treatments initiated before cisplatin infusion, and for 14 days compared to placebo

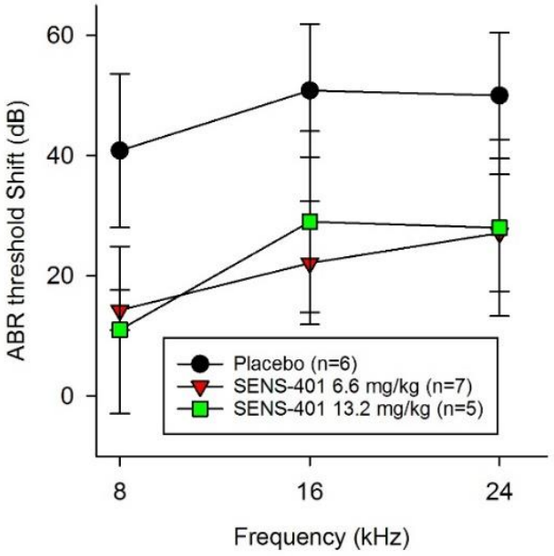


Daily oral SENS-401 treatment significantly reduces Cisplatin-induced hearing loss in rats

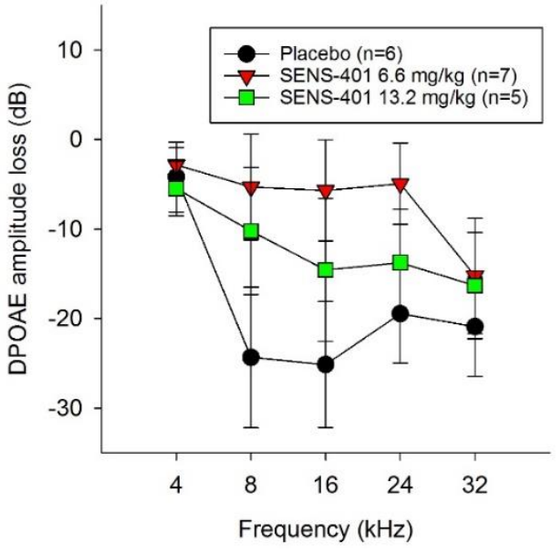
Significant improvement of ABR compared to Placebo for both doses:

- 23-28 dB with 6.6 mg/kg (p<0,010)
- 22-30 dB with 13.2 mg/kg (p<0,013)

ABR threshold shifts



DPOAE amplitude loss



Results

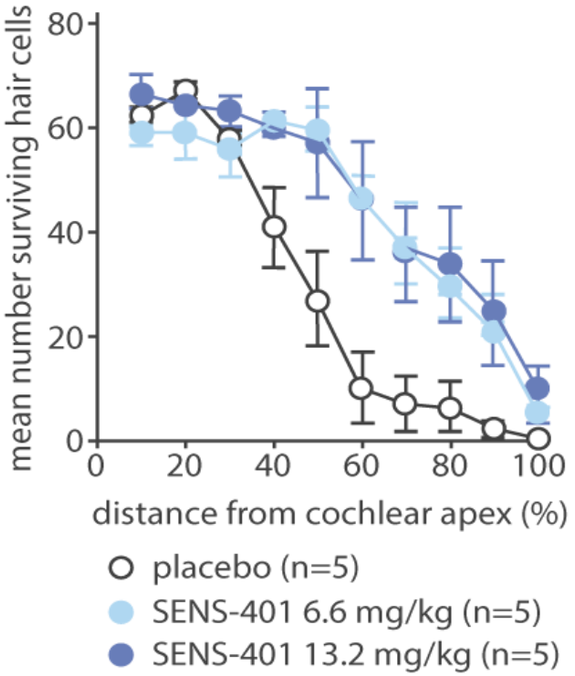
- SENS-401 significantly reduces cisplatin induced ABR threshold shifts (up to ~79% reduction)
- SENS-401 significantly reduces cisplatin induced DPOAE amplitude losses (up to ~78% reduction)

