What you need to know about drug therapies for treating hearing loss

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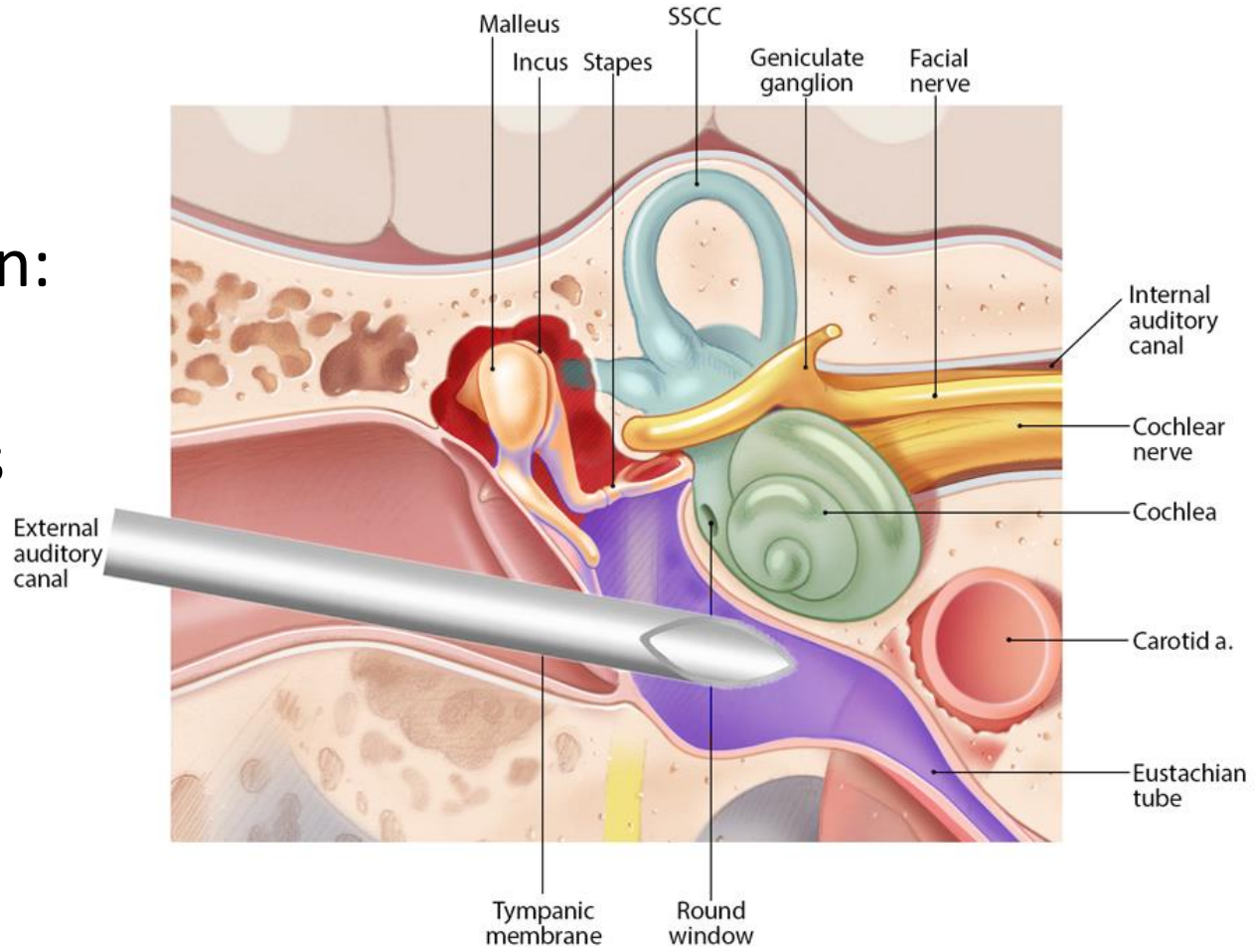
Overview

- Routes of administration in clinical practice
  - Intratympanic injection
  - Direct Injection into the inner ear
  - Drug elution from devices (cochlear implants)
- Limitations of cochlear diagnostics, and implications for new therapies
- Efforts to improve diagnostics – a dialogue between ENT and Audiology

Intratympanic treatments

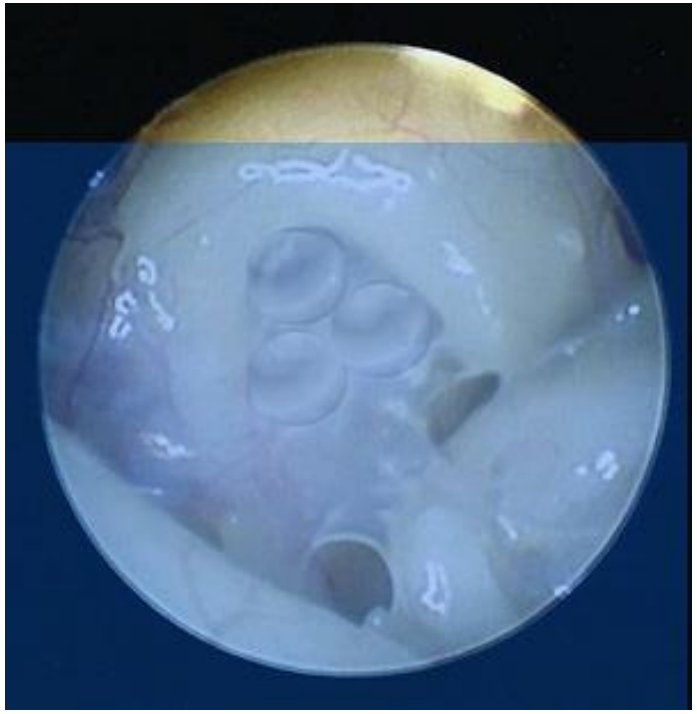
Entry into the cochlea depends upon:

- Molecular weight of the drug
- Access to the round/oval windows
- Membrane permeability of drug
- Its consistency: Liquid vs gel



Getting drug into the round window: middle ear variability

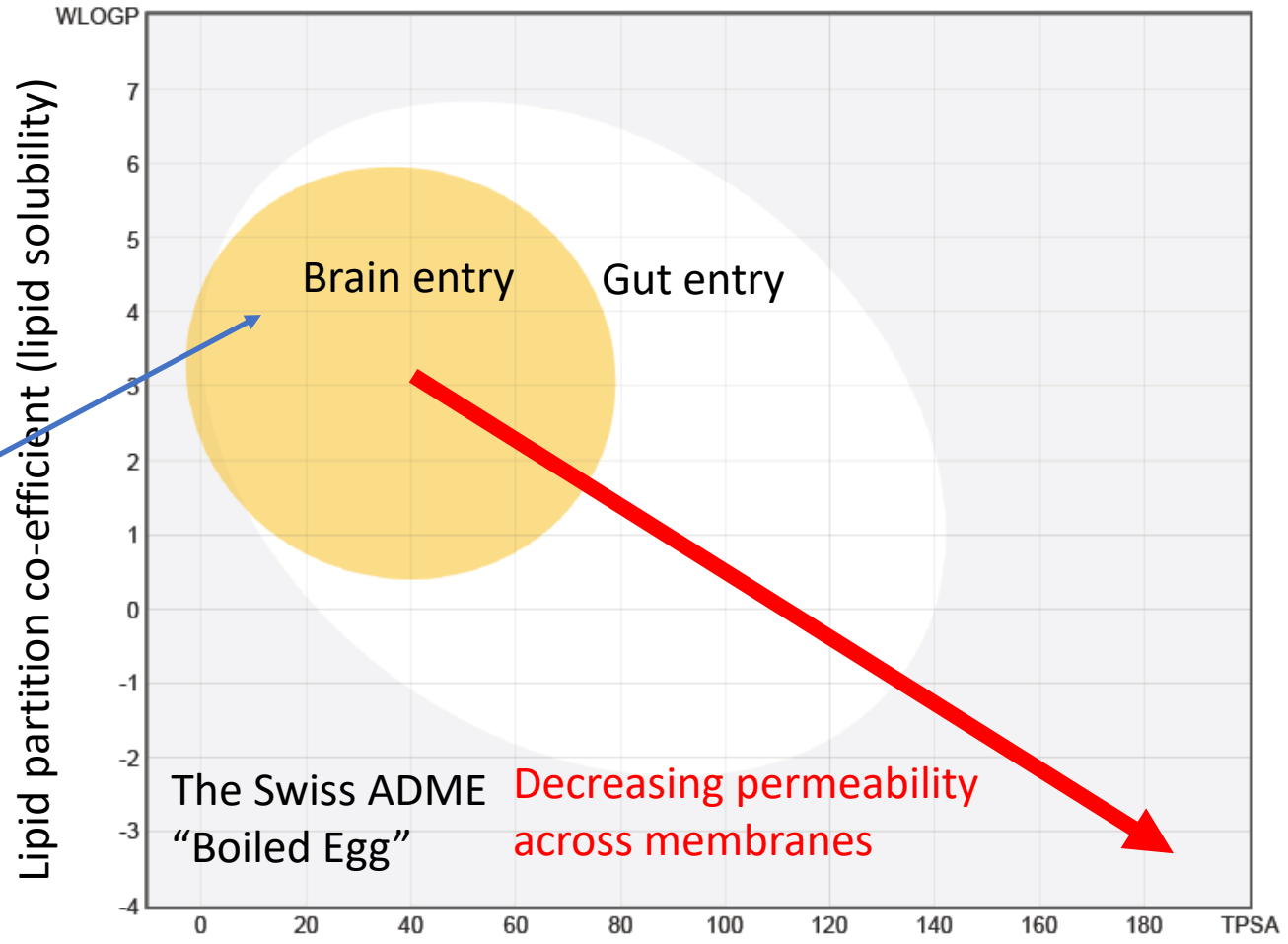
Bubbles beneath mucosal folds



Drug properties and cochlear entry/elimination

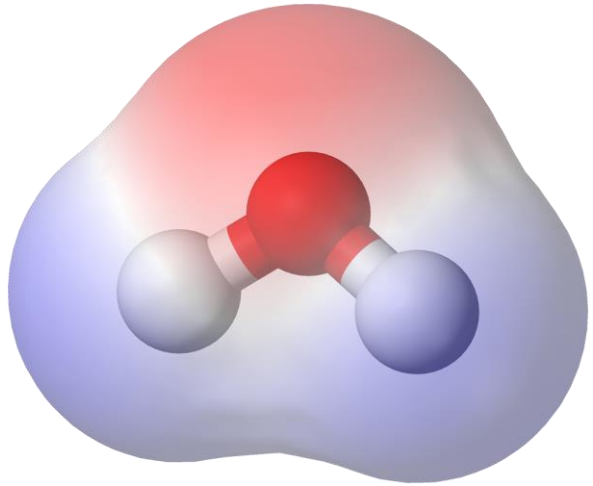
Drugs that are
- Lipophilic (high WLOGP) i.e. dissolve in fats
- Small
- Non-polar

cross membranes readily



A measure of the topological **polar surface area**

Water, a polar molecule
Wikipedia Public Domain,
https://commons.wikimedia.org/w/index.php?curid=1498405

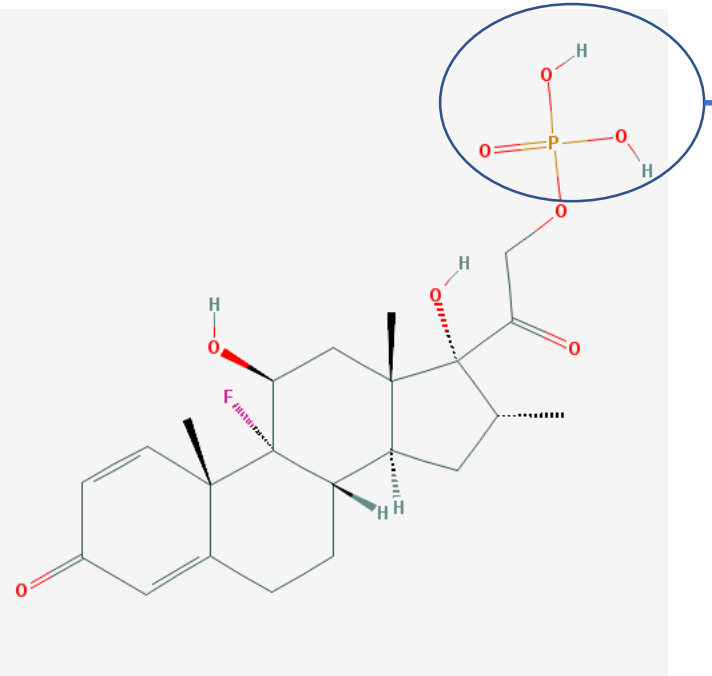


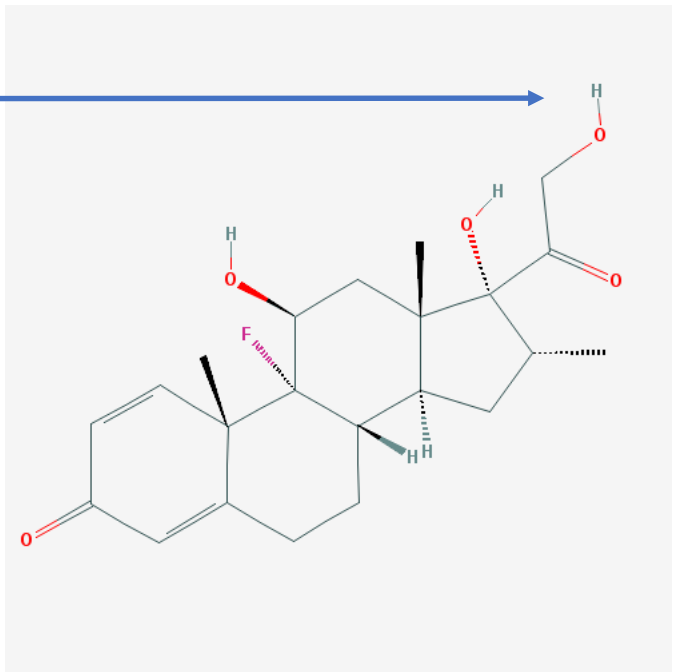
Dexamethasone for intratympanic injection

Pro-drug

Active form

Cleaved





Dexamethasone Phosphate

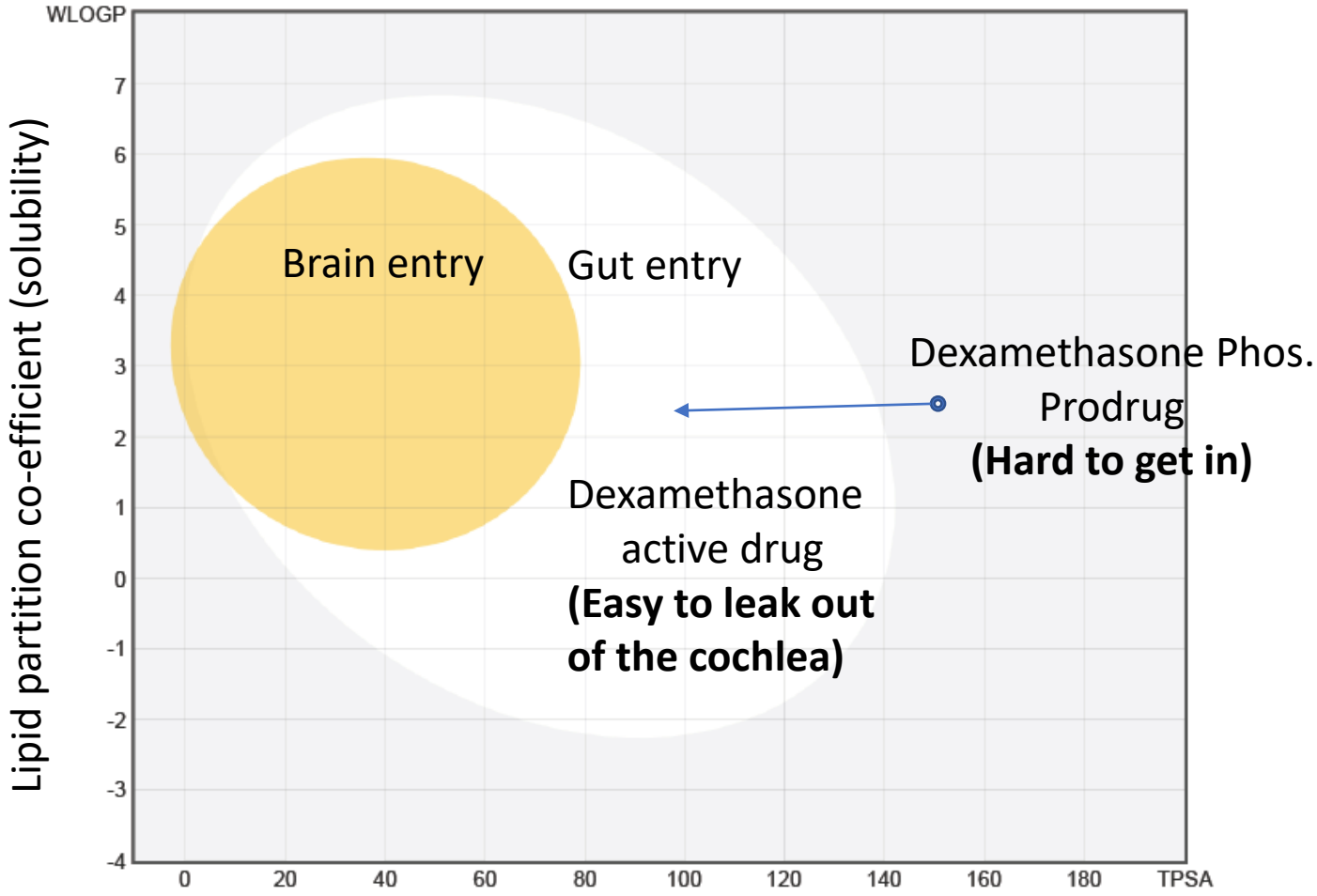
Highly polar
Water soluble (injectable)

