The future of inner ear drug delivery

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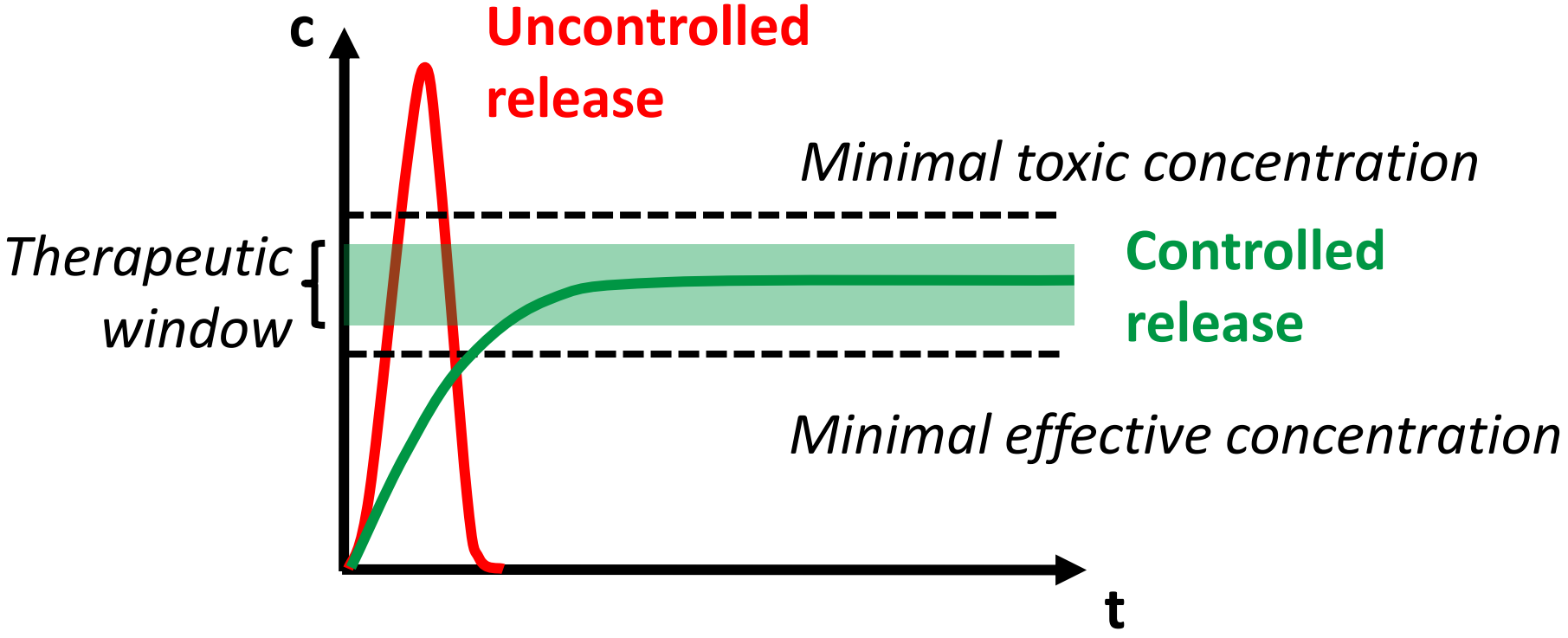
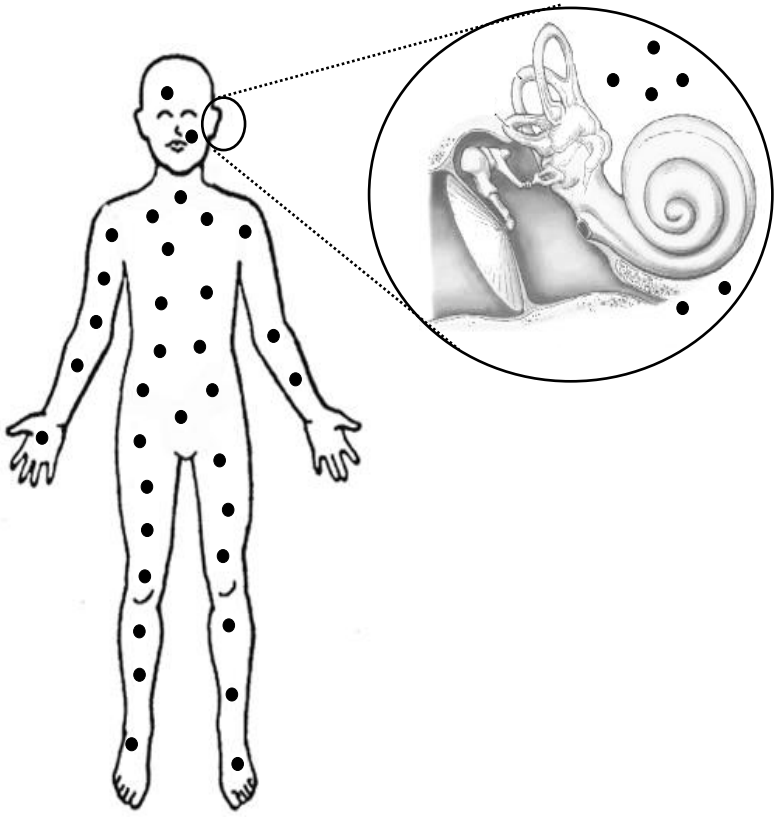
Inserm U1008: Controlled Drug Delivery Systems and Biomaterials

Why Controlled Drug Delivery?

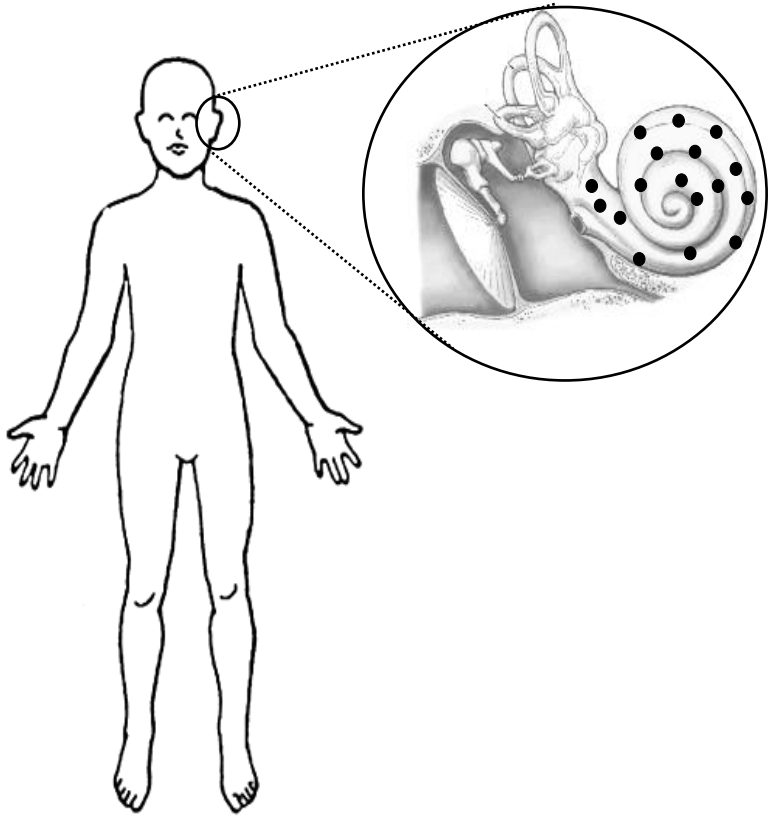
Drug concentration at the site of action ⇨ **Efficacy & Safety**