Reference paper: Petremann et al, Otol Neurotol, 2017

Daily oral SENS-401 treatment significantly enhances OHC survival in rats

Significant (p<0.001) enhancement of Outer Hair Cells survival 22-264% for both doses

Survival of cochlear Outer Hair Cells



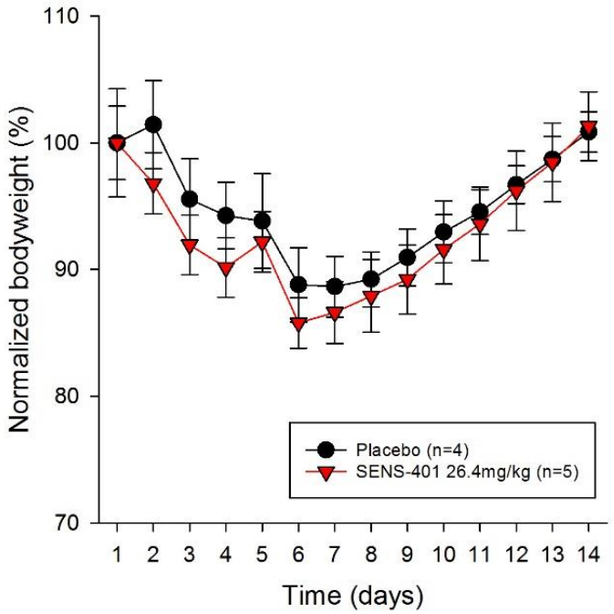
Results

- SENS-401 significantly enhances OHC survival (up to 11-fold more in the basal turn of the cochlea)

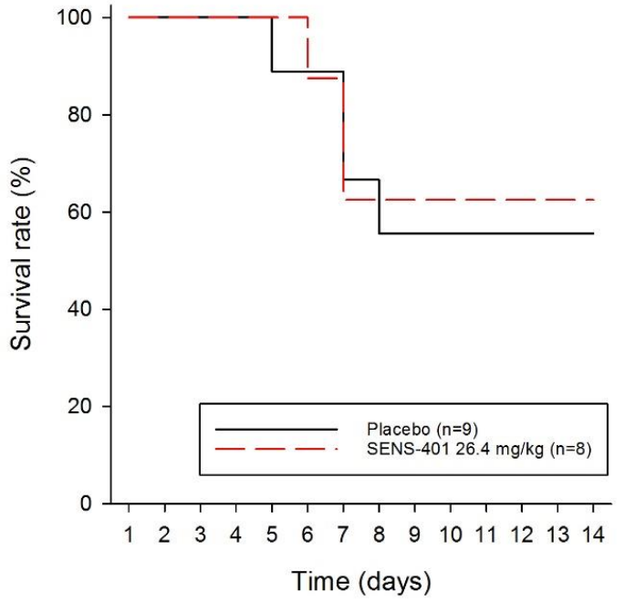
Reference paper: Petremann et al, Otol Neurotol, 2017

Daily oral SENS-401 treatment does not impact the general toxicity of cisplatin in rats

Rat body weight



Animal survival rate



Results

- SENS-401 does not impact weight loss and recovery
- SENS-401 does not impact cisplatin-induced mortality