Dexamethasone

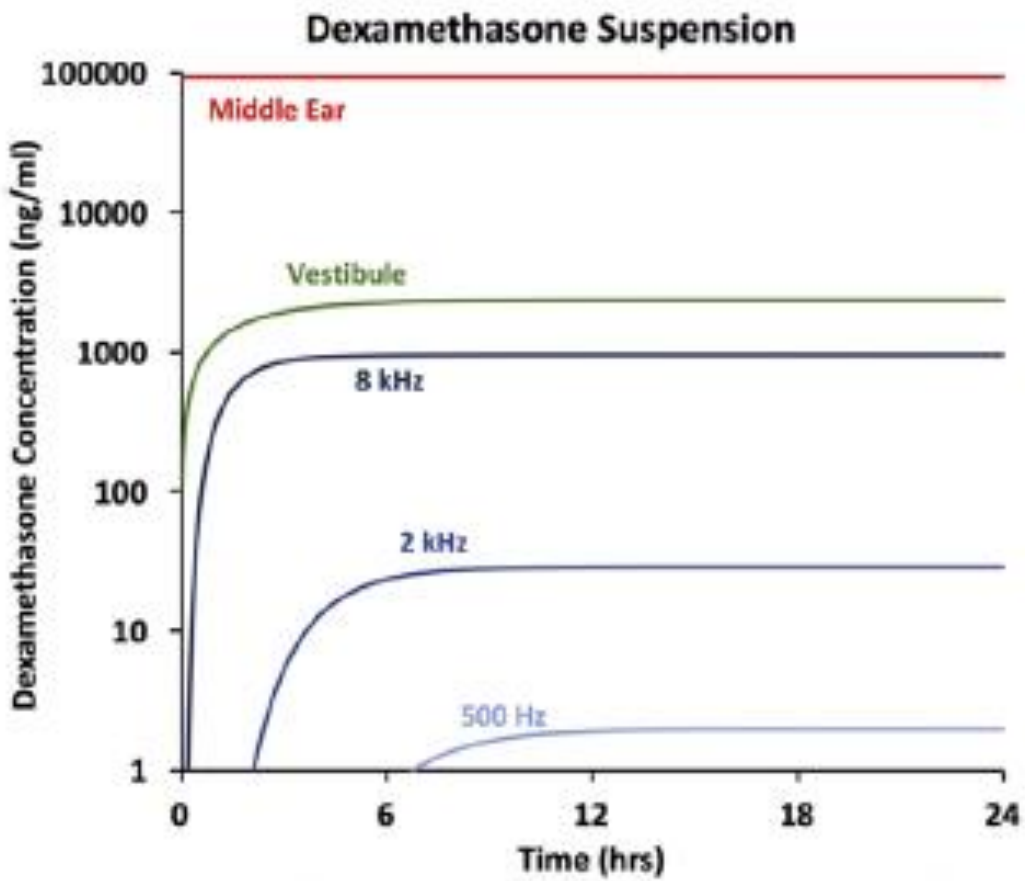
Water insoluble, lipid soluble

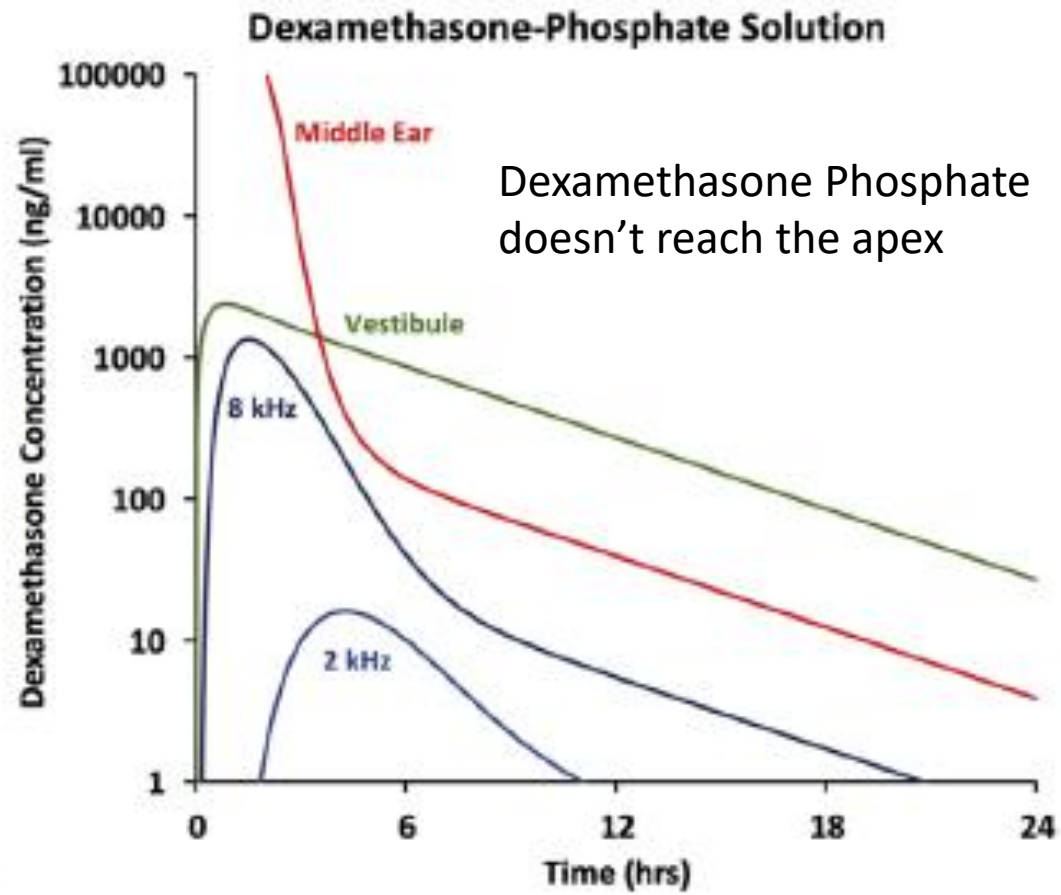
Dexamethasone's properties & cochlea delivery

- Dexamethasone is hard to get in, and easy to leak out of the cochlea.



A measure of the topological polar surface area





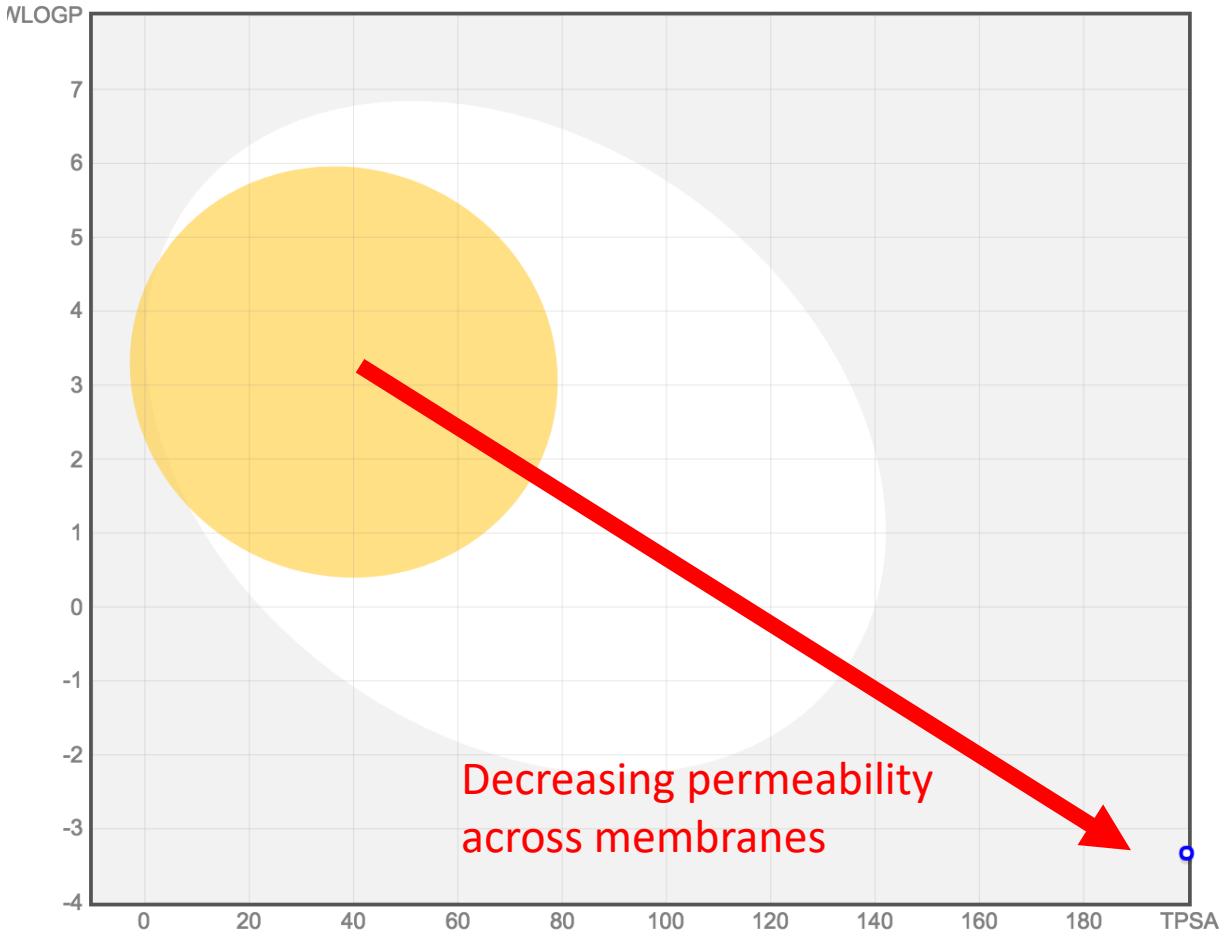
Dexamethasone Phosphate doesn't reach the apex

Salt and Plontke, Hear Res. 2018 Mar 11.
pii: S0378-5955(17)30620-2.
doi: 10.1016/j.heares.2018.03.002. [Epub ahead of print]

Intratympanic Gentamicin for Meniere's Disease

- Gentamicin does not across into the cochlea easily.

- But once it does, it "stays there" for a long time, and does not cross the blood-labyrinthine barrier easily.



Liquids

- Readily eliminated via the eustachian tube, or into the mastoid
- Can “sneak” around corners readily
- Good for single-dose applications
- But plagued by variable absorption into the cochlea
- Clinical examples:
  - Intratympanic steroids for Meniere’s Disease, Sudden and Fluctuating sensorineural hearing loss
  - Intratympanic gentamicin for Meniere’s Disease.

Gels

- Liquid at room temperature, and gel at body temperature
- More viscous: more likely to form “bubbles” in the RWM niche
- Can run out of the middle ear before they gel
- Higher dose, more controlled and sustained delivery

OTONOMY®

Miconised Dexamethasone (base) in Poloxamer 407 gel

For Meniere’s Disease

spiral therapeutics

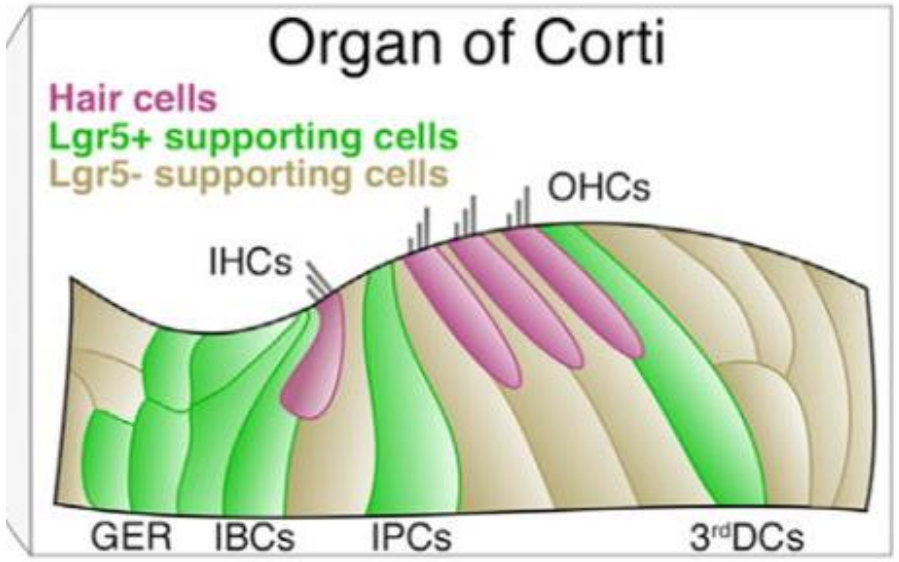
LPT99 (antioxidant) in a hydrogel

Commencing clinical trials this year

Chemotherary-induced hearing loss

FREQUENCY THERAPEUTICS

Gels



Cell Rep. 2017 Feb 21; 18(8): 1917–1929.
doi: 10.1016/j.celrep.2017.01.066

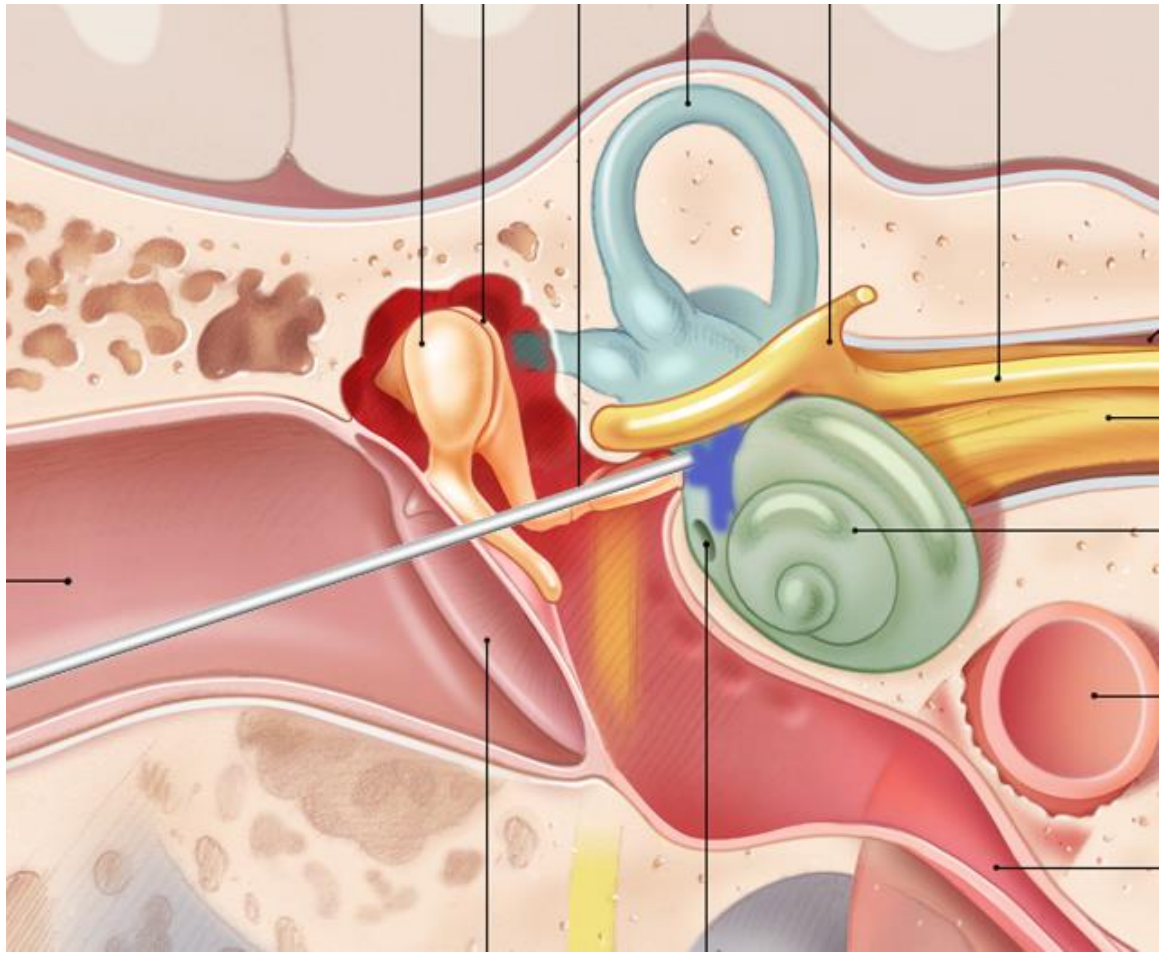
Targeting hair cell regeneration

- FX-322:
  a glycogen synthase kinase 3β inhibitor (FX03) and valproic acid in a Poloxamer 407 gel
- **Expands Lgr5+ stem cells that transdifferentiate into hair cells**
- We led the first-time-in-human's Phase 1 trial in Melbourne in 2017

Intracochlear delivery: Gene therapy

NOVARTIS

- Direct injection through the stapes
- Gene therapy (Atoh1) [GCF166]
- To replace missing hair cells
- Injecting 20-60 µl aliquots
- **There has been some hearing loss from the drug delivery**
- **There have been some responders**