Drug delivery to the inner ear

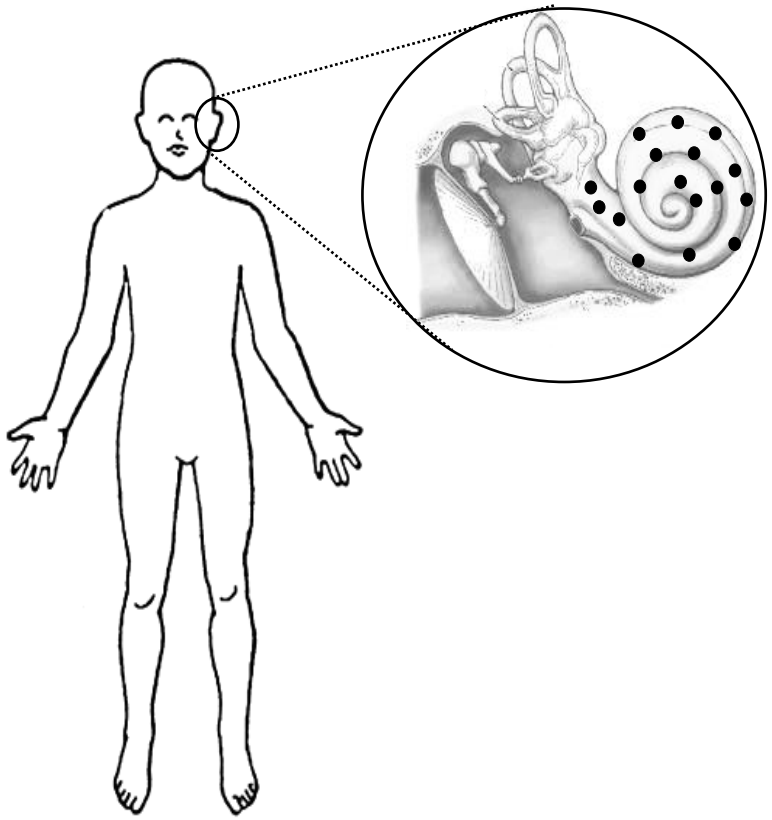


General administration



Intra-cochlear administration

Blood-Cochlear barrier



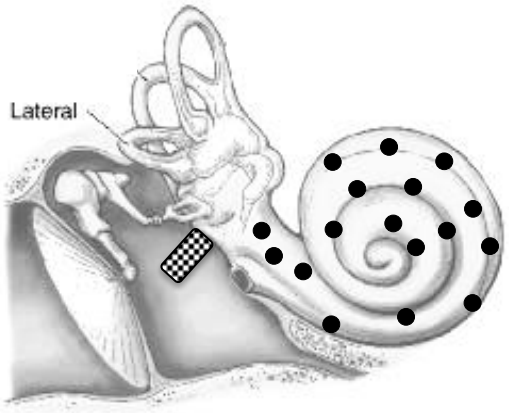
1- Middle ear administration and cochlear diffusion via the round window

2- Cochlear injection

3- Cochlear administration with controlled diffusion: drug eluting devices

Intracochlear devices

Extracochlear devices



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Ear Cubes for local controlled drug delivery to the inner ear

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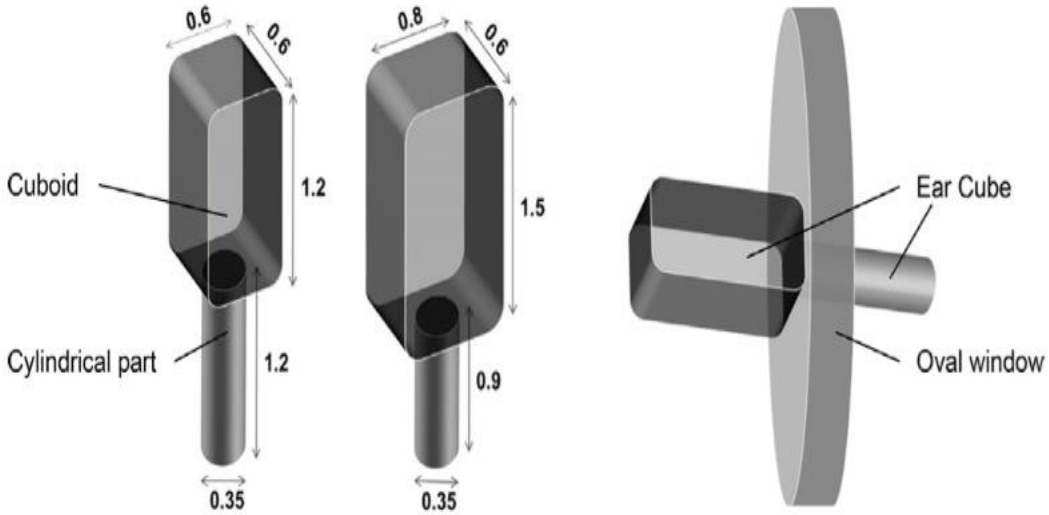


Results: DXM Release

Silicone-based implants

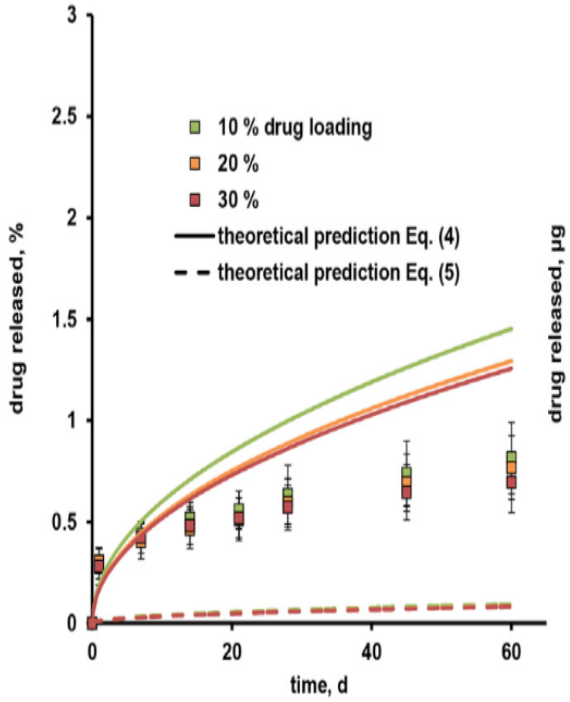
Drug release was prolonged and continuous during the observation period (90 days for implants).

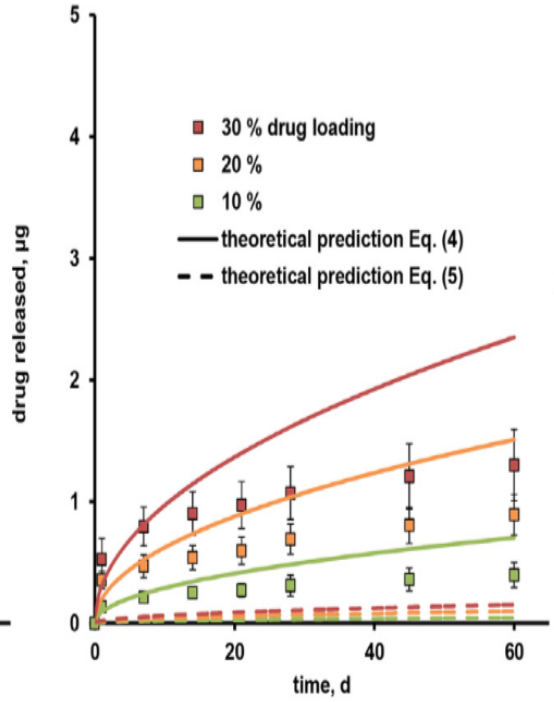
$$\frac{M_t}{M_\infty} = 1 - \frac{8}{\pi^2}\sum_{n=0}^{\infty}\frac{1}{(2n+1)^2}\exp\left(\frac{-D(2n+1)^2\pi^2 t}{L^2}\right)$$