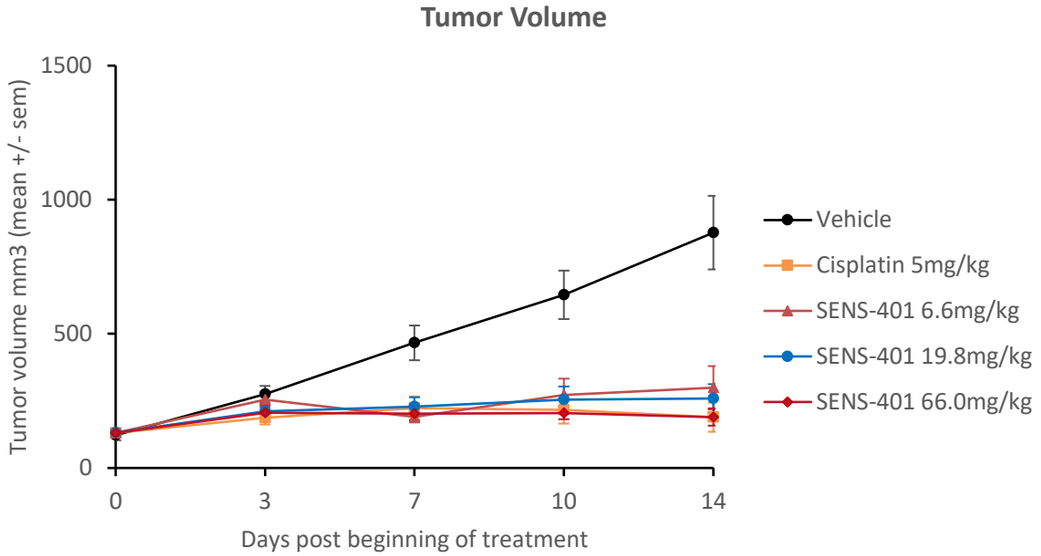
SENS-401 does not interfere with cisplatin efficacy *in vivo*

Available studies

- In vivo impact assessment of SENS-401 used at different doses on the antitumor activity of cisplatin in the HB-217-VER patient-derived liver cancer xenograft nude mouse model

Female athymic nude mice with growing 75.0 to 196.0 mm3 HB-217-VER tumor (mean/median tumor volume 130.4/126.0 mm3)

- **Group 1:**
  - Vehicle 5 ml/kg, p.o., qdx1 + bid x13 + qdx1
- **Group 2:**
  - Cisplatin 5 mg/kg, 10 ml/kg, i.p., qwkx2
- **Group 3:**
  - SENS-401 6.6 mg/kg, 5 ml/kg, p.o., qdx1 + bid x13 + qdx1
  - Cisplatin dosed at 5 mg/kg, 10 ml/kg, i.p., qwkx2
- **Group 4:**
  - SENS-401 19.8 mg/kg, 5 ml/kg, p.o., qdx1 + bid x13 + qdx1
  - Cisplatin dosed at 5 mg/kg, 10 ml/kg, i.p., qwkx2
- **Group 5:**
  - SENS-401 66.0 mg/kg, 5 ml/kg, p.o., qdx1 + bid x13 + qdx1
  - Cisplatin dosed at 5 mg/kg, 10 ml/kg, i.p., qwkx2.