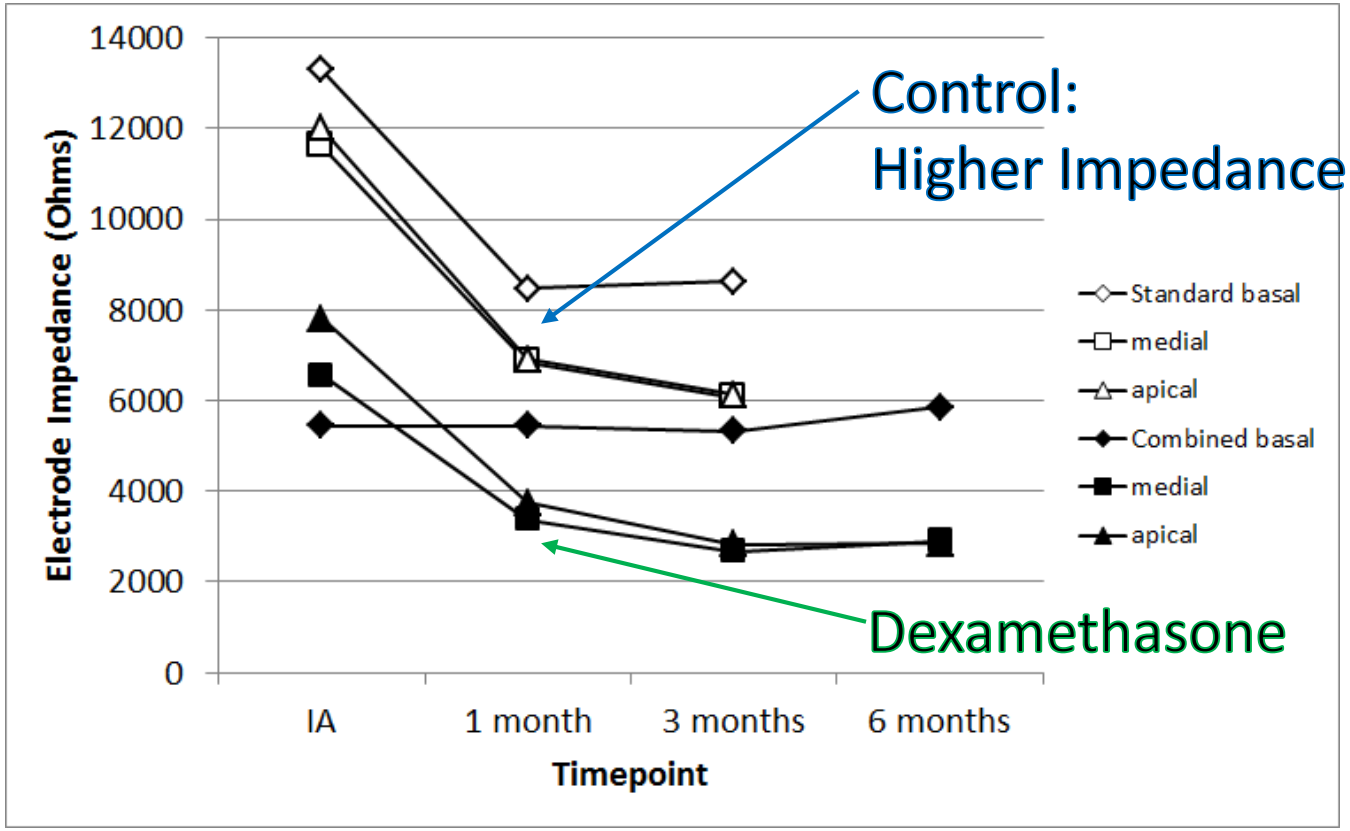
Intracochlear delivery: Steroid elution from CI

Cochlear®

"Combined Device" Trial: Dexamethasone (Melbourne)

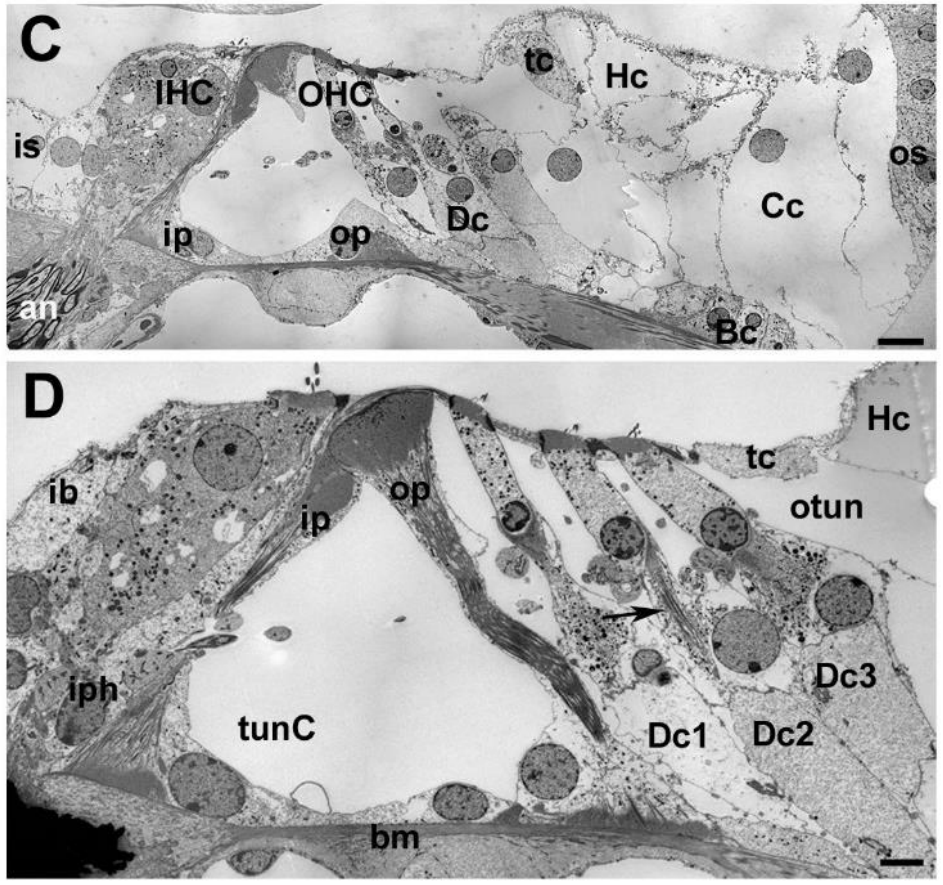
Intracochlear delivery: Steroid elution from CI

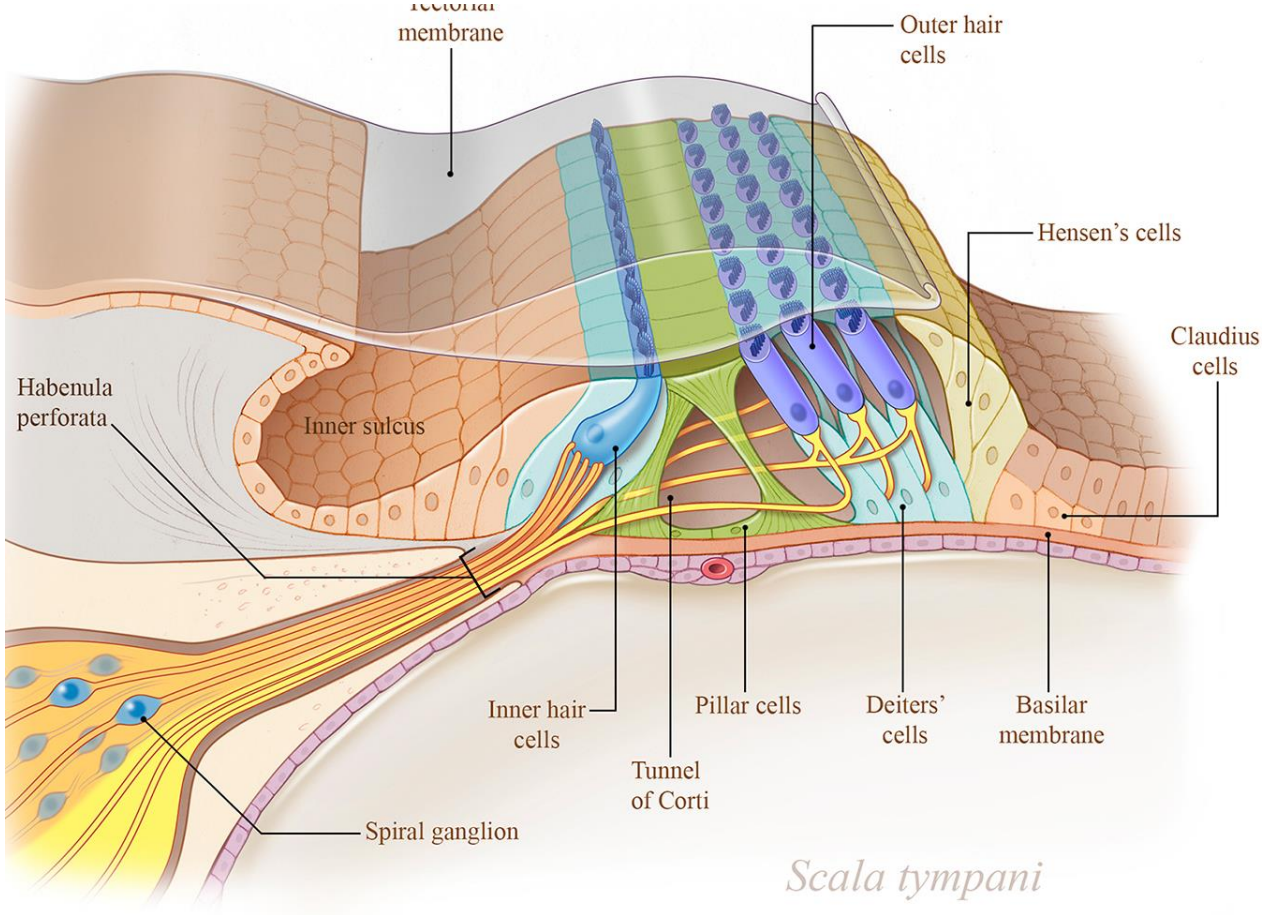
Cochlear®



"Combined Device" Trial: Impedances substantially reduced

Chosing candidates for regenerative therapies





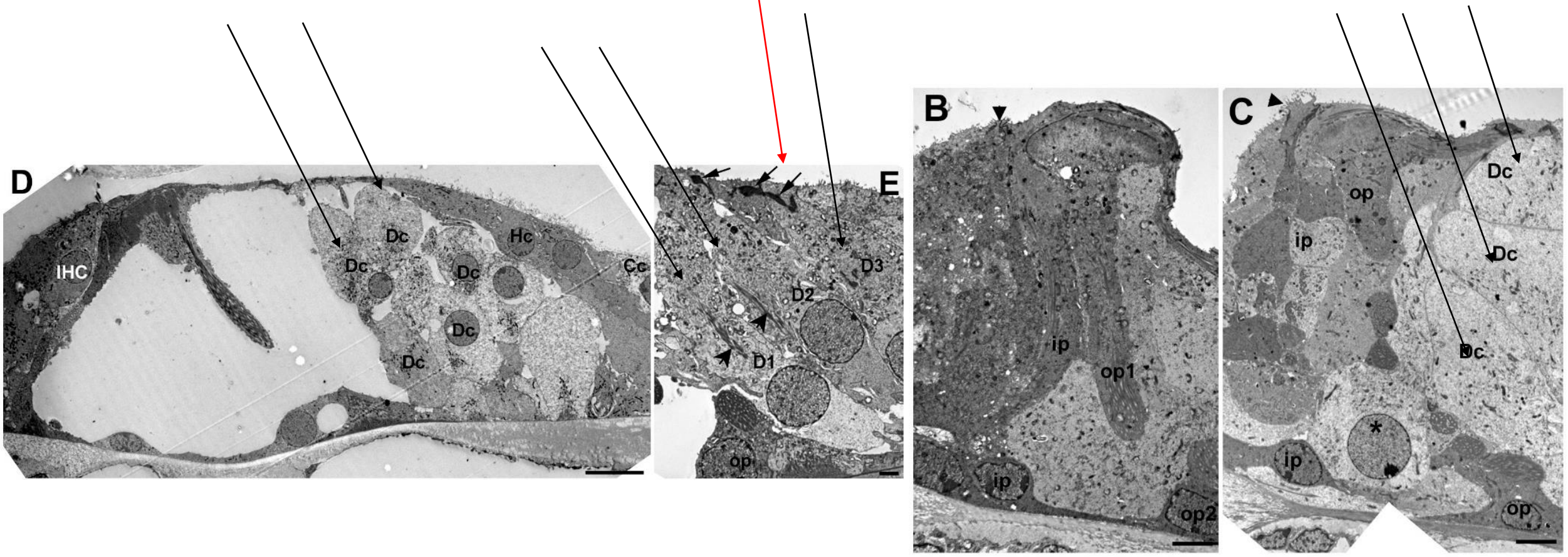
Images from Dan Jagger's laboratory (with thanks):
Taylor RR, Jagger DJ, Forge A (2012) Defining the Cellular Environment in the Organ of Corti following Extensive Hair Cell Loss: A Basis for Future Sensory Cell Replacement in the Cochlea. PLoS ONE 7(1): e30577. doi:10.1371/journal.pone.0030577

Supporting cell expansion after hair cell loss

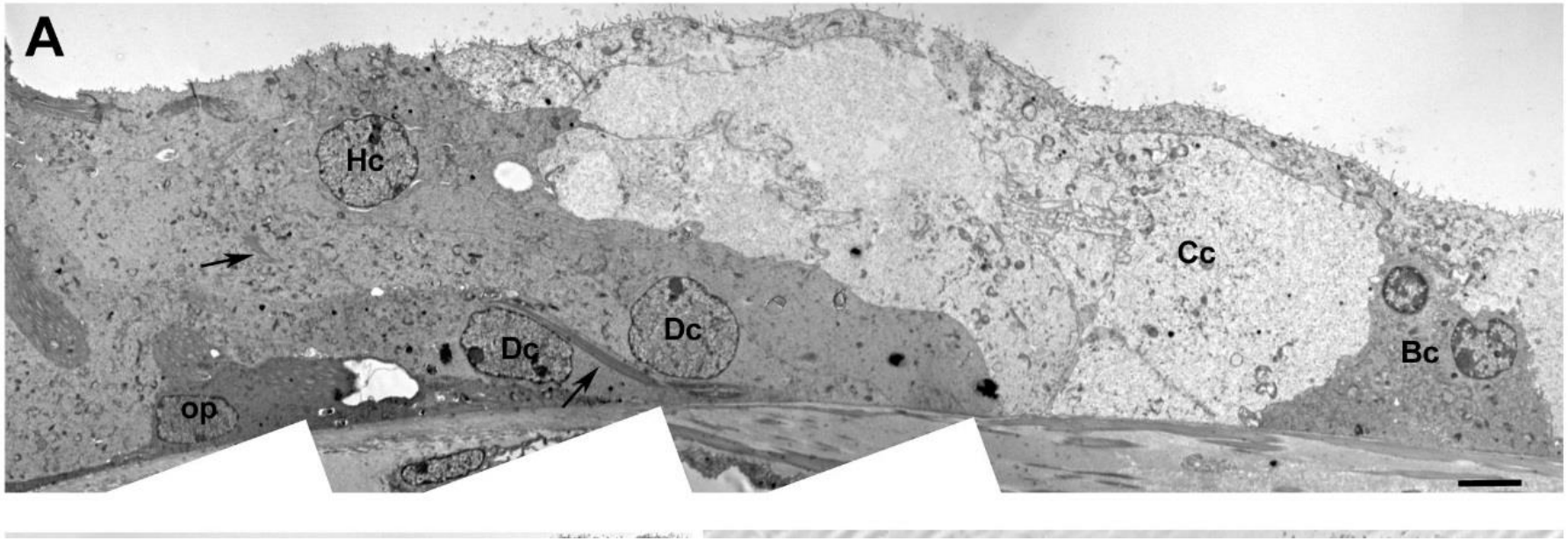
Dead hair cell remnant being “pushed out” by Deiter’s cells)

Deiter’s cells (supporting cells)

Deiter’s cells (supporting cells)

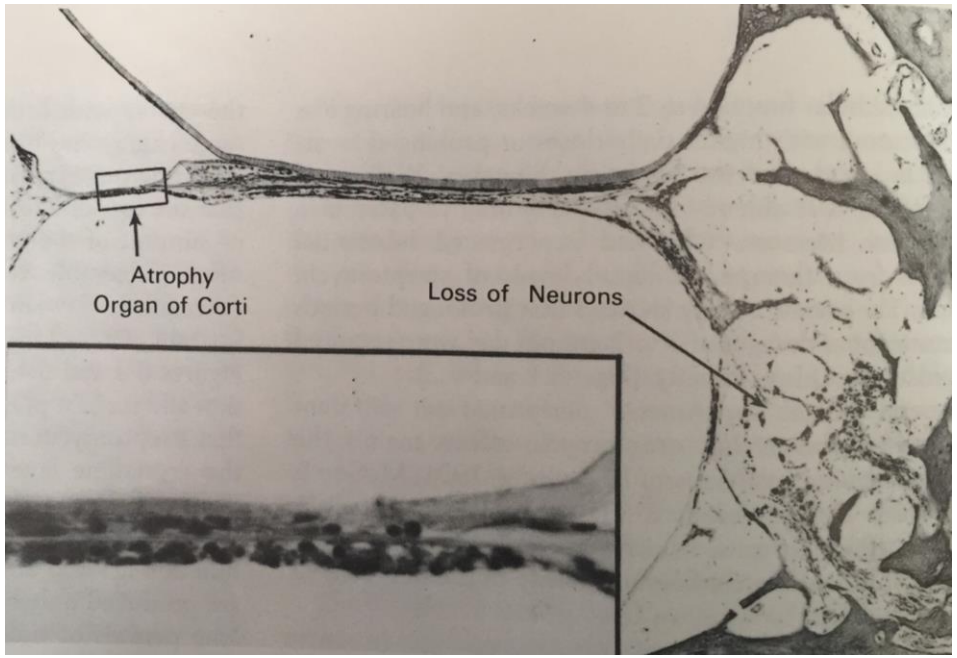


End-stage disease - “flat” epithelium



Taylor RR, Jagger DJ, Forge A (2012) Defining the Cellular Environment in the Organ of Corti following Extensive Hair Cell Loss: A Basis for Future Sensory Cell Replacement in the Cochlea. PLoS ONE 7(1): e30577. doi:10.1371/journal.pone.0030577

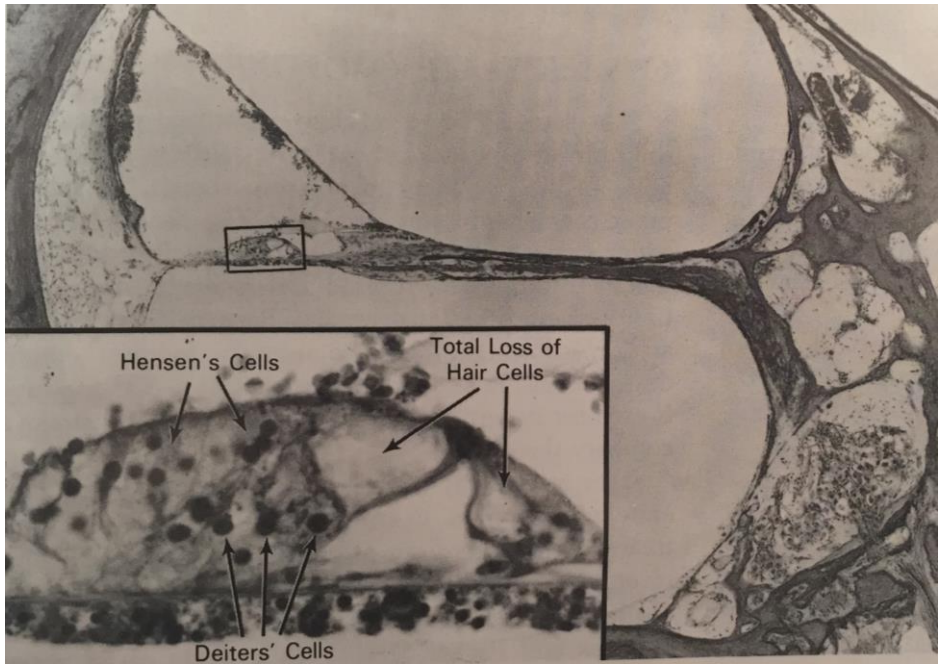
Which patients might have cochleae “permissible” for regeneration?