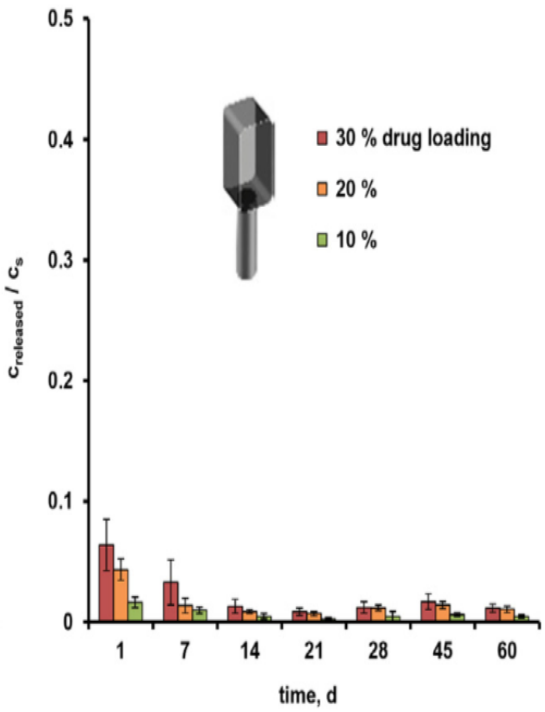
relative drug release

absolute drug release

drug saturation

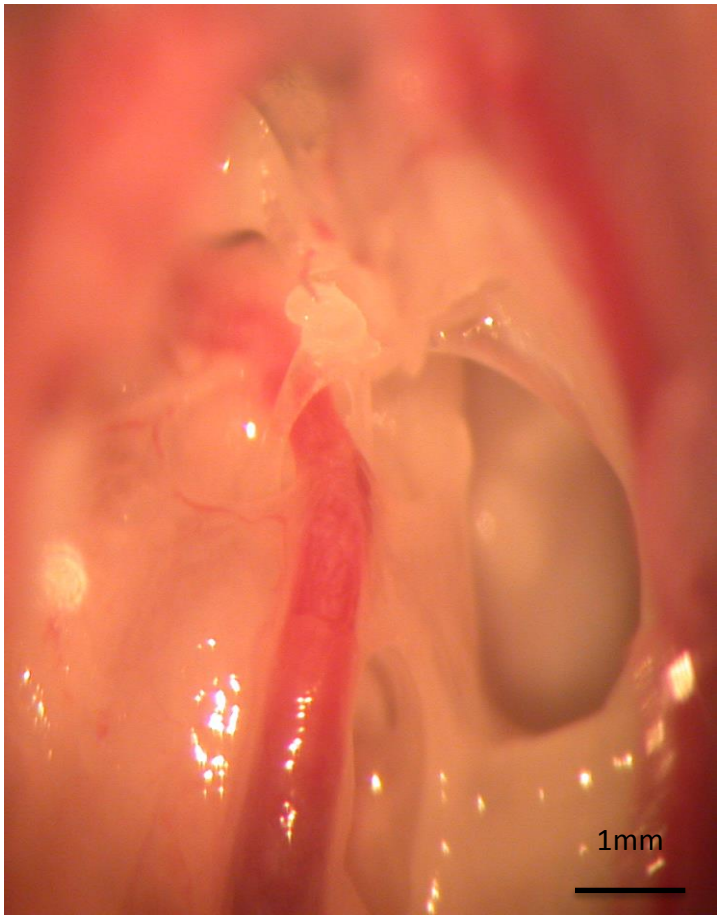


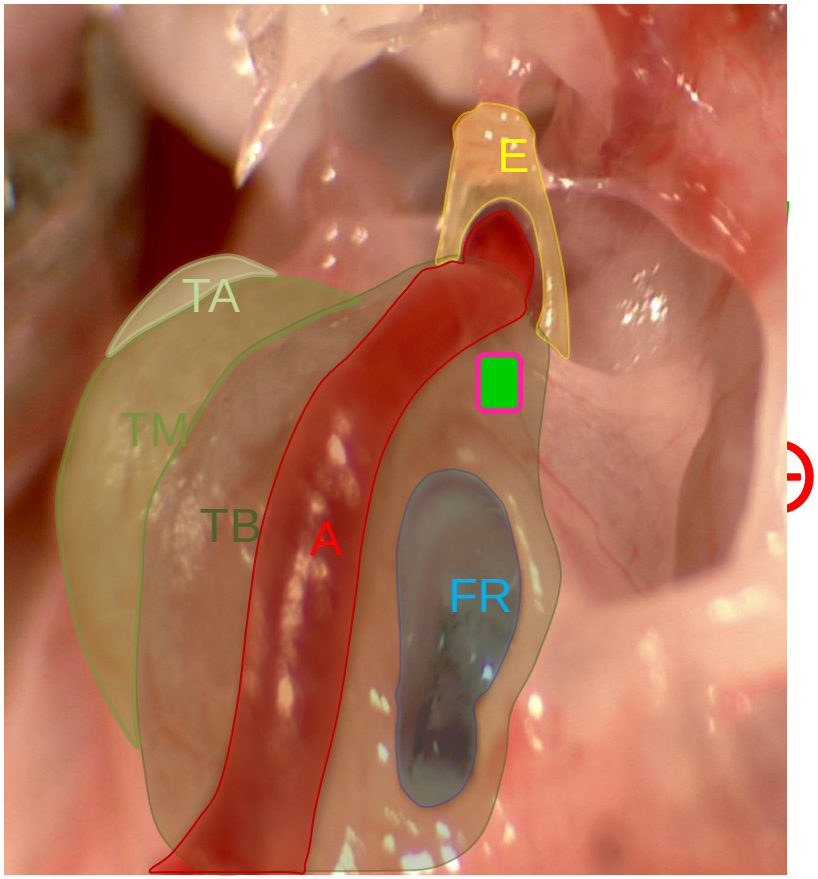




Materials and methods: Implantation

12 Mongolian gerbils implanted bilaterally





Risoud et al, Hear res, 2016

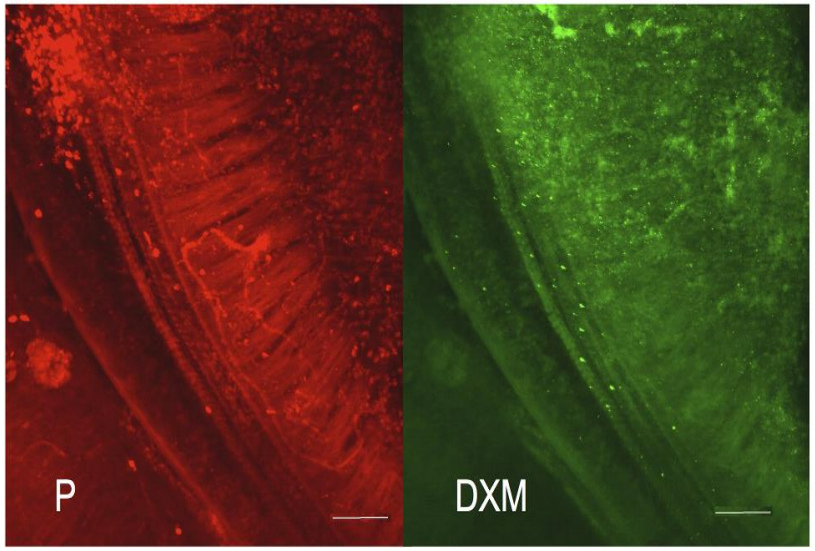
Materials and Methods

- Cochlea preparation: dissection,fixation (and decalcification for the whole cochlea)