Results

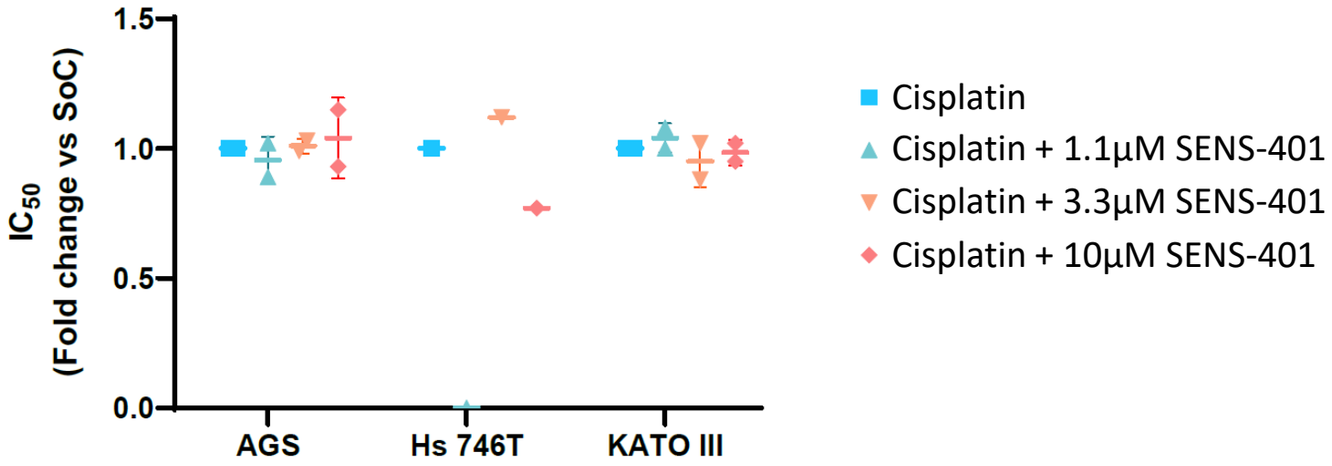
- No impact of SENS-401 on chemotherapeutic efficacy of cisplatin in vivo (all SENS-401 / cisplatin groups vs cisplatin alone: p>0.05)
- SENS-401 tumor penetration confirmed, no effect on tumor cisplatin levels (D14)
- SENS-401 levels documented in blood plasma samples: 1-10 µM (350-3500 ng/mL)

SENS-401 has no impact on cisplatin and other SOCs cytotoxicity *in vitro*

Available studies

- Cytotoxic activity study of SENS-401 combined with cancer SoC in a panel of 20 tumor cell lines

Anti-proliferative effect of Cisplatin in three stomach cancer cell lines



AGS - Gastric adenocarcinoma
Hs 746T - Gastric carcinoma, derived from metastatic site
KATO III - Derived from a metastasis of a gastric carcinoma

Results

- SENS-401 does not show any effect on cisplatin and other SoCs IC_{50} in the studied cell lines

Summary

- SENS-401 reduces cisplatin-induced hearing loss in rat and increases the Outer Hair Cell survival
- SENS-401 does not interfere with the general toxicity of cisplatin, suggesting inner ear specific protection
- SENS-401 Phase I in Healthy Volunteers shows a safety profile comparable to placebo
- Safety results so far show that SENS-401 is well tolerated
- Initiation of a Phase IIa study in neoplastic patients with ototoxicity induced by cisplatin

CIO

Planning to submit the CTA[1] for the NOTOXIS study by year end

SUBJECT TO REGULATORY APPROVAL

An Exploratory, Phase IIa, Multicenter, Randomized, Controlled, Open-label Study to Evaluate the Efficacy of SENS-401 to Prevent or Treat the Ototoxicity due to Cisplatin in Adult Subjects with a Neoplastic Disease

SCREENING PERIOD	RANDOMIZATION	EVALUATION PERIOD
Patients suffering from a neoplastic disease for which the treatment protocol includes a chemotherapy with cisplatin and having a medical profile with a higher risk of ototoxicity induced by the cisplatin treatment	**Arm A: Control group**	**Cisplatin only**
	Arm B: Preventive 20 patients	**SENS-401 initiated before the first cycle of cisplatin and during cisplatin cycles**
	Arm C: Therapeutic 20patients	**SENS-401 initiated as soon as a preliminary signal of ototoxicity is detected and continuation during remaining cisplatin cycles**

[1]*Clinical Trial Application*

THANK YOU

Large unmet medical need and untapped market opportunity

Current Landscape

- ~500,000 patients treated with Cisplatin in 2017 in G7 countries
- ~ 3000 children in Europe and 2000 children in the USA treated with Cisplatin
- 350 to 450 per 100,000 patients suffering from hearing Loss

CIO Market Potential

- No satisfactory preventive treatment
- No treatments approved by FDA/EU
- Hearing aids or cochlear implants proposed to adults/children with severe Cisplatin-induced ototoxicity
- Opportunity to create Standard of Care treatment
- Initial focus on adult patients