Definitely not

Streptomycin

Fig 6.2 Schuknecht’s Pathology of the Ear, Ed. 1

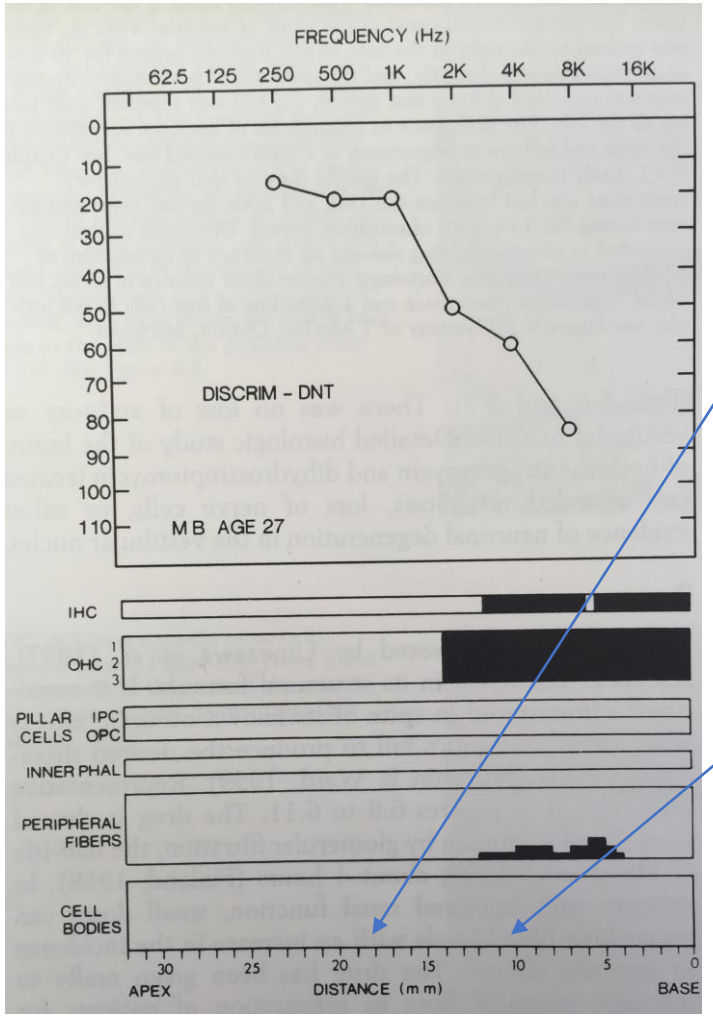


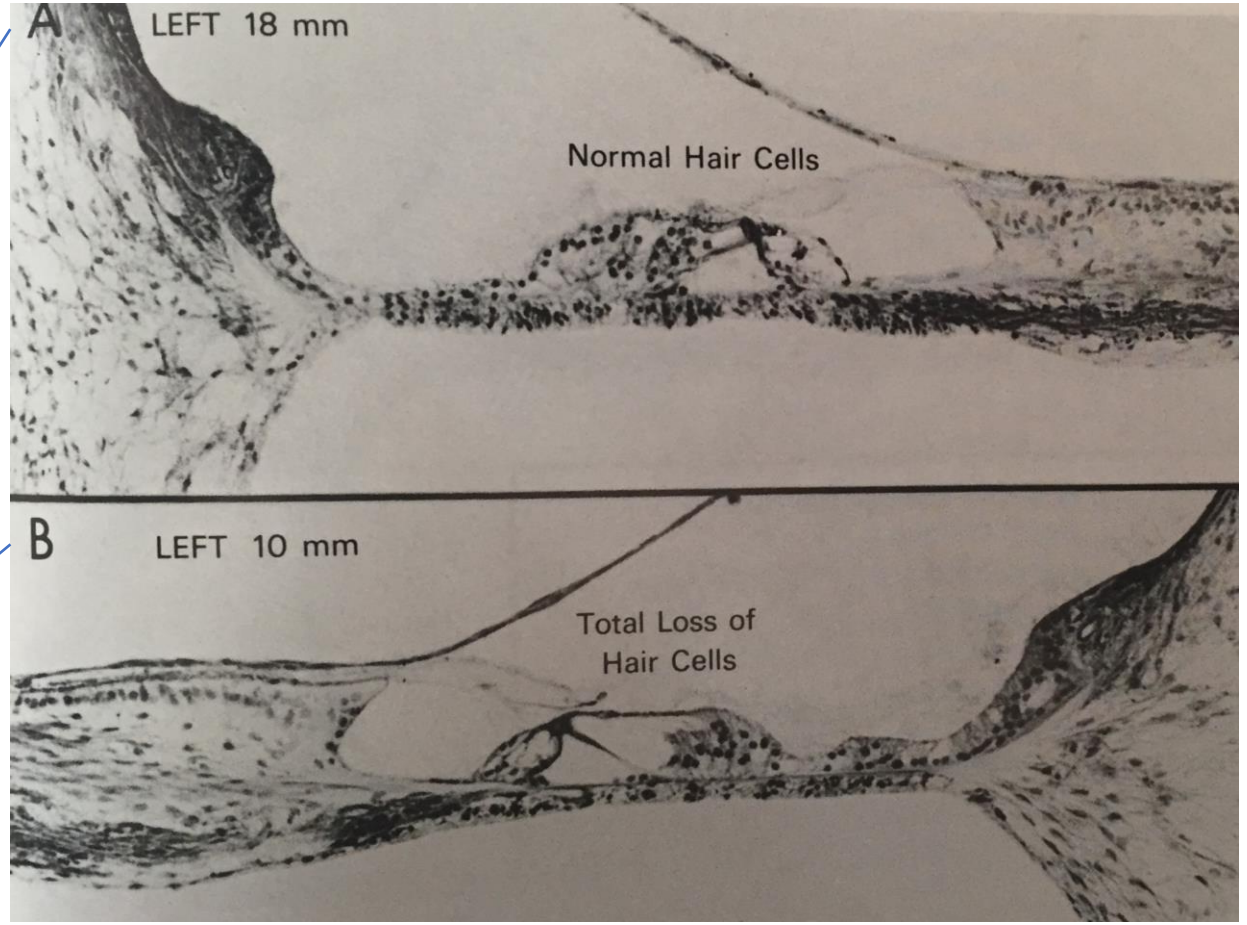
Possibly

Gentamicin

Fig 6.20 Shuknecht

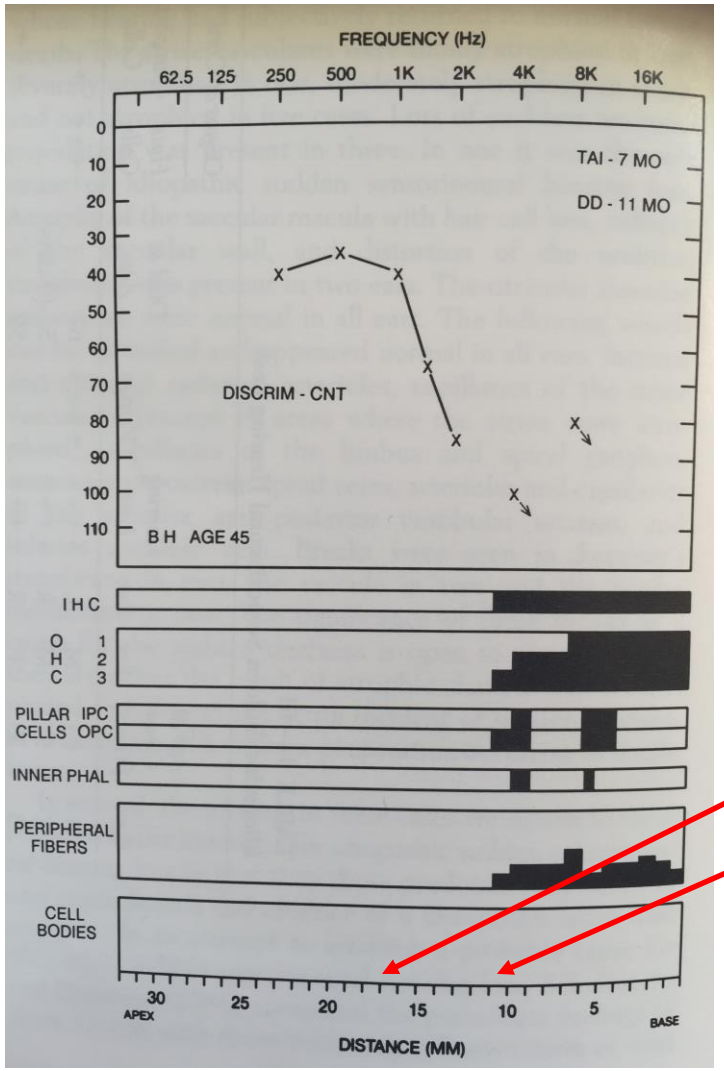
Can we predict “permissive” cochleae from hearing?

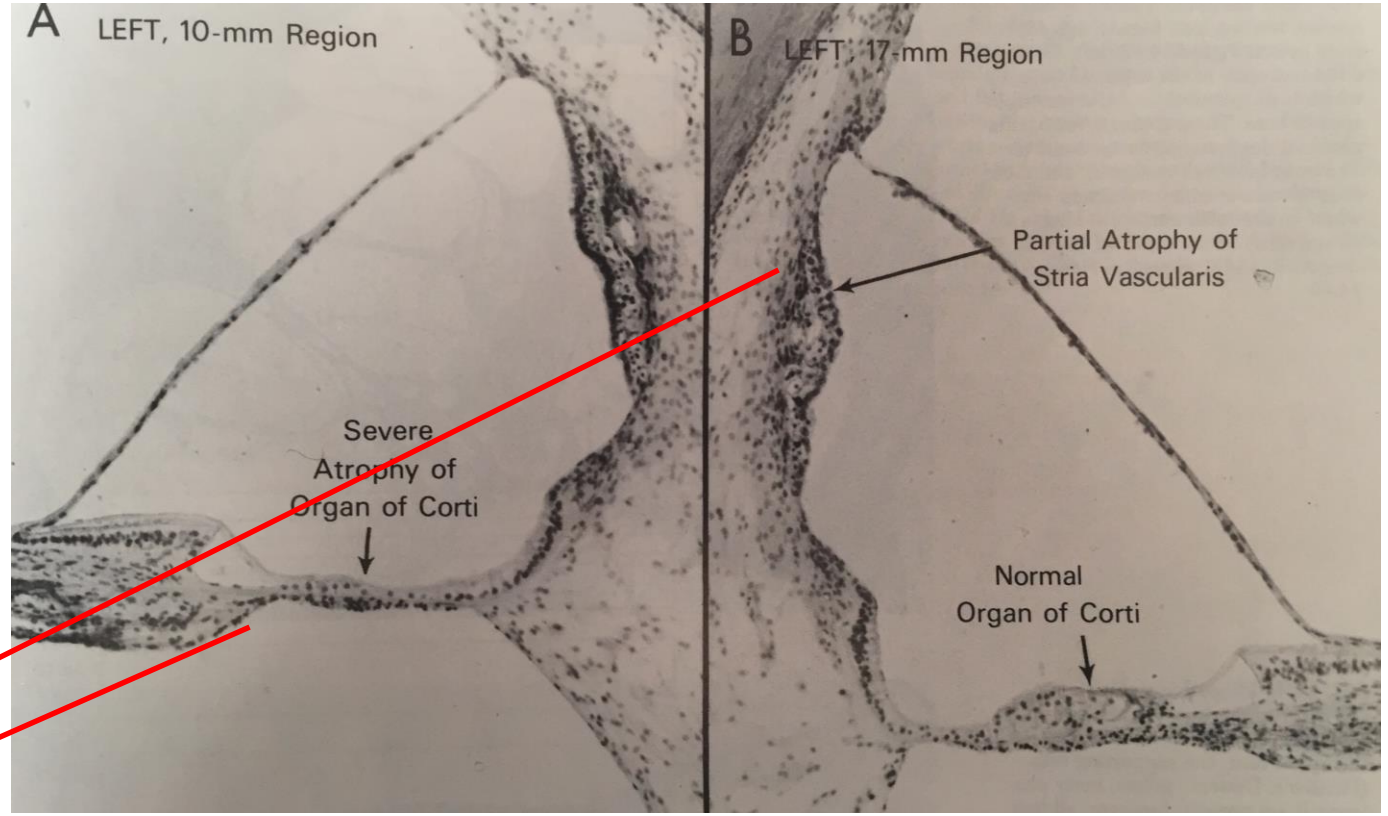




Schuknecht Fig 6.8, 6.9. Kanamycin toxicity

Idiopathic Sensorineural Hearing Loss

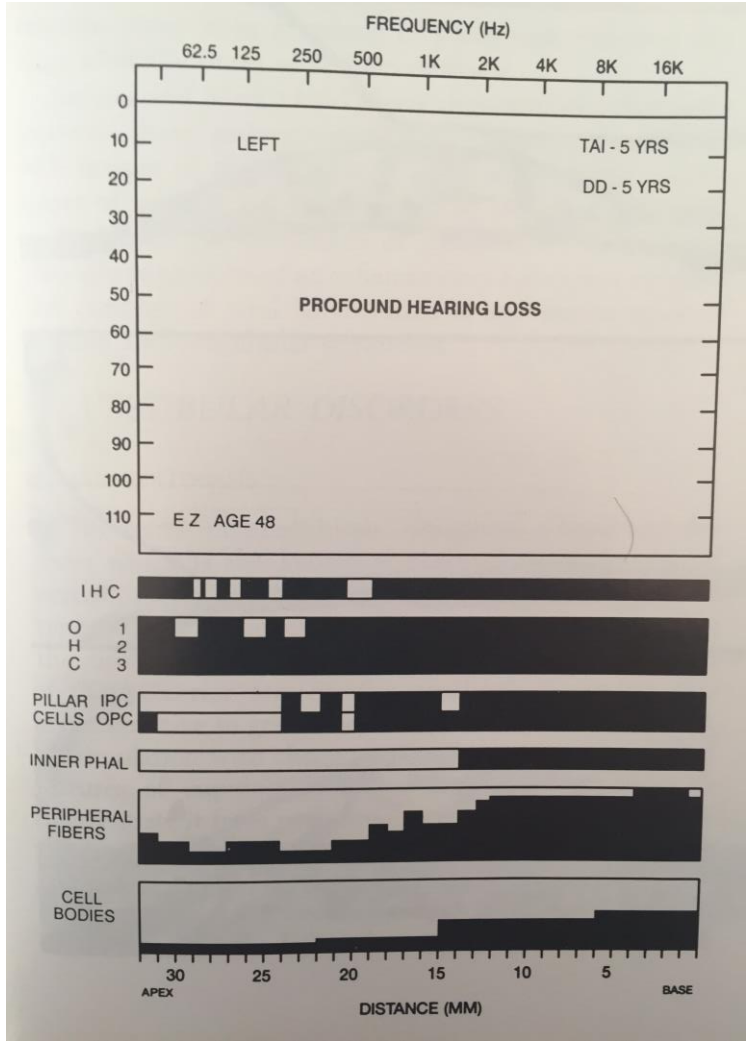


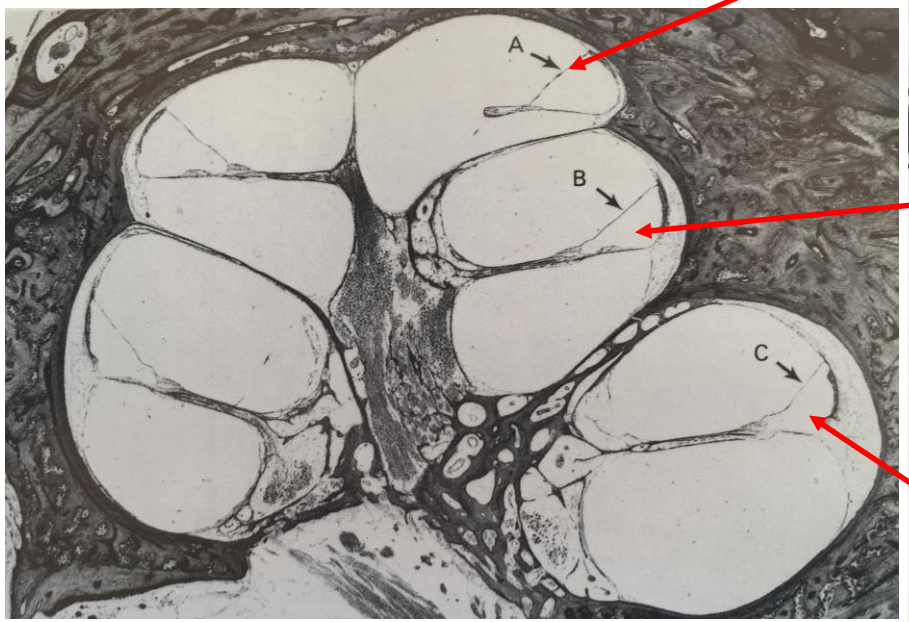


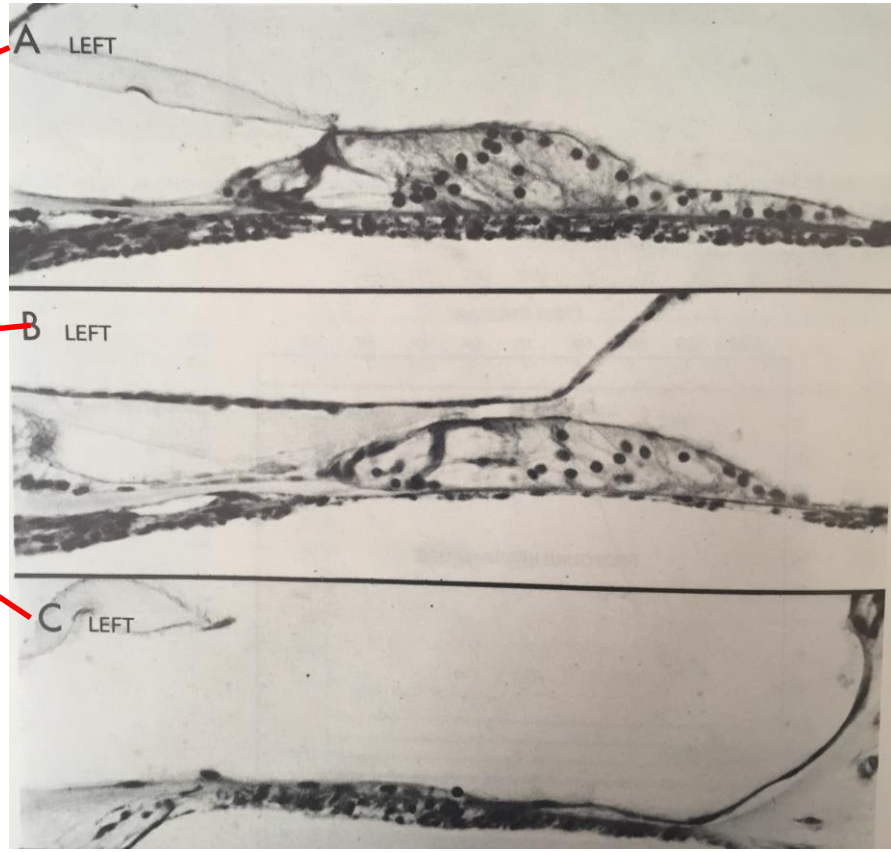
No possibility of regeneration at cochlear base

Strial injury more likely than hair cell loss at 1 kHz

Idiopathic Sensorineural Hearing Loss







Summary: Regenerative capacity can't be predicted from the audiogram

- Regeneration presumably requires
  a relatively "normal" architecture of organ of Corti.