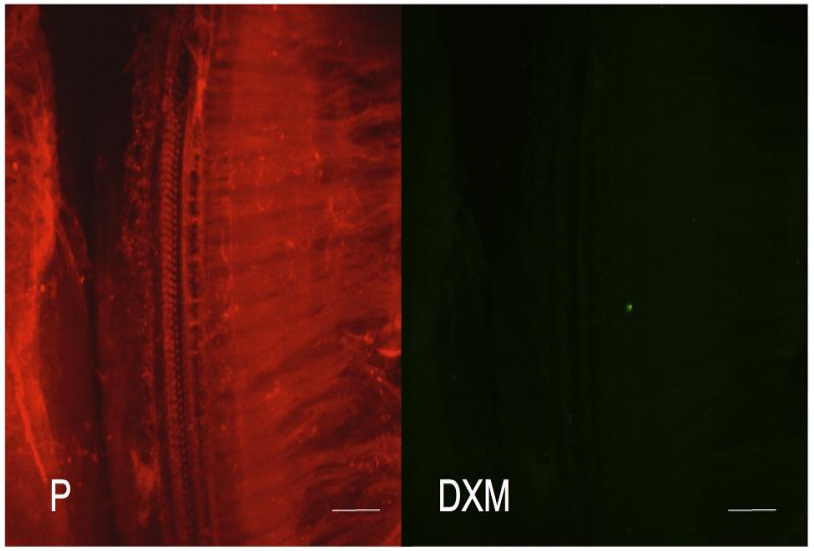
organ of Corti

whole transparent cochlea

Controls



Positive: DXM intratympanic injection

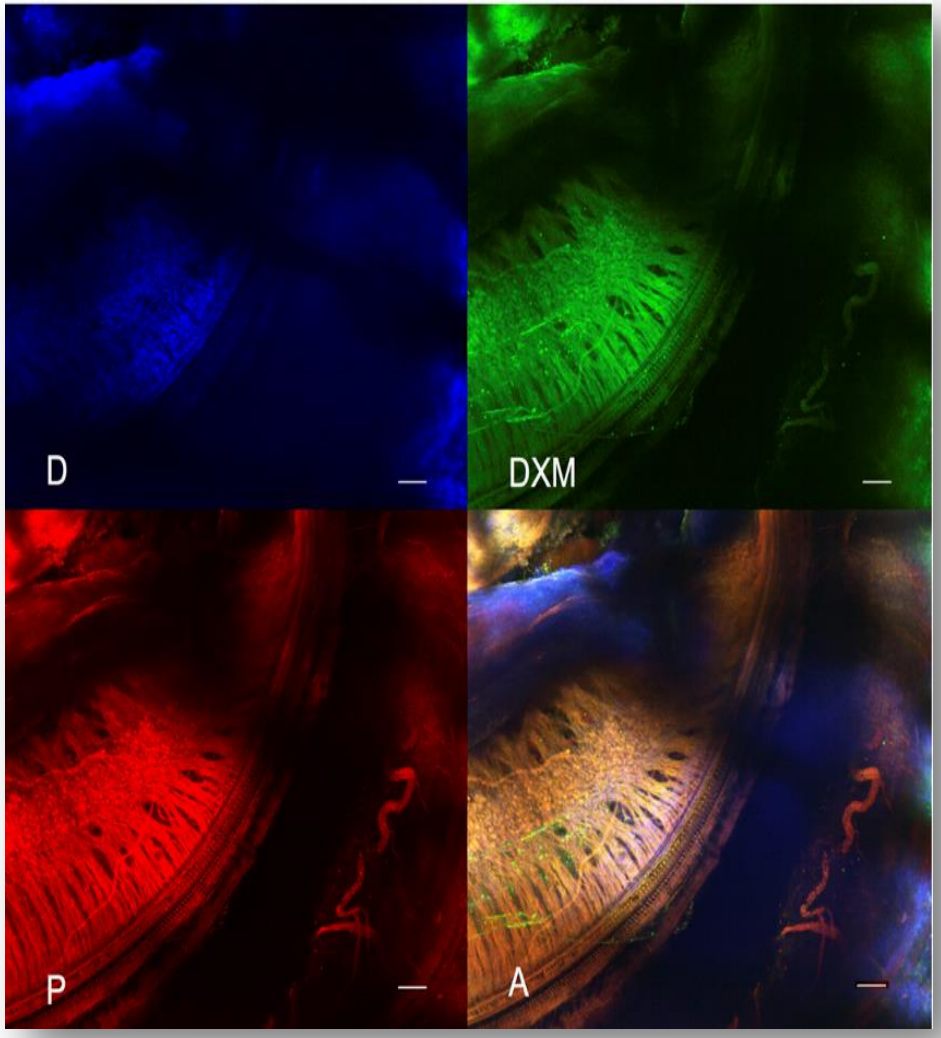


Negative: saline & unloaded ear cube

Results: Confocal Microscopy with DXM cube

Detection of specific anti-DXM fluorescence (green labeling) in the hair cells

DAPI



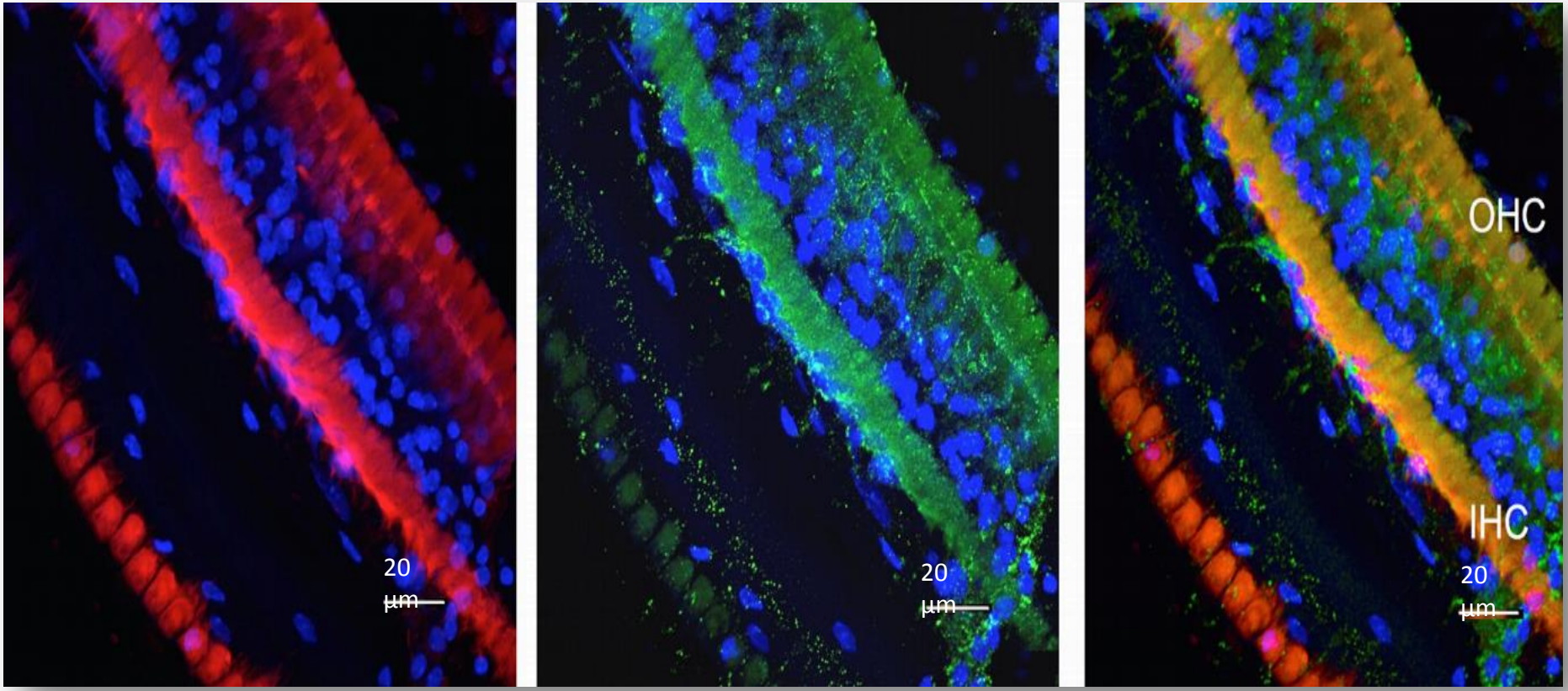
Anti-DXM labeling

Phalloidin

3 labeling

Results: Specific labeling

Location of anti-DXM labeling in inner hair cells and outer hair cells of organ of corti