- This is more likely to be seen at mild-to-moderate hearing loss, but
  - With mild-moderate loss the cause might be **strial** (i.e. the "battery") instead
  - With profound loss, the architecture of the organ of Corti can look either relatively normal or "flat" epithelium.

There is poor correlation between cellular damage and audiograms

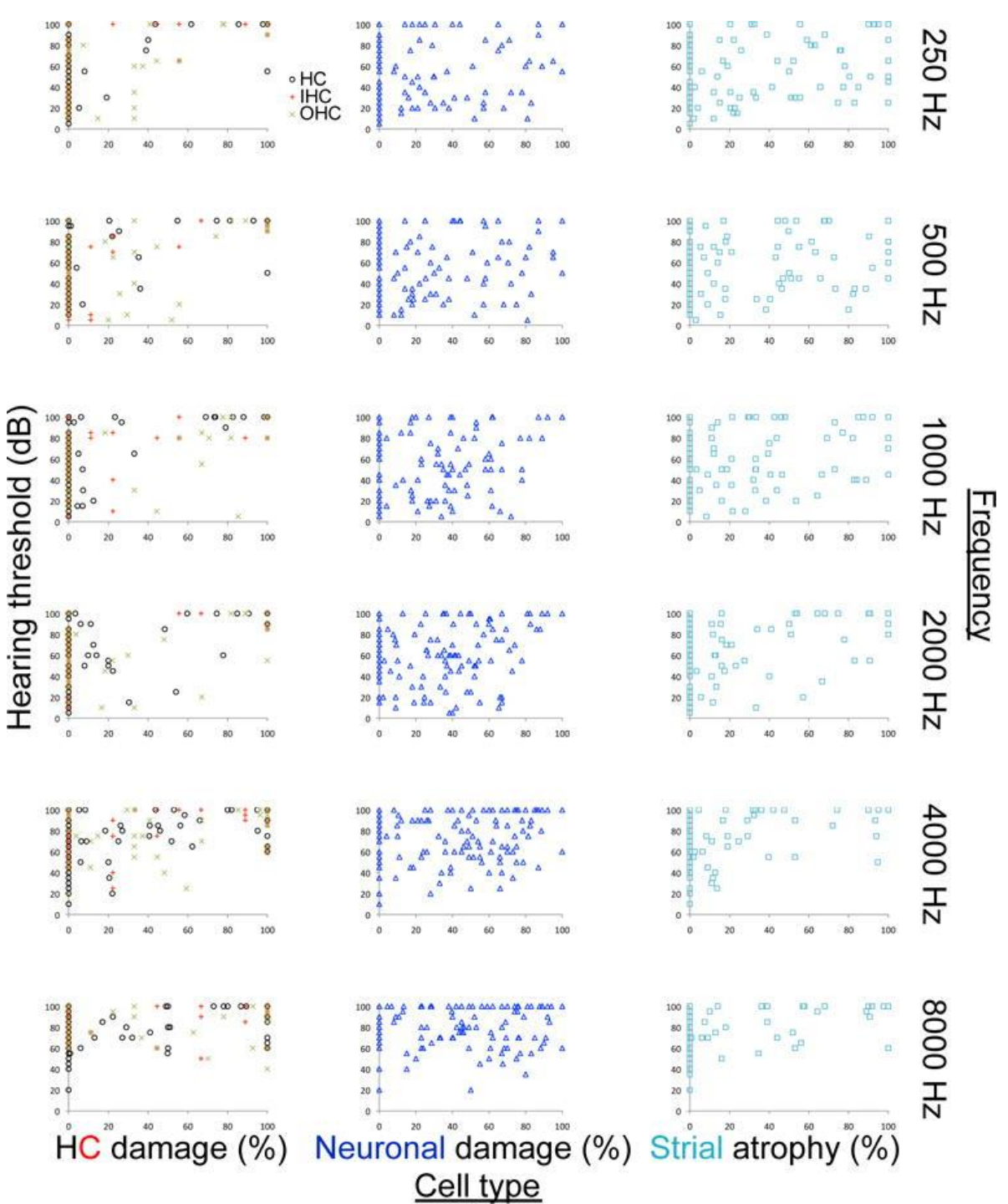


Fig 7. Landegger et al, Hear Res 2016

Note that the correlations between hearing loss and cellular injury are moderate at best

		Cell type				
		HC	IHC	OHC	SGN	Stria
Frequency (Hz)	250	0.38*	0.67*	0.53*	0.08	0.22*
	500	0.42*	0.52*	0.48*	0.03	0.21*
	1000	0.47*	0.67*	0.63*	0.04	0.30*
	2000	0.45*	0.70*	0.49*	0.02	0.26*
	4000	0.49*	0.52*	0.40*	0.08	0.24*
	8000	0.41*	0.49*	0.32*	−0.06	0.11
Word recognition		0.37*	0.38*	0.23	0.10	0.27

* $p<0.05$, Table 1, Landegger et al Hear Res 2016

Speech understanding too correlates poorly with cochlear cellular damage

100% hair cell survival, yet 0% word recognition!

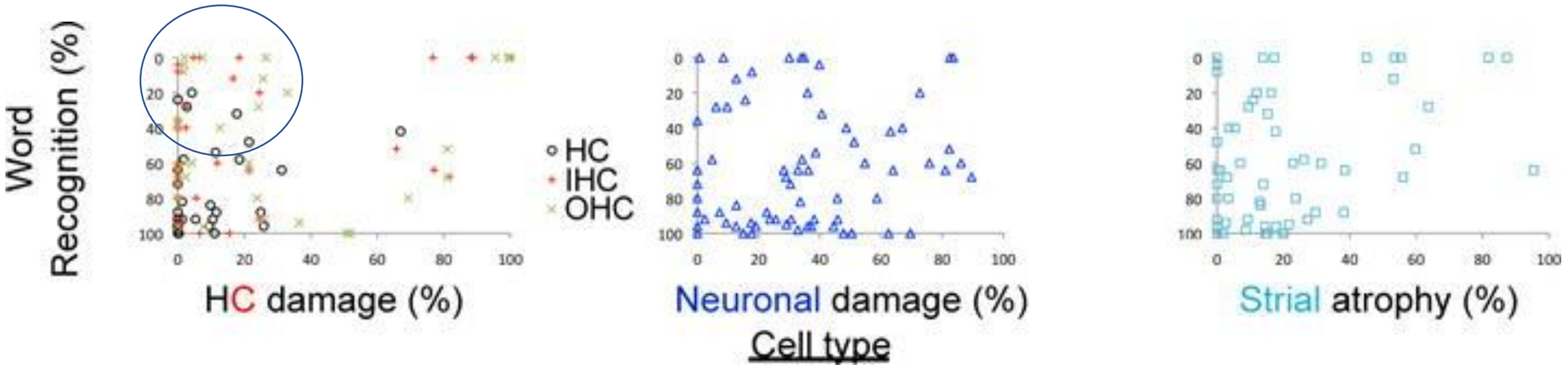
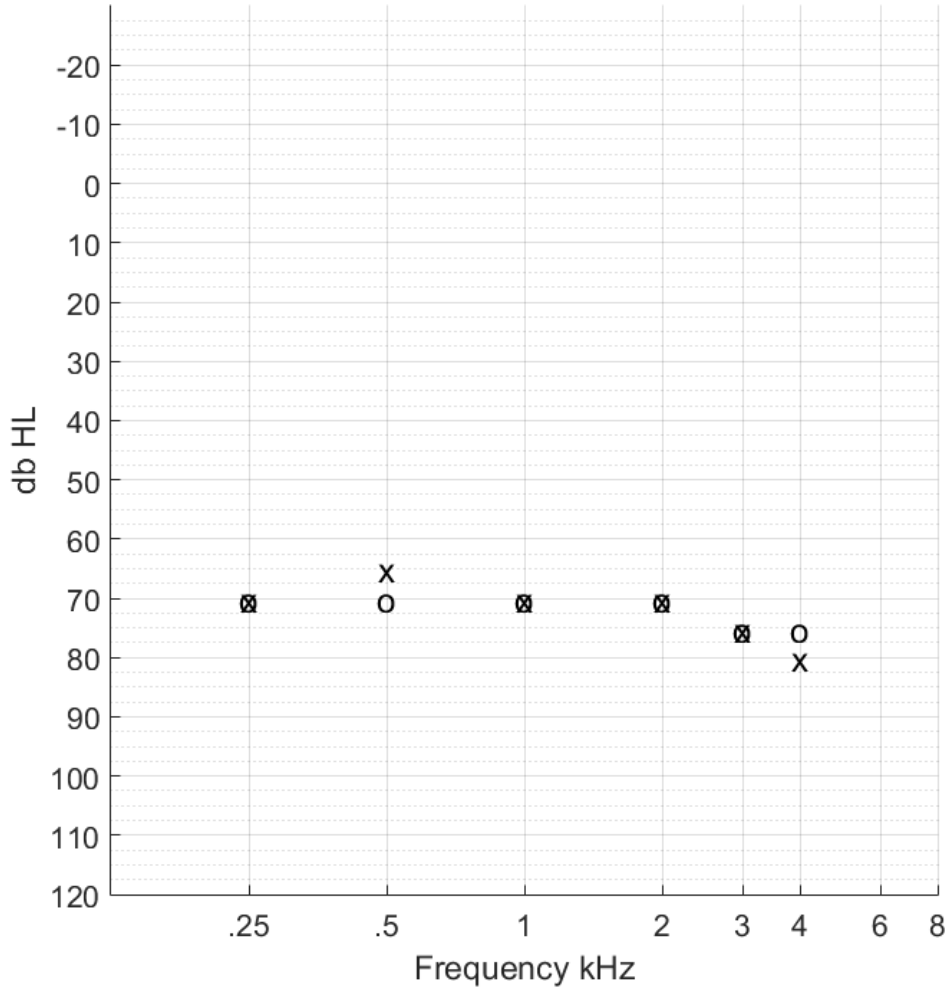


Fig 7. Landegger et al, Hear Res 2016

This is presumably why audiograms do not predict speech recognition well



Speech Recognition

The diagnostic dilemma

- Audiograms and speech testing do not predict cochlear pathology.
- Specific (Mendelian) genetic lesions seen in <10% adults hearing loss. (~40-50% of children with hearing loss)
- Genetic variation *points towards* neuronal, hair cell or strial dysfunction, but is not specifically diagnostic.

- Accurate diagnostics requires an assessment of the ***function of surviving cochlear hair cells, neurons and stria***, but we lack these tools for severe-profound hearing loss.

New approaches to functional assessment

We are using the cochlear implant to assess
function of surviving cochlear hair cells, neurons and stria

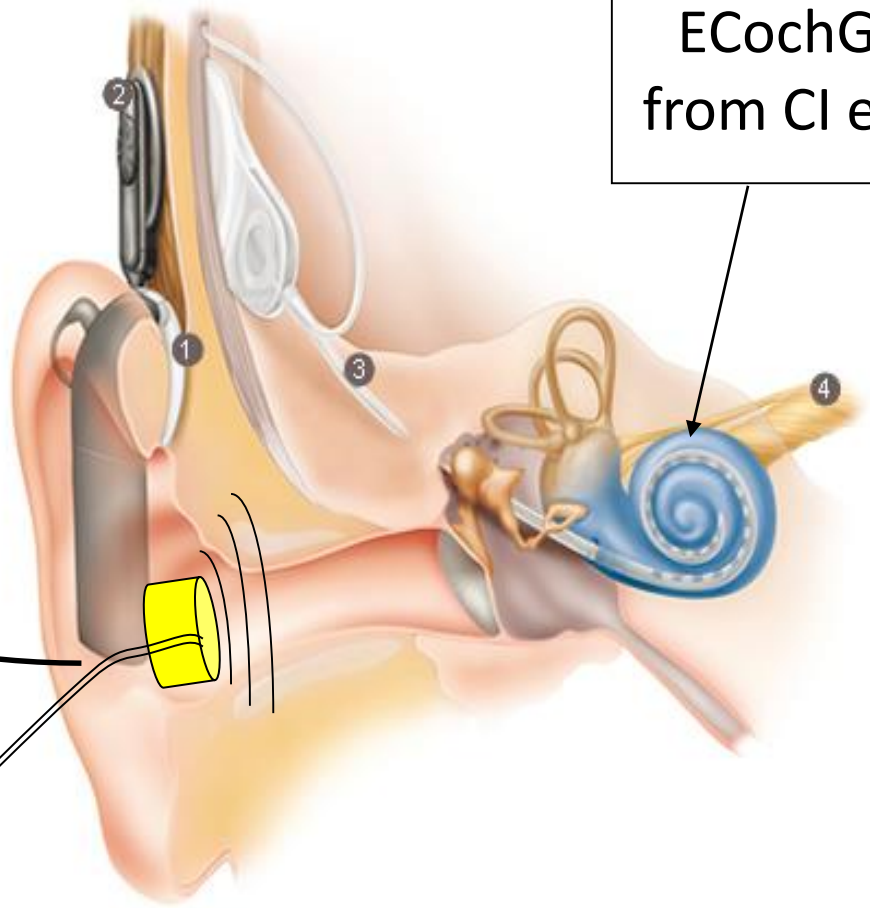
Cochlear Response telemetry

USB Cochlear Implant Communication Pod

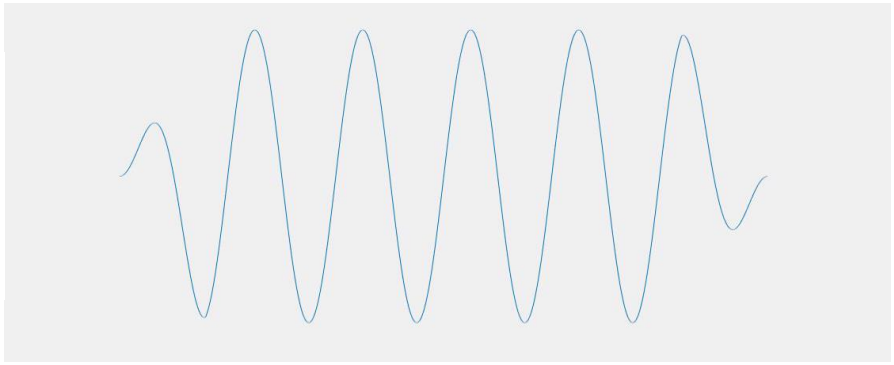
Laptop
Sound card
(signal generation and recording)

Custom Software

Insert
Tube
Phone

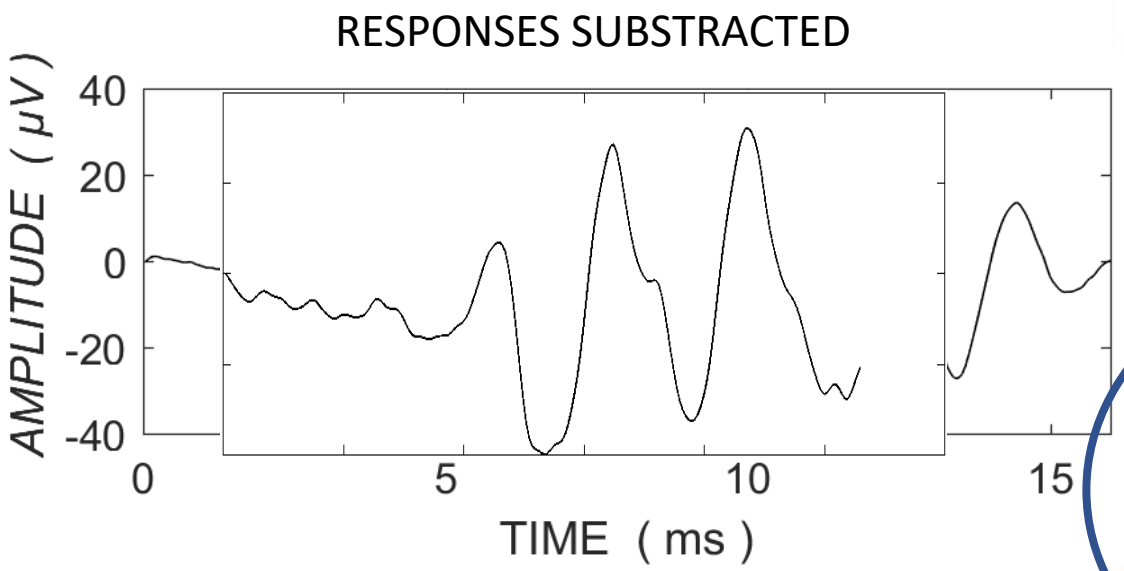


ECochG directly from CI electrodes



The Cochlear Microphonic

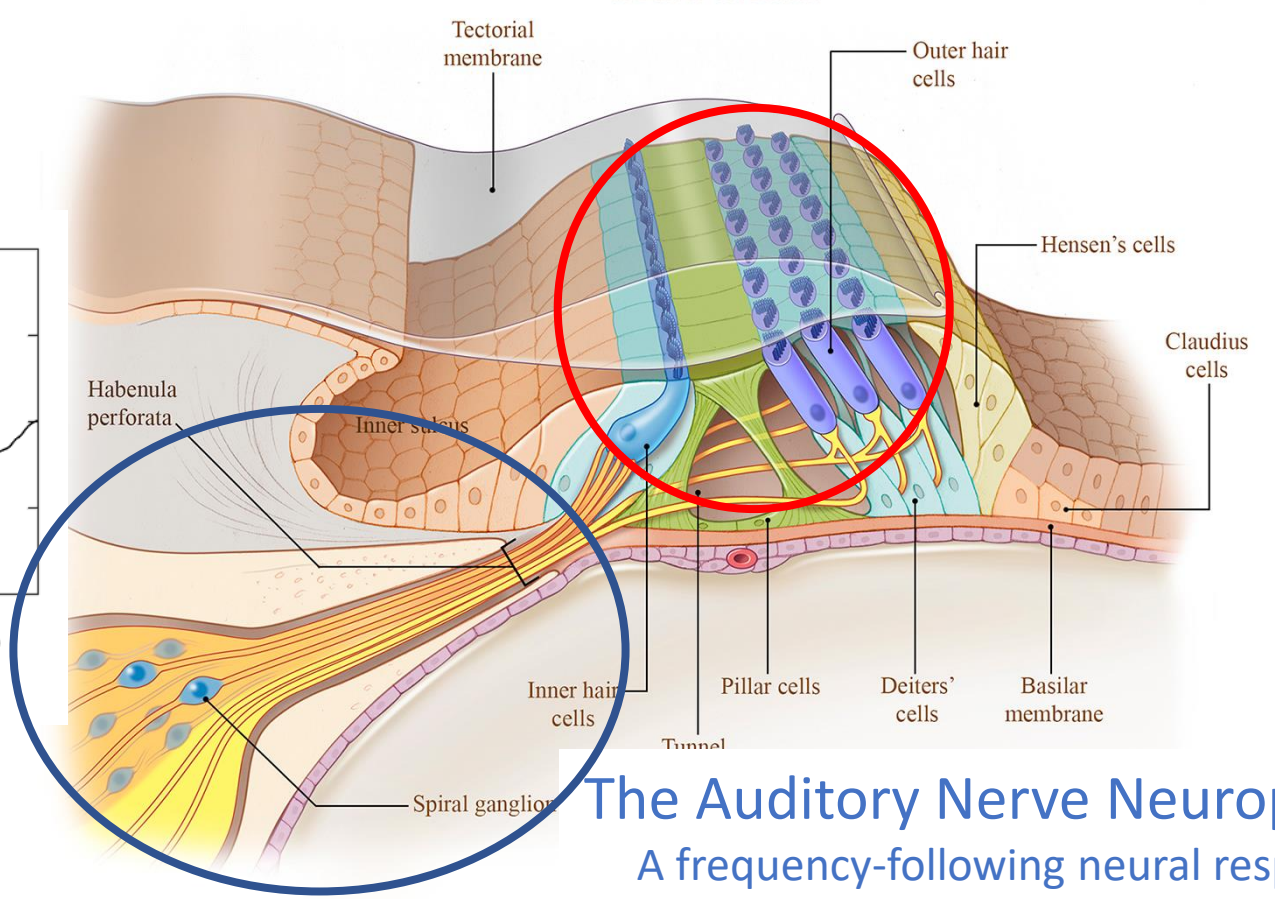
A frequency-following hair cell response



”Pure” Cochlear Response

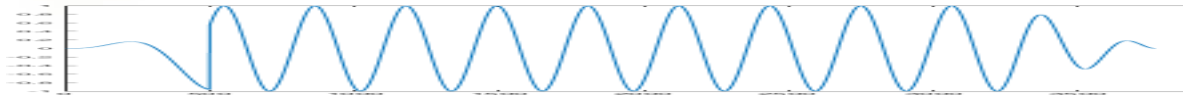
and

Auditory Nerve Neurophonic



The Auditory Nerve Neurophonic

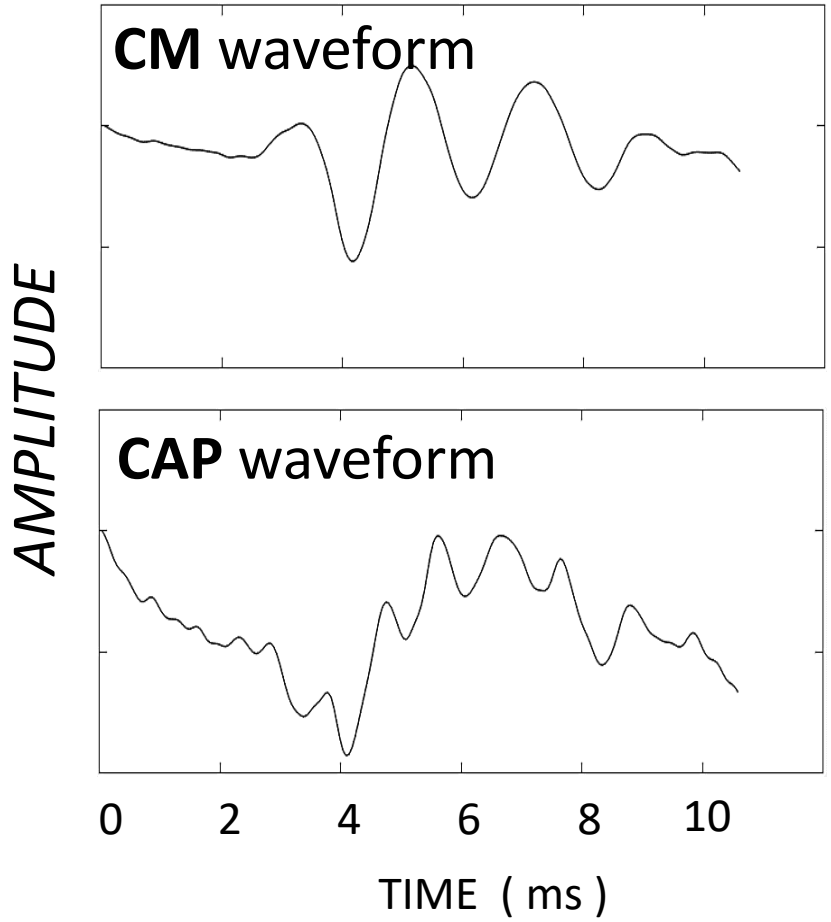
A frequency-following neural response



Separating the Hair cell - Cochlear Microphonic (CM) and the Neural - Auditory Nerve Neurophonic responses

CM without Auditory Neurophonic (ANN)

Participant #5: ANN weak or absent



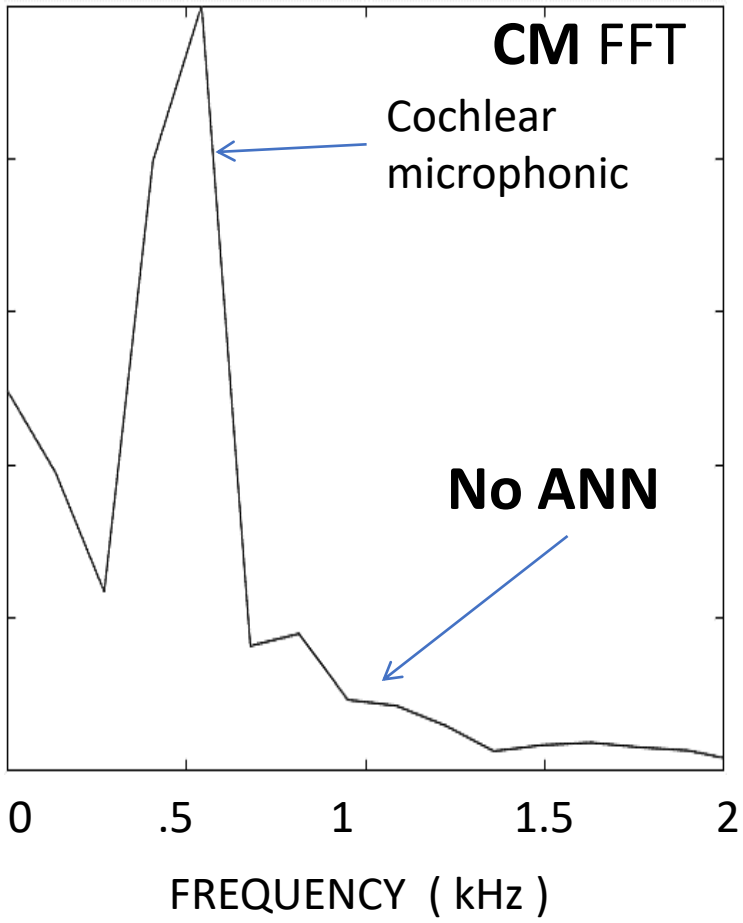
We analyse the frequency components of the CM response using the Fast Fourier Transform.

CM without Auditory Neurophonic (ANN)

- Hair cell responses: At the first harmonic (fundamental)

- Neural (ANN) response is at the second harmonic

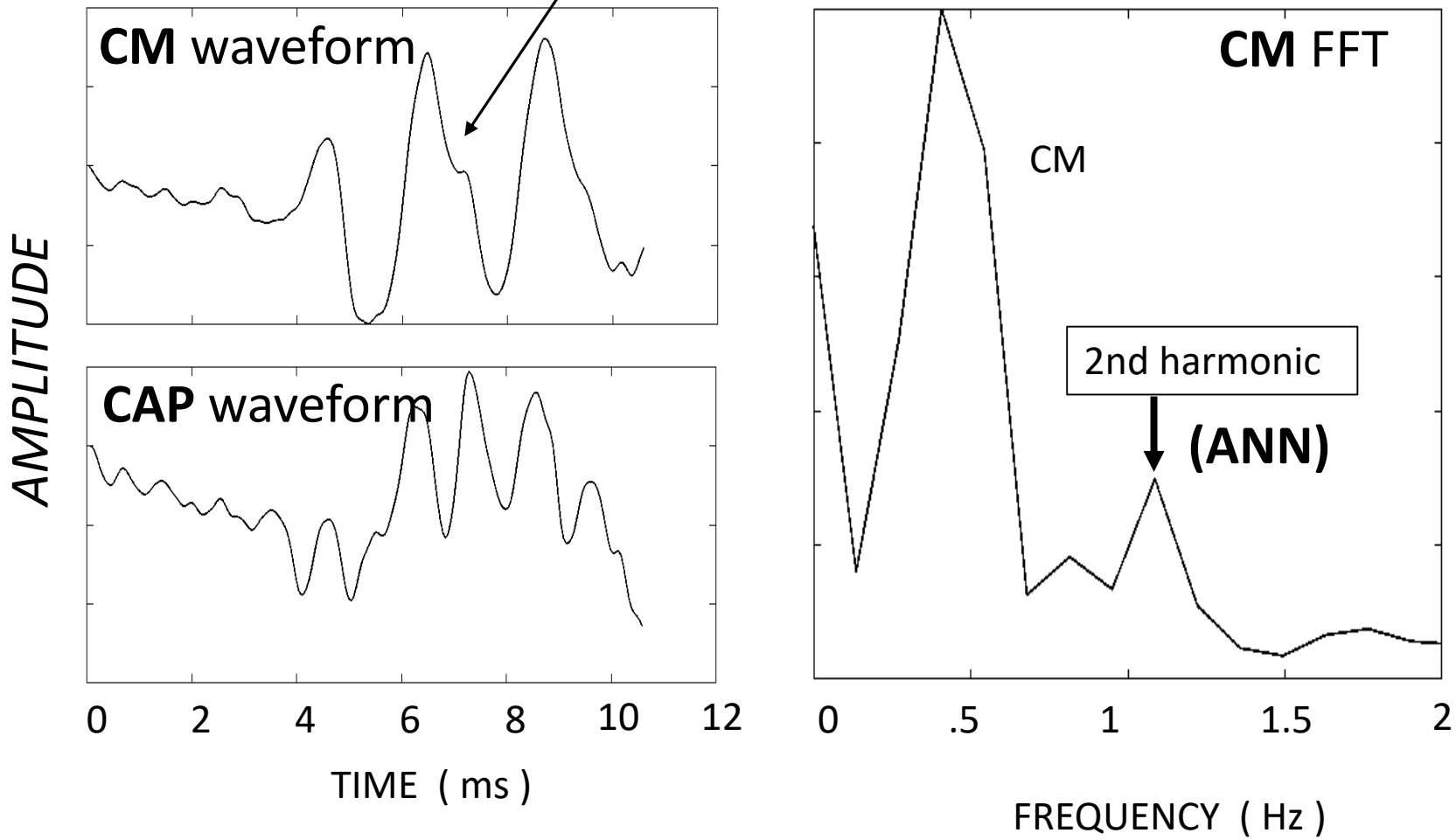
(work pioneered by
Doug Fitzpatrick, UNC)



CM with ANN

When distortion is synchronous with the fundamental, the second harmonic may be due to hair-cell distortion

Participant #5: **Late in insertion** ANN present

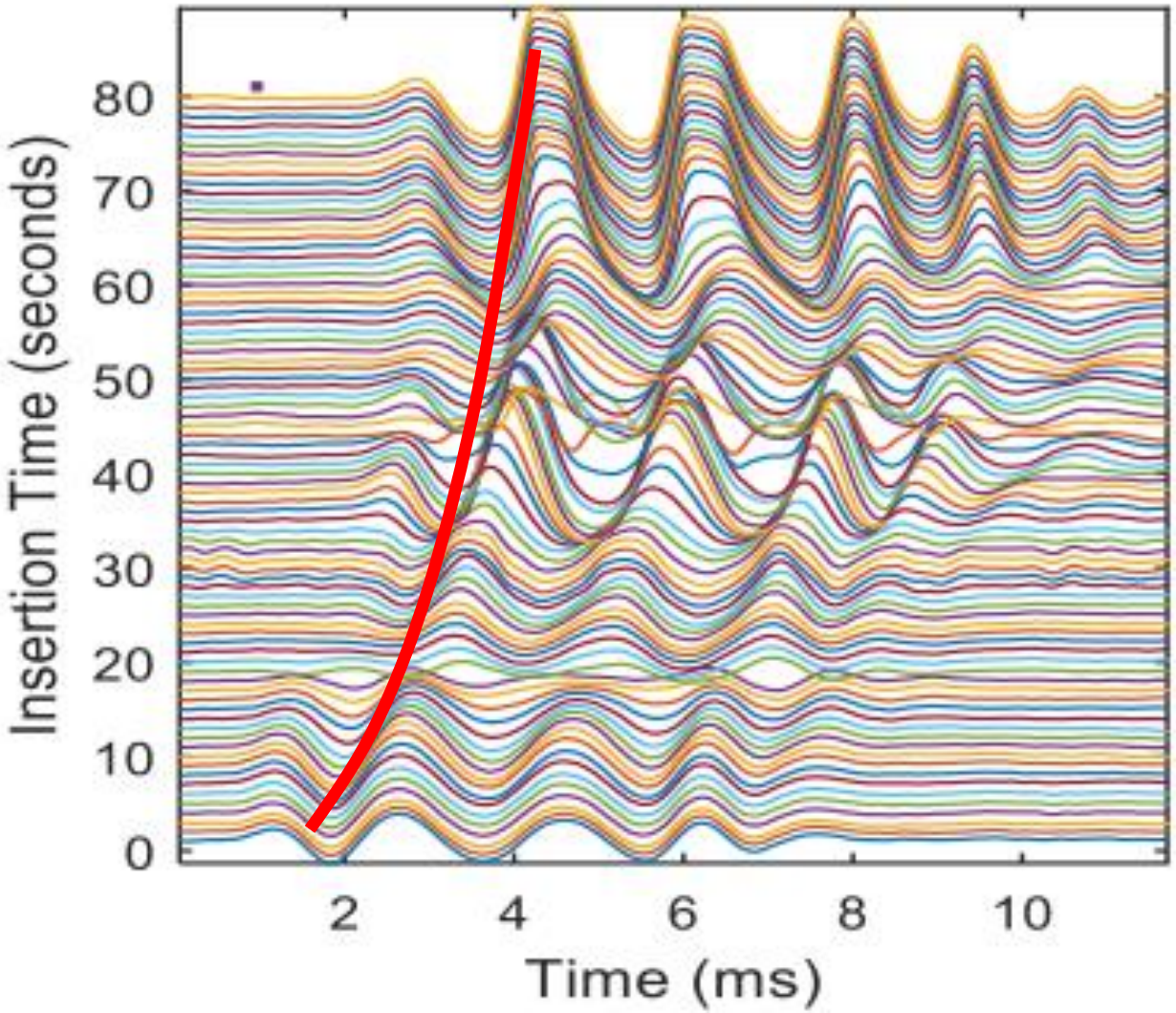


Separation of Hair cell and neural responses

- Contributions from
  hair cells: (CM and distortion products) and
  neurons: (Auditory neurophonic)
  can be derived by analysis of frequency analysis of the “CM” trace.