Phalloidin, *DAPI*

DAPI, *anti-DXM labeling*

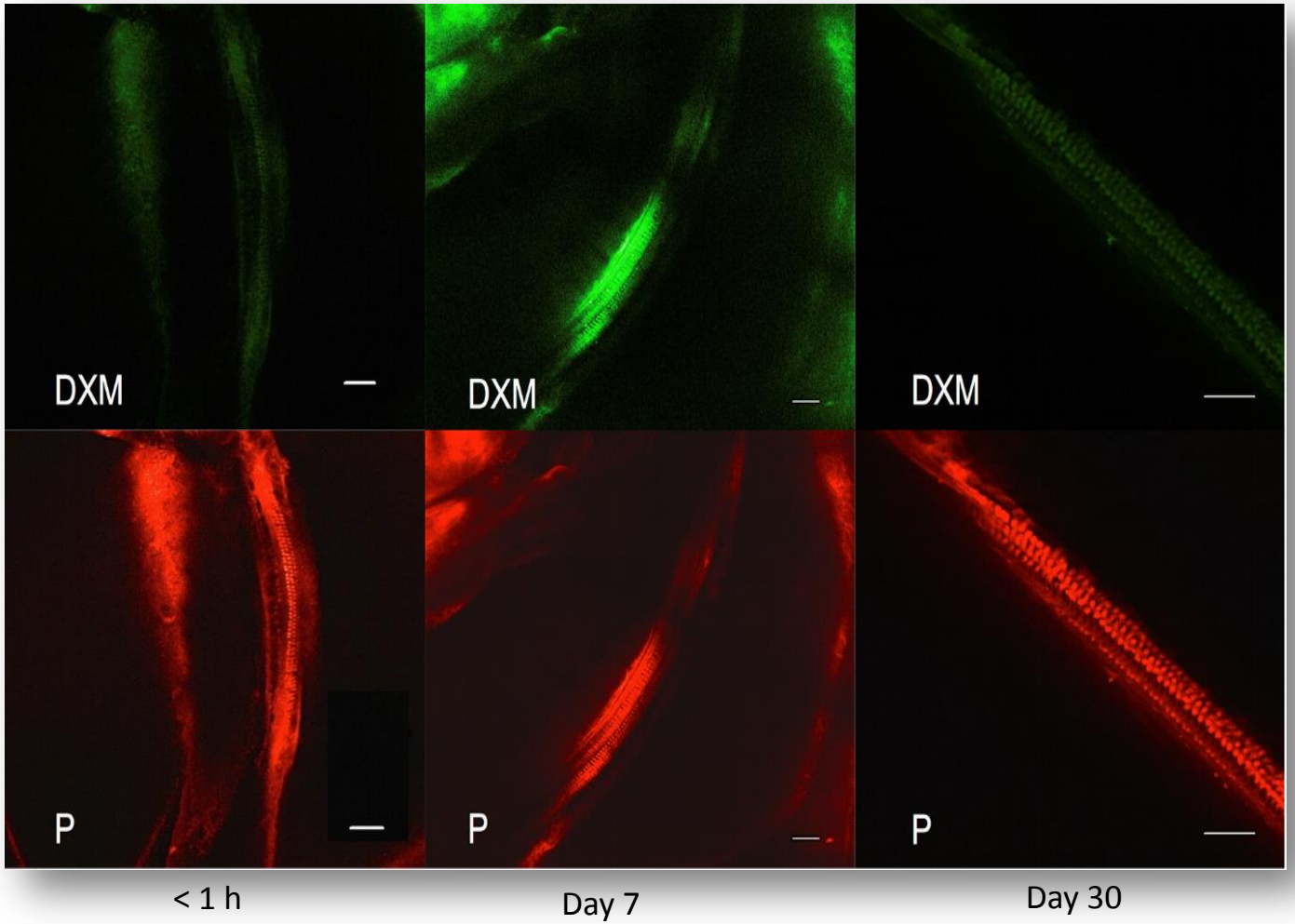
Phalloidin, *DAPI*, *anti-DXM labeling*

Results: Staining intensity

Detection of anti-DXM labeling inside hair cells 20 min post-implantation and even at day 30. Climax for the cochlea collected at day 7 post-implantation.

Anti-DXM labeling

Phalloidin



Conclusion

- A new device for local drug delivery into the inner ear using a non-degradable polymeric silicone matrix placed at the level of the oval window
- Continuous and prolonged release from DXM-loaded implants for 90 days adapted for chronic ear disease treatment
- Carrier for other drugs or therapies (e.g. gentamycin, diuretics…).

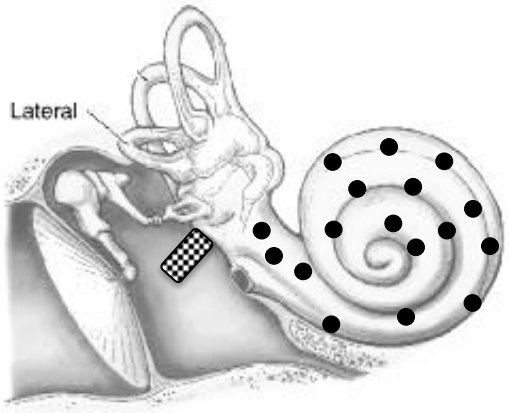
J. Sircoglou et al.
Otol Neurotol. 2015 Sep;36(9):1572-9.

M. Gerhke et al.
Int J Pharm. 2016 Jul 25;509(1-2):85-94.

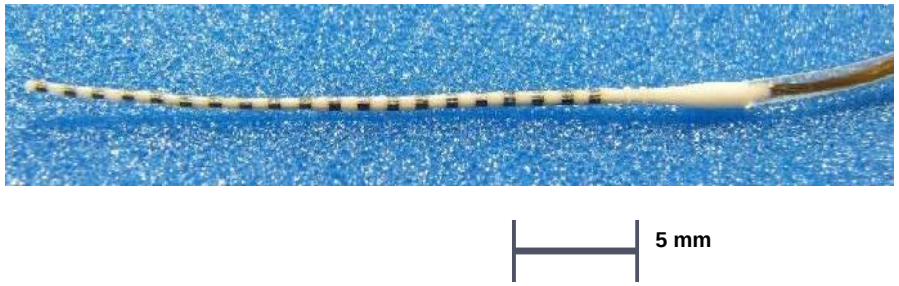
M. Gehrke et al.
Eur J Pharm Biopharm. 2016 Mar;100:27-37.

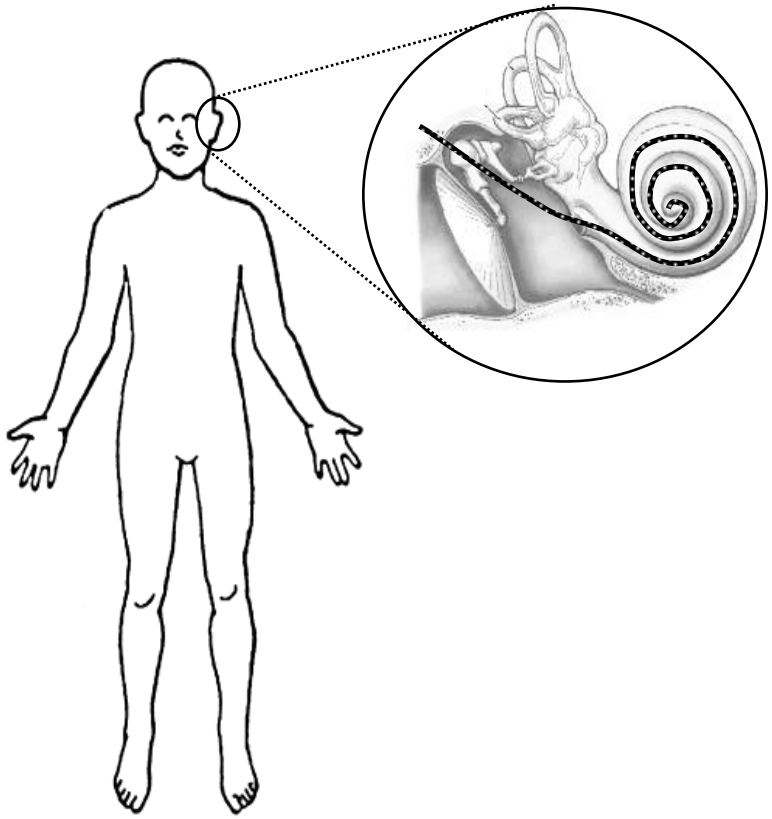
Intracochlear devices

Extracochlear devices



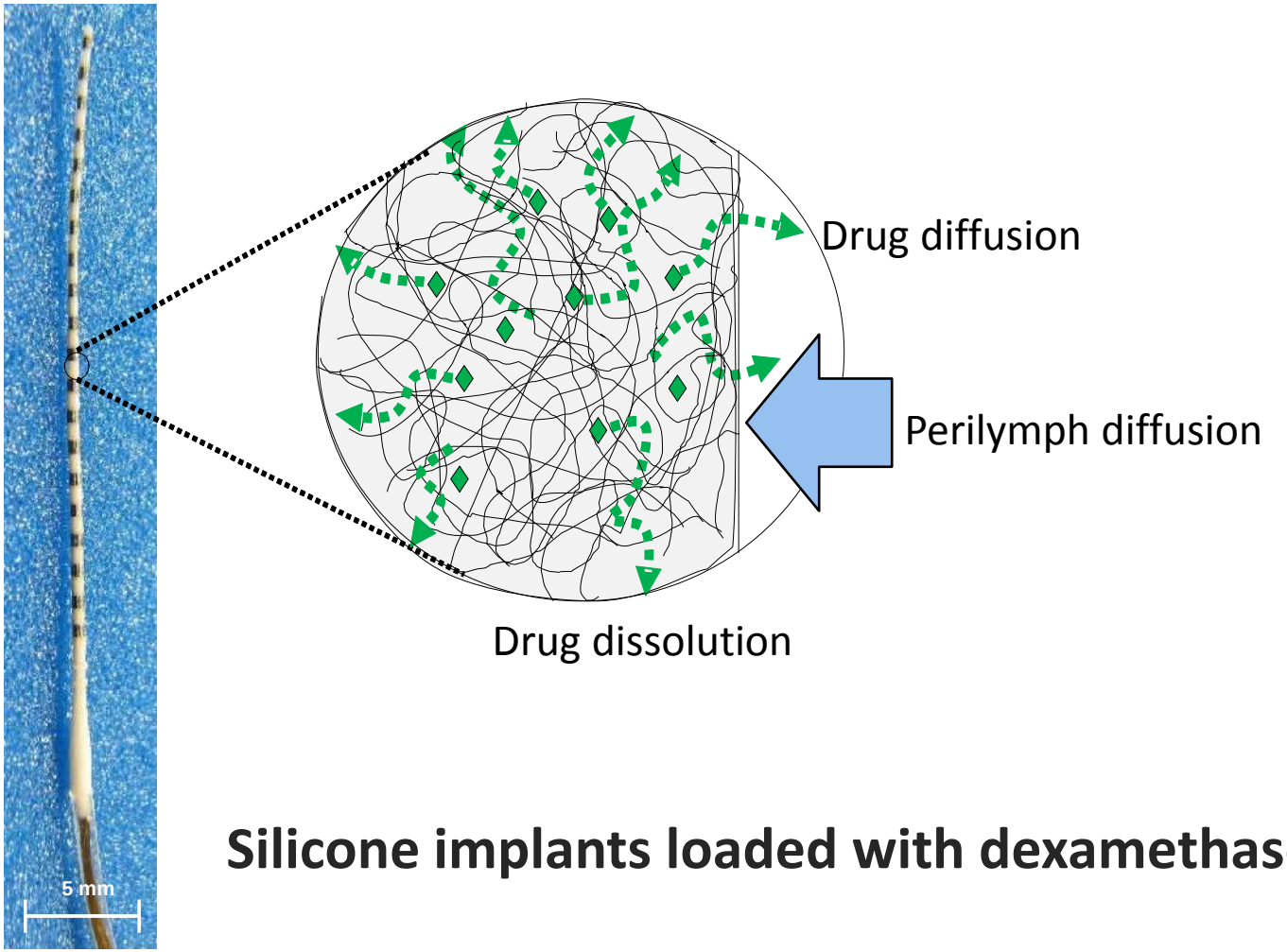
Modified electrode: Drug is added to the silicone matrix