- CM & ANN vary between patients,
  and at different places within the cochlea

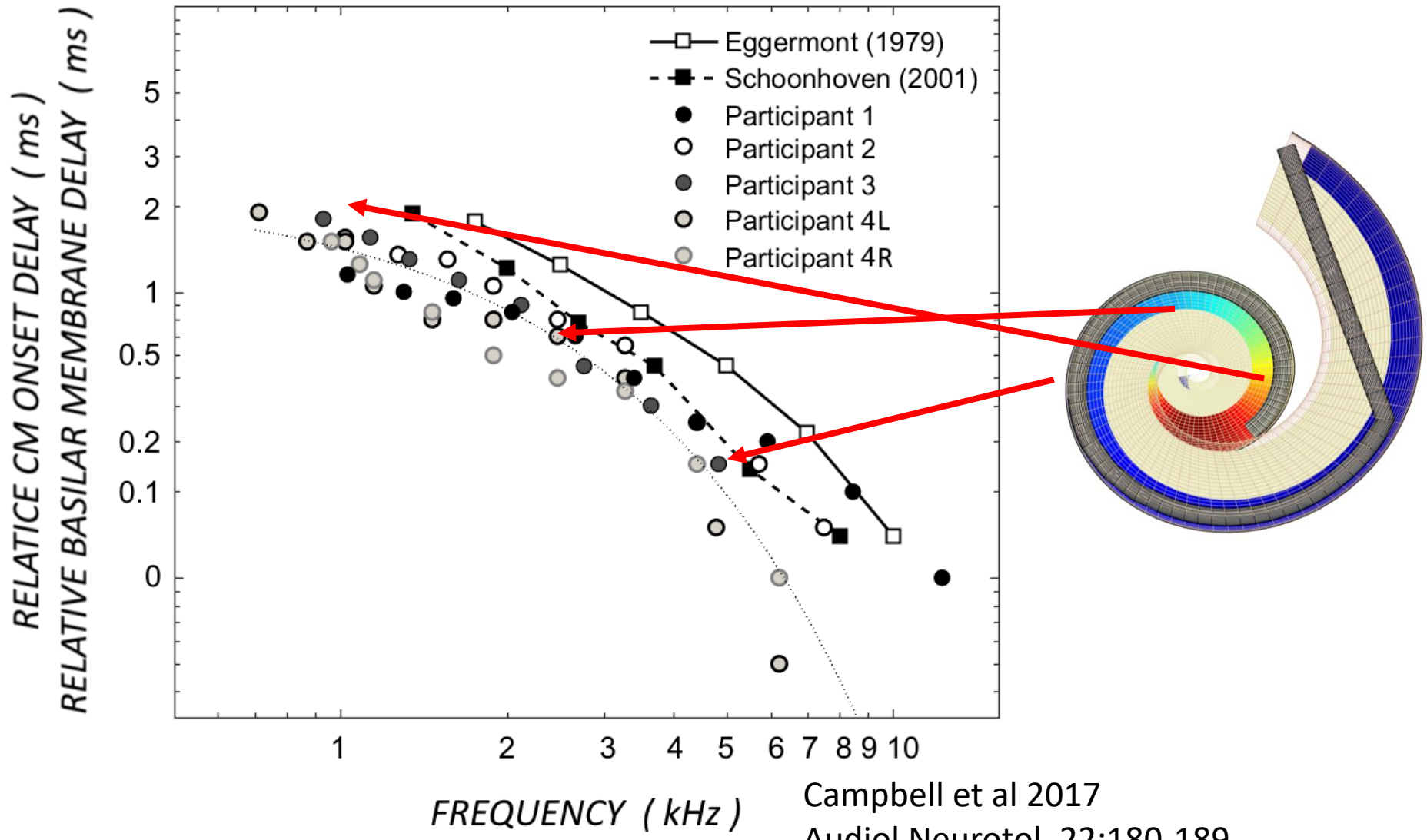
Biomarker 2: Latency



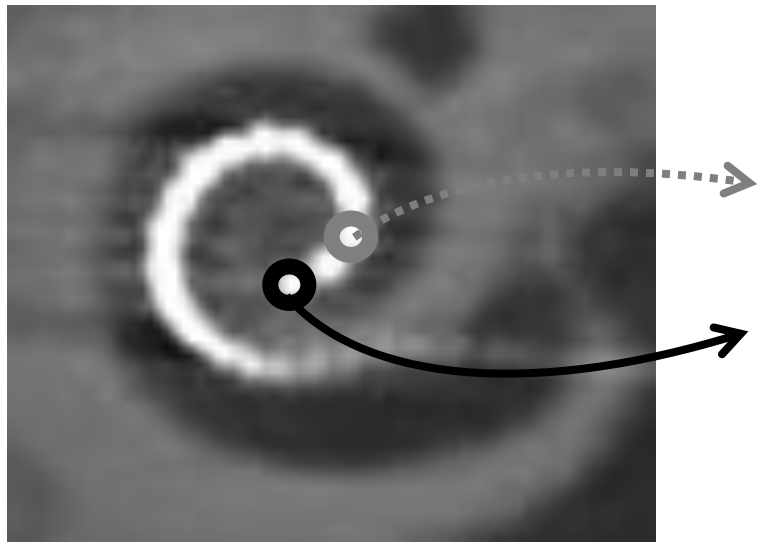
CM in patient with Auditory neuropathy (good hair cell survival)

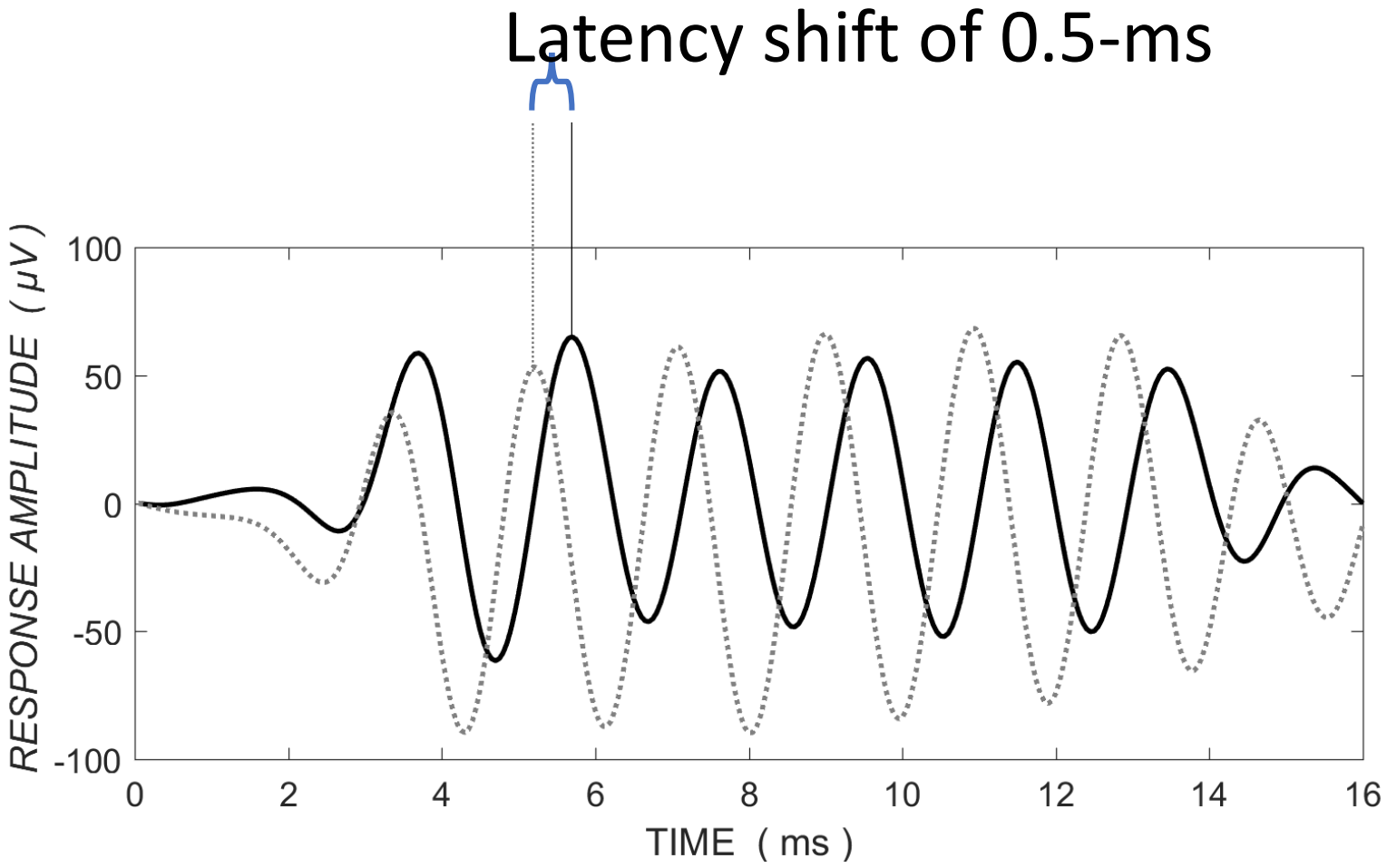
Latency increases as electrode advances into the cochlea

Latency: tells us where the response arose from



Campbell et al 2017
Audiol Neurotol, 22:180-189



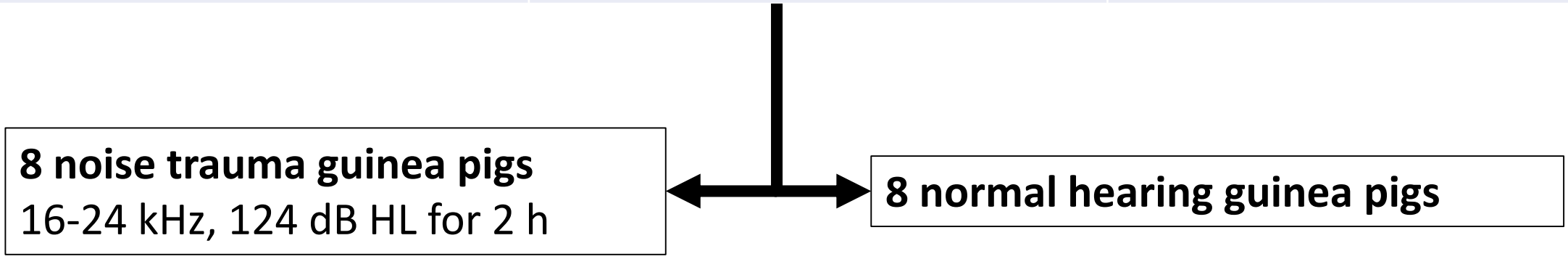


Hypothesis:

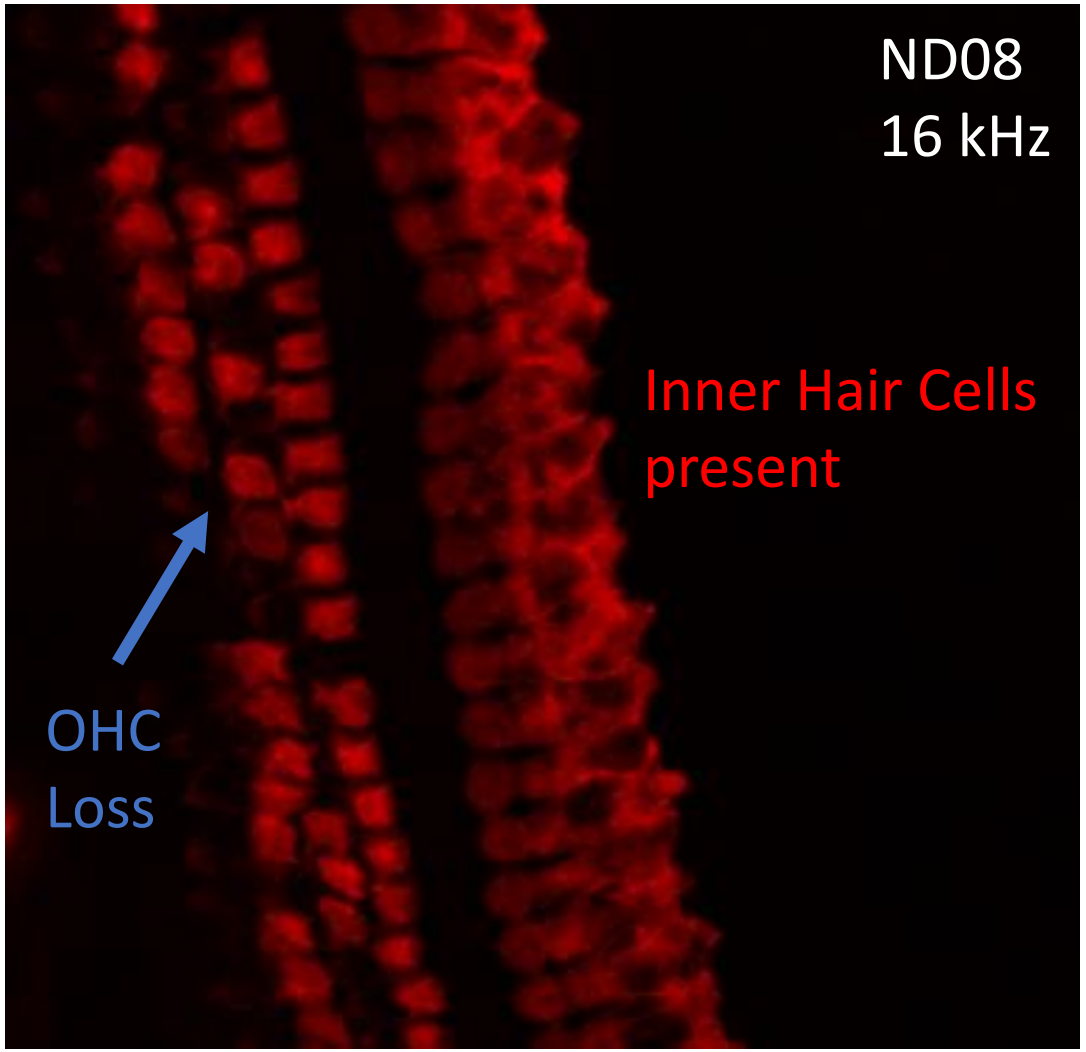
Latency shift is a biomarker for local Outer Hair Cell Survival

Confirmation in animal model of CI

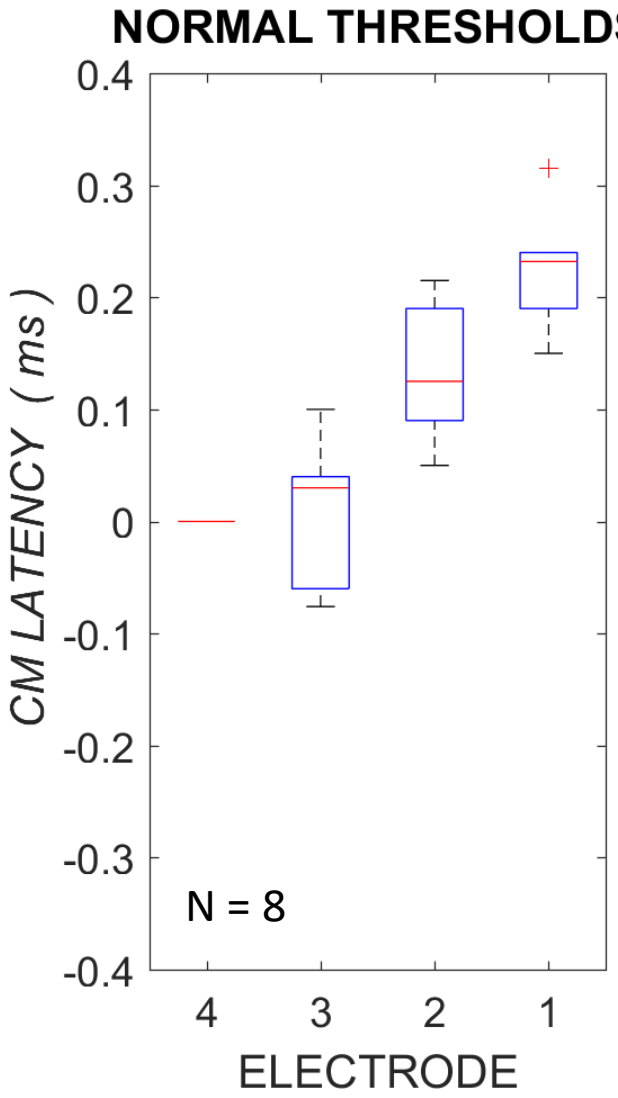
	Guinea Pig Array	Human Array
# Intra-cochlear electrodes	4	22
Typical insertion depth	5mm	20-25mm
Frequency range covered	32 to 16 kHz	20 to 1 kHz
Histology possible	**YES**	