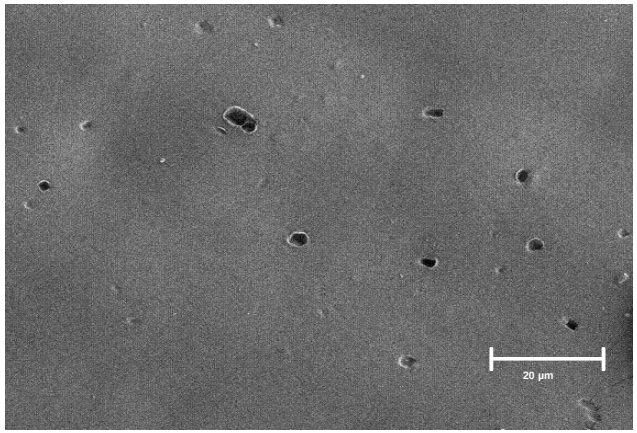
Intra-cochlear implants

Drug release mechanisms

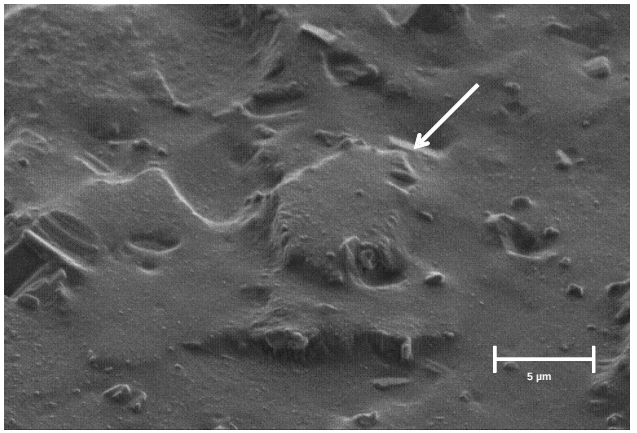


Silicone implants loaded with dexamethasone

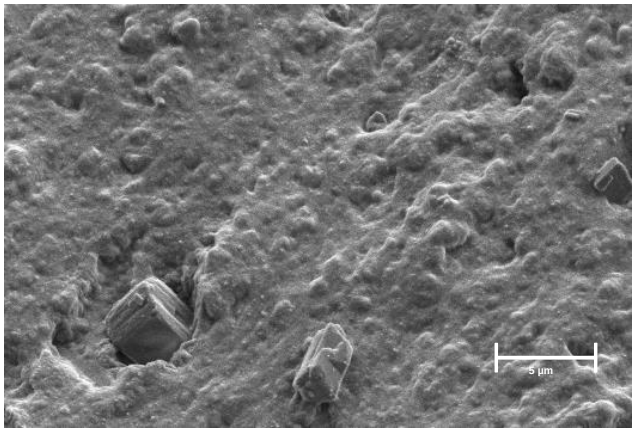
Physical state of the drug: SEM of cross sections

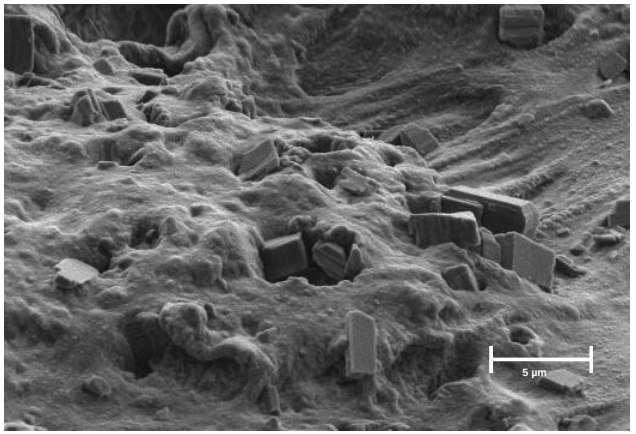


surface of a polymeric film loaded with 10 % DXM,
cross section of an extrudate loaded with 1 % DXM



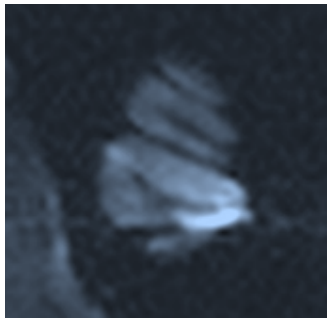
cross section of a polymeric film loaded with 10 % DXM
cross section of an extrudate loaded with 10 % DXM.





Implantation of DXM+ and DXM - electrodes

- Pre-op hearing testing
- Implantation of 20 gerbils:
  - one ear with a DXM+ electrode (1 & 10 %),
  - the other with a DXM- electrode
- Post-op hearing testing @ 1 month and 1 year



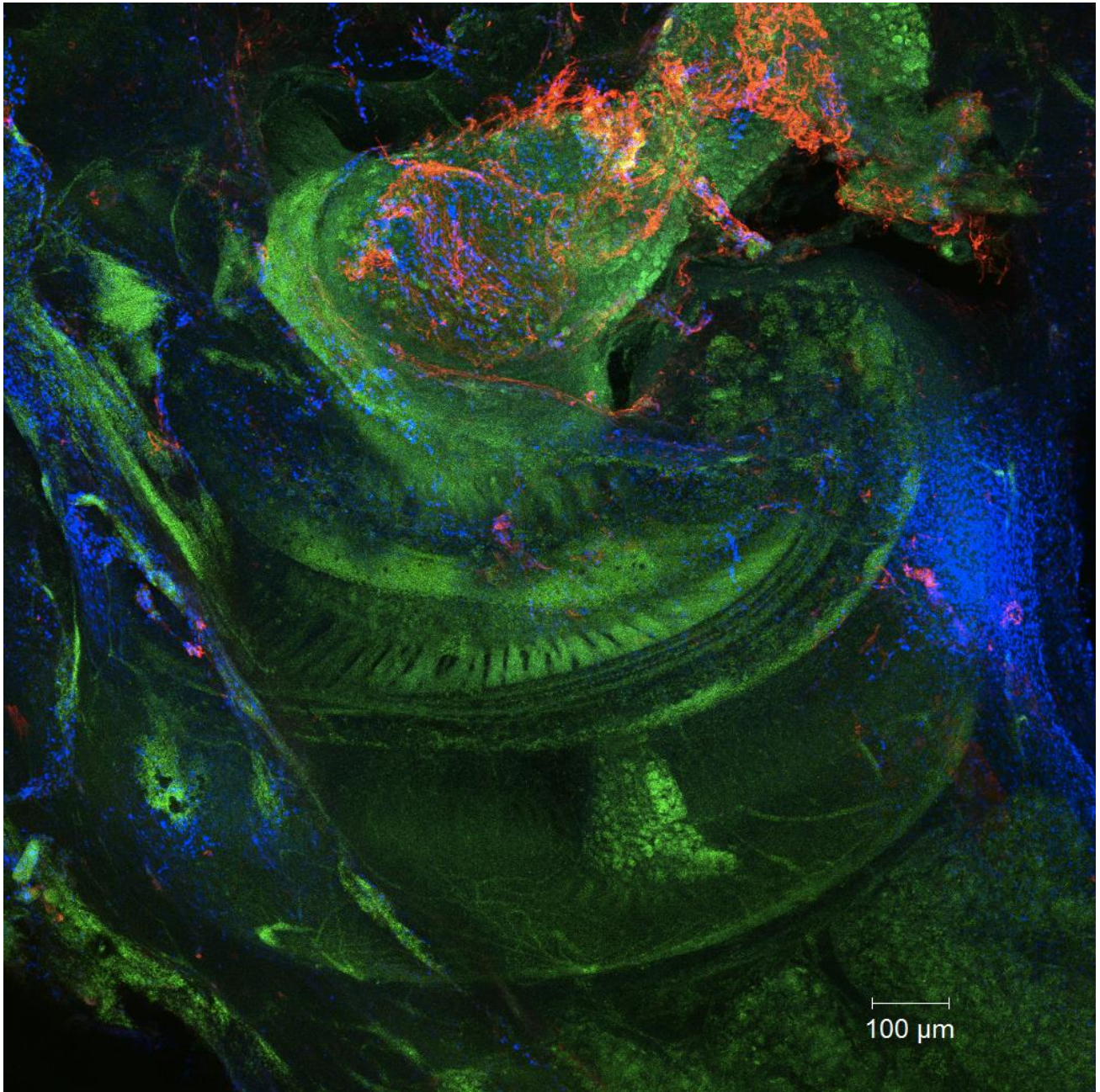
In vivo study

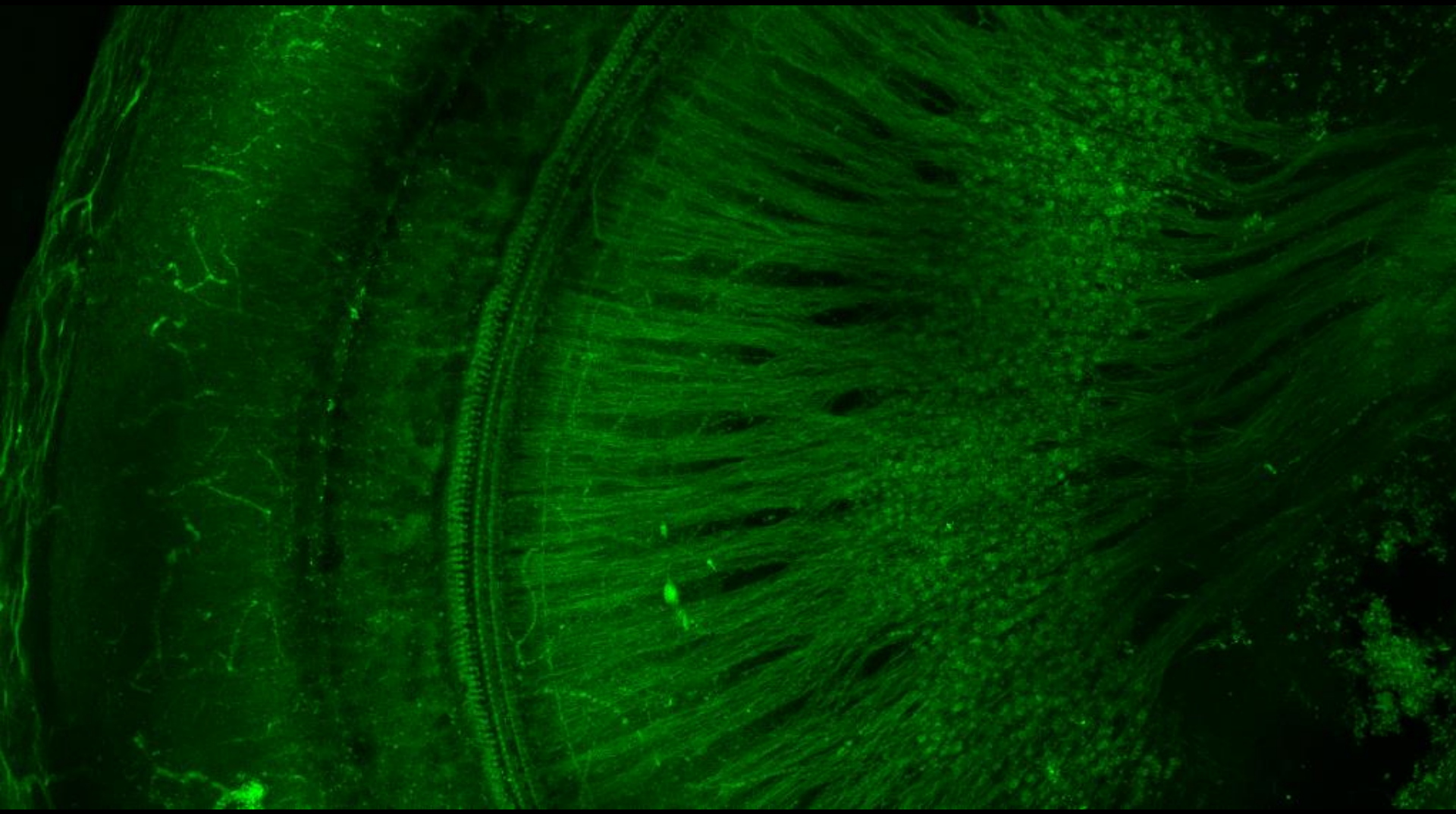
- Active dexamethasone electrode array with controlled release allows a better conservation of hearing thresholds at 1 month for 500, 1000, 2000, 4000 and 16000 Hz and at 1 year for 16000 Hz in our gerbil model.

Krenzlin et al, J Control Release (2012)
Douchement et al, Cochlear Implants Int (2014)

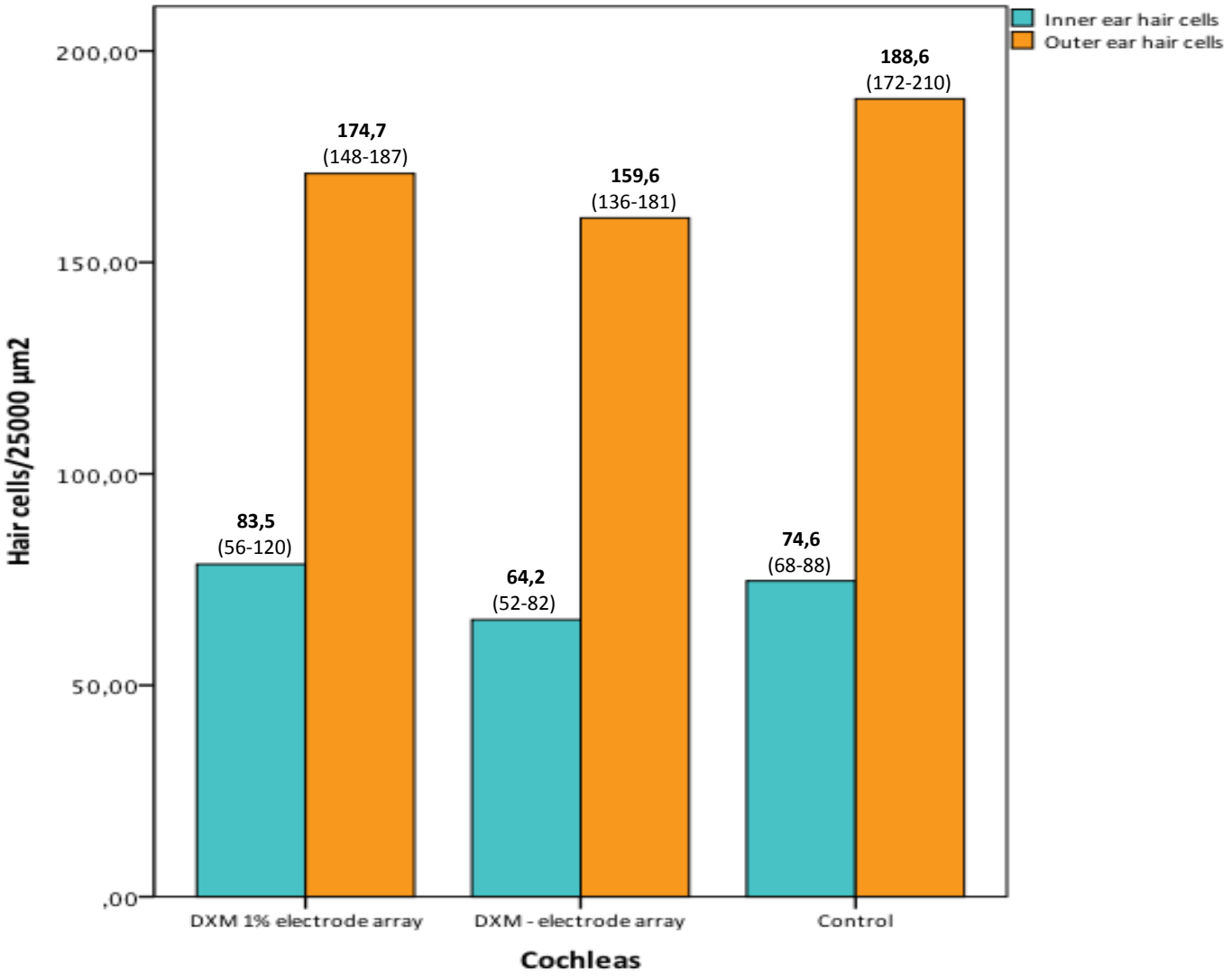
Cochlear implants: long term safety ?