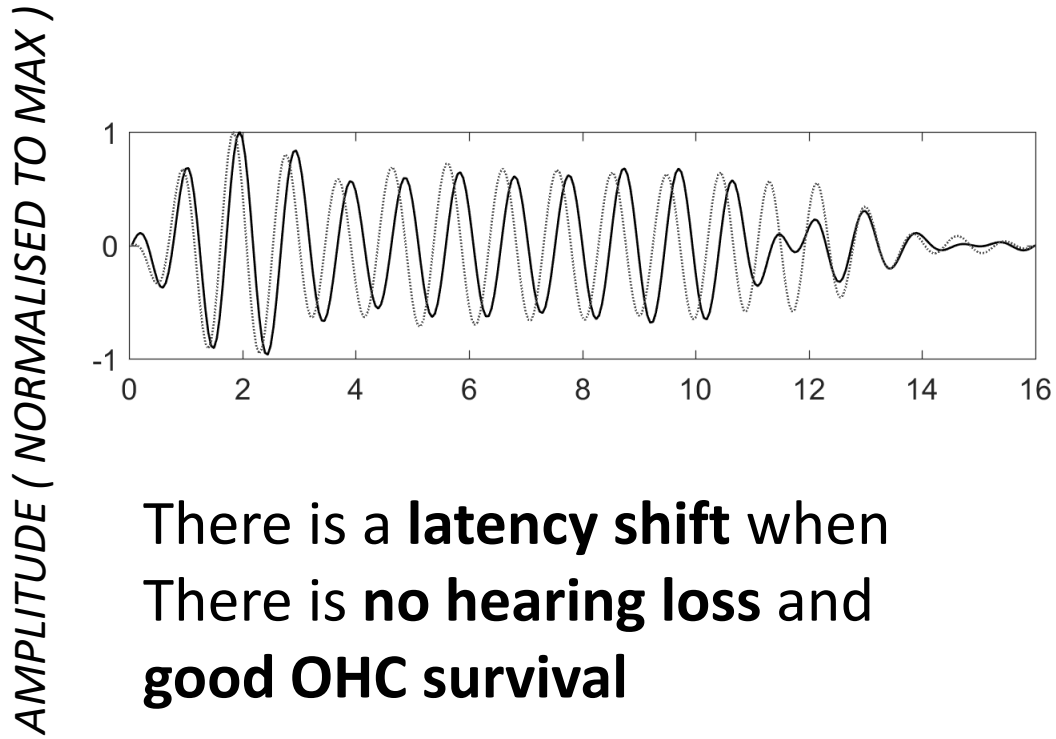


Outer hair cell loss at 16 kHz after noise



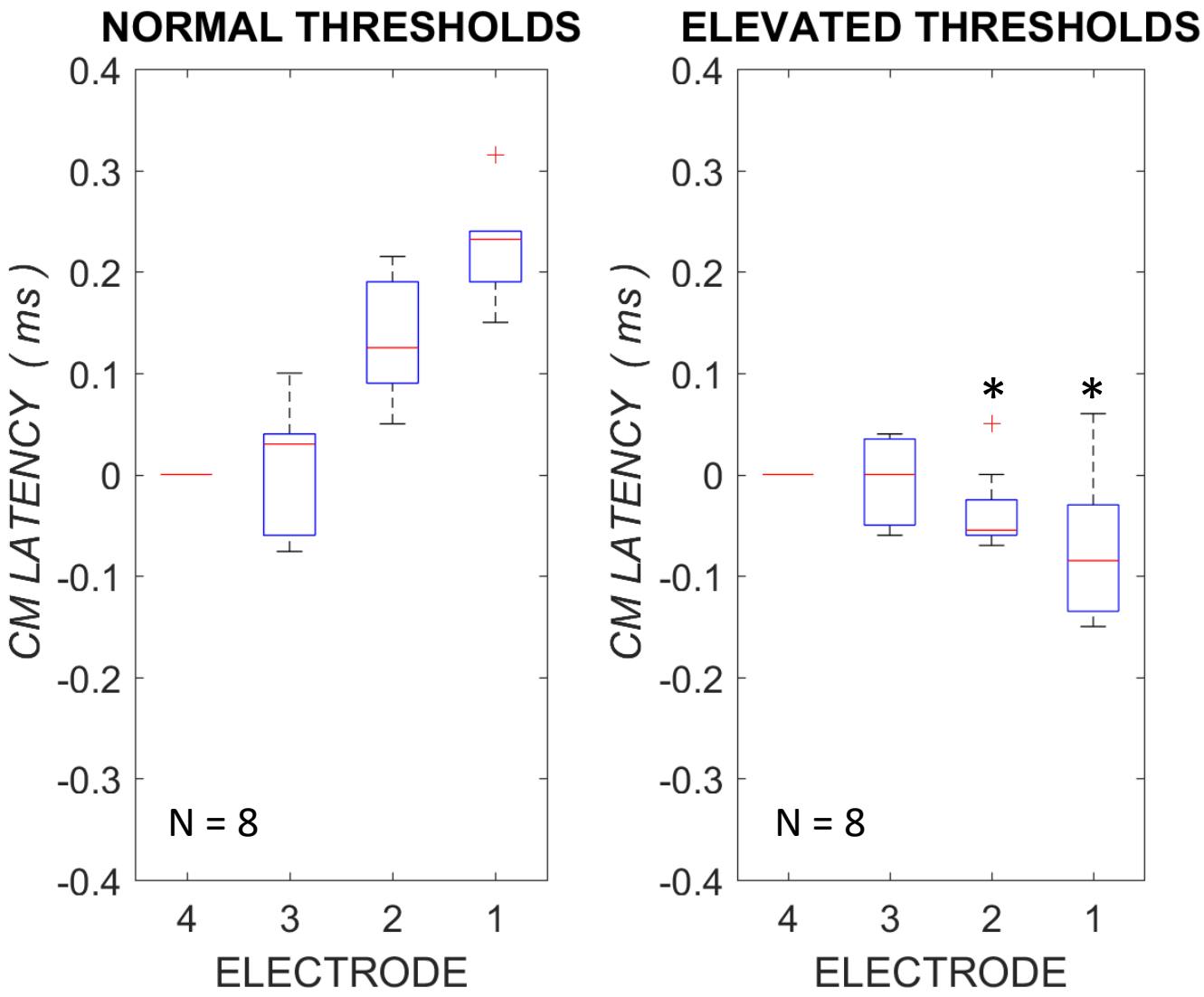
Latency shift when OHC present

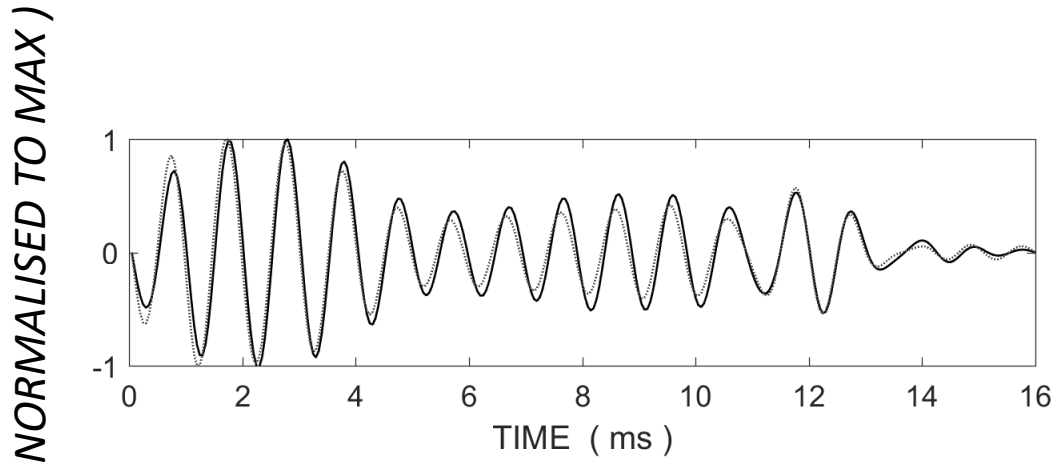




There is a **latency shift** when There is **no hearing loss** and **good OHC survival**

No latency shift when few OHC survive

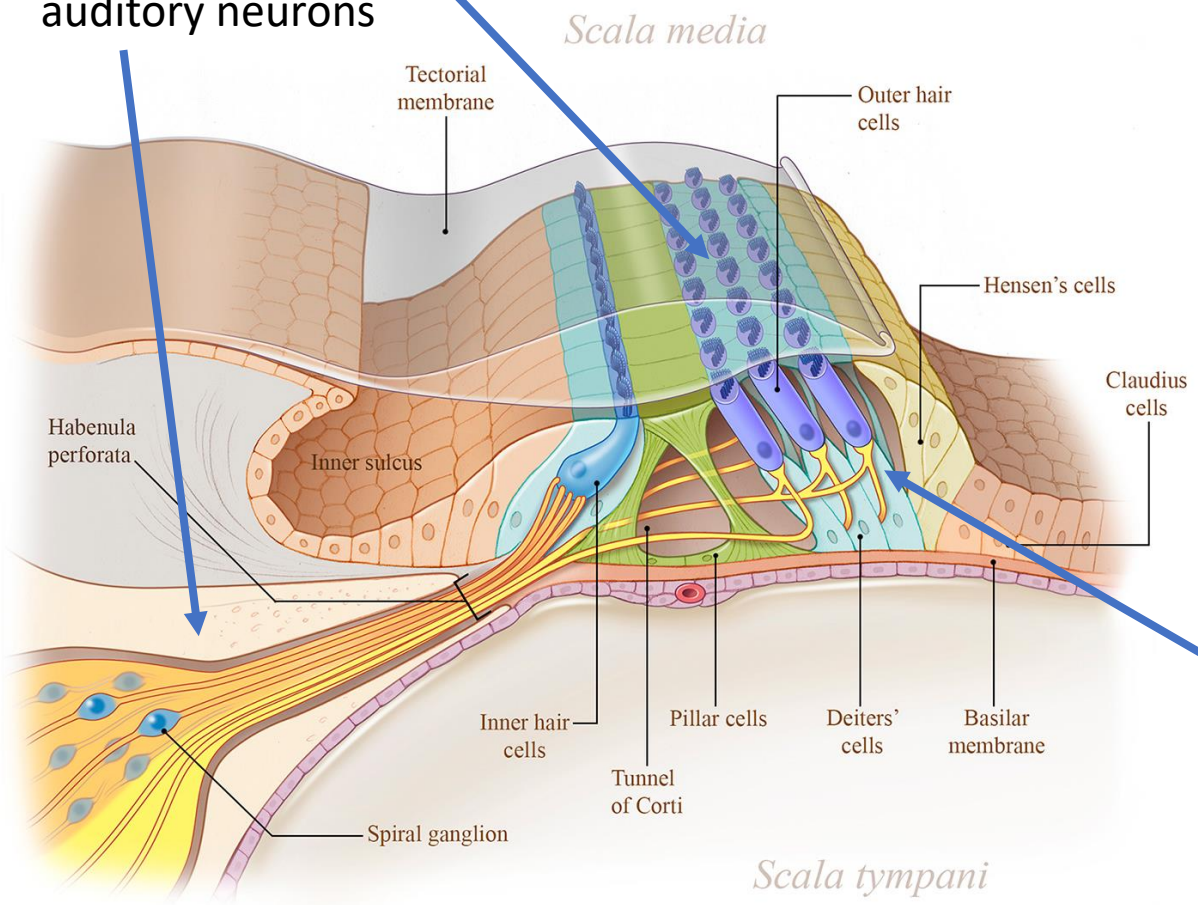


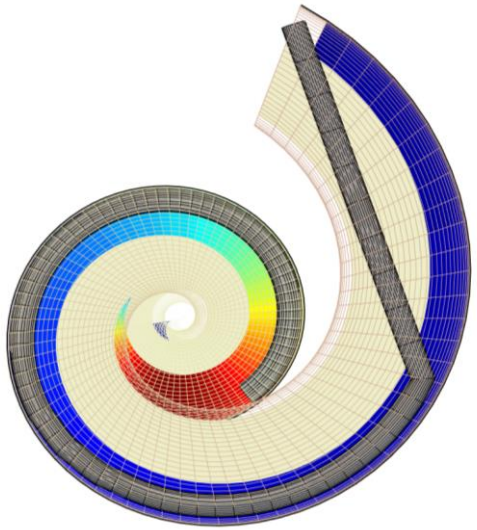


No latency shift when there is **hearing loss and OHC loss**

New diagnostics from CI derived ECochG

We can determine when there are functioning hair cells and auditory neurons

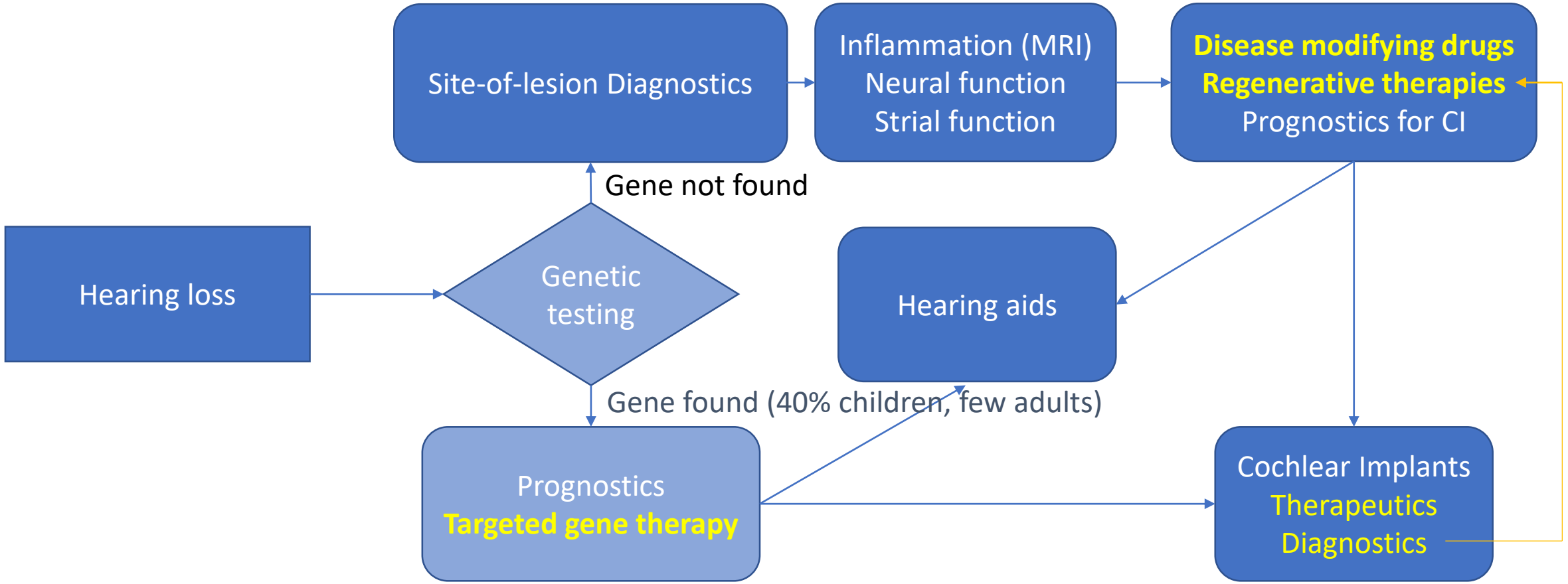




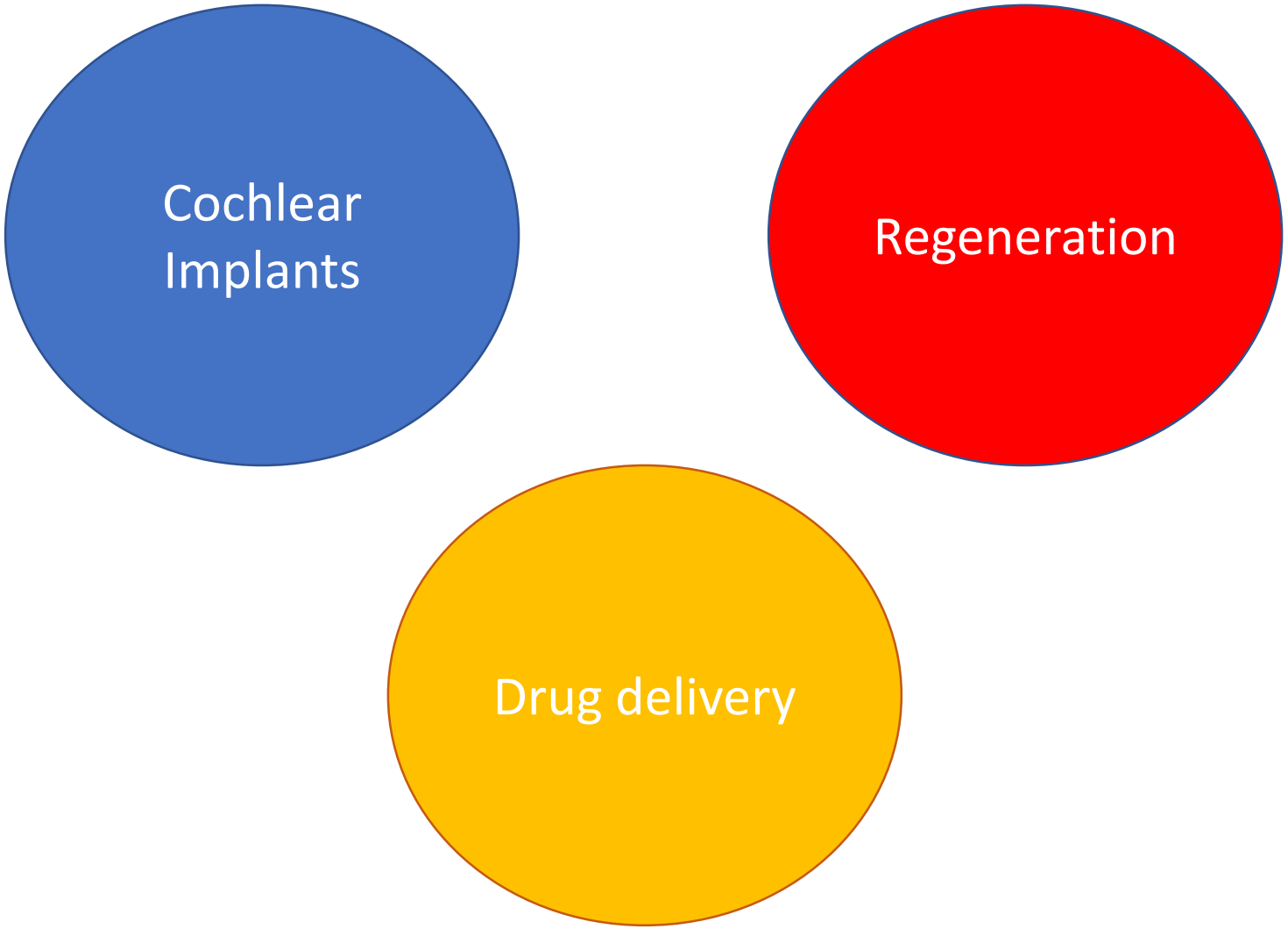
Latency:
We can tell where in the cochlea these are located

Latency-shift:
Appears to be a specific "biomarker" for outer hair cell function above the electrode.

Treatment of hearing now, and in the future



The future?



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