Confocal microscopy on whole transparent cochlea

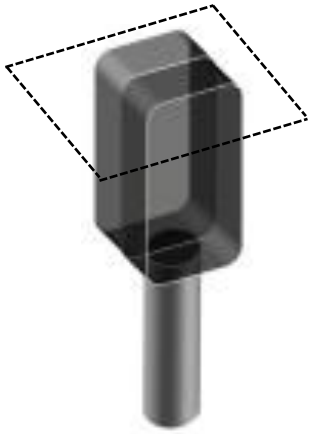




Cell population

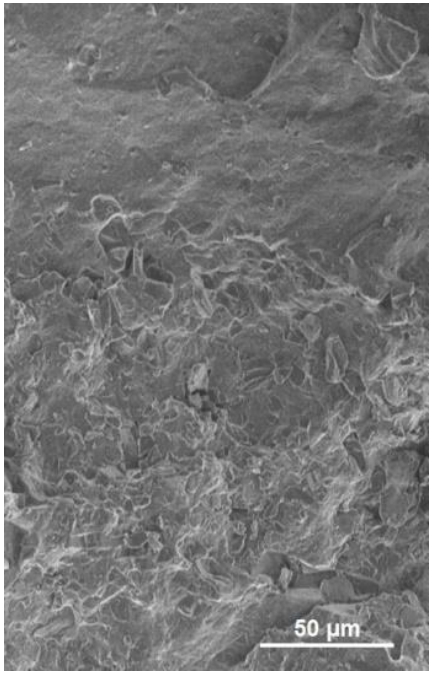


The drug loading was 10 and 30 % dexamethasone.

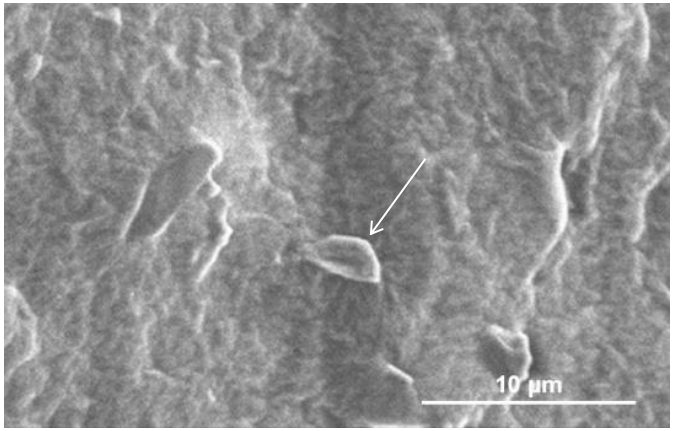


10 %

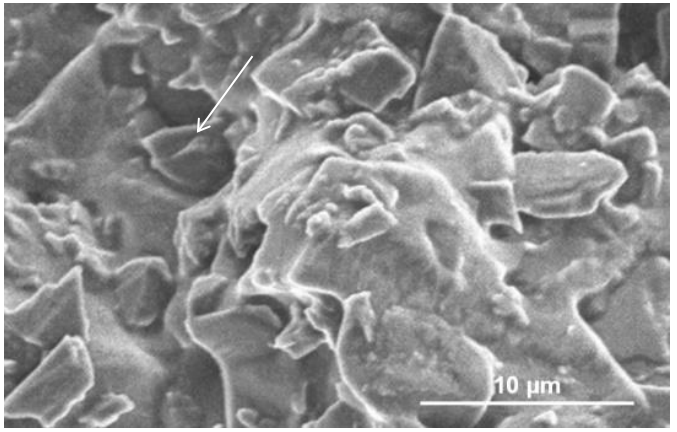
30 %



10 %



30 %

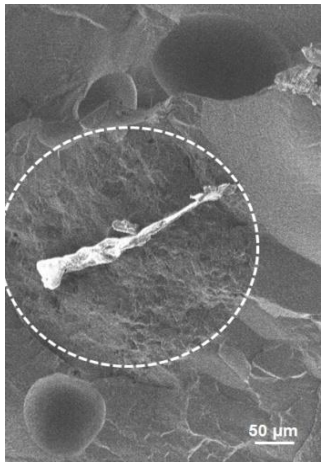


Sircoglou et al, Otol Neurotol . 36:1572-79 (2015)

t = 0 days

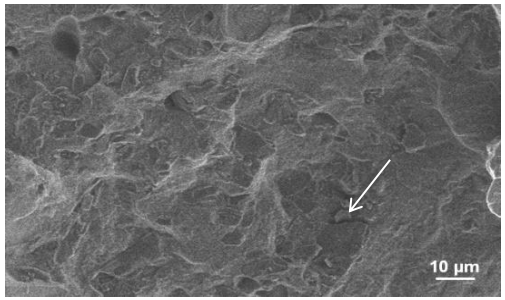
10 %

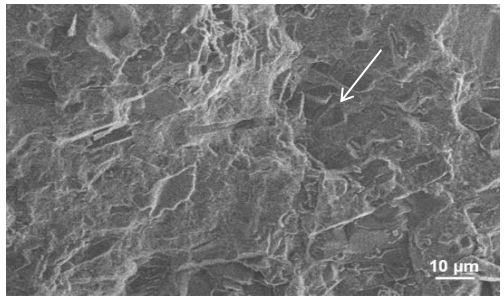
30 %



10 %

30 %

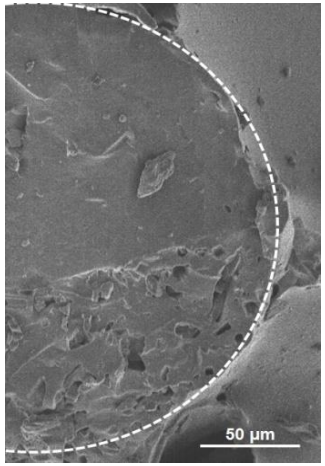




t = 200 days

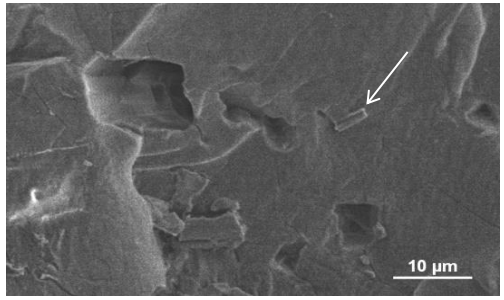
10 %

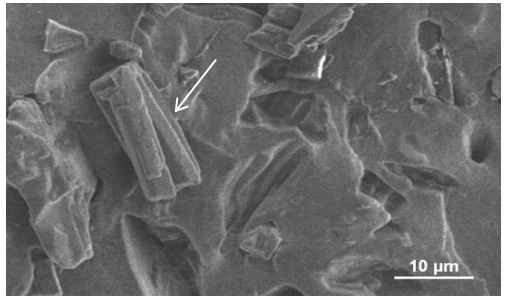
30 %



10 %

30 %





DXM + electrode & chronic implantation

- Change in the electrode/tissue interface
- Lower impedances than compared to the DXM – side
- Imaging of transparent whole cochleas
  - confocal microscopy
  - lightsheet microscopy
- Study large surfaces and volumes
  - fibrosis: lower impedance=less fibrosis (to be confirmed!)
  - other intracochlear phenomenoms (apoptosis…)
- Difficult to obtain statistical significance (more animals)

Preservation of cochlea after cochlear implantation

- Preservation of structure
  - less invasive electrode
  - better preoperative analysis of the cochlea
  - better control of insertion, better quality control
- Preservation of function
  - drug eluting electrodes
  - DXM is a starting point (‘’cochlear cocktail’’?)
  - Controlled drug delivery is mandatory

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