

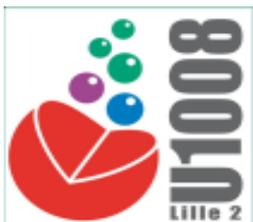
The future of inner ear drug delivery

C. Vincent, J. Siepmann

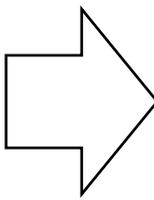
Otology and Neurotology Department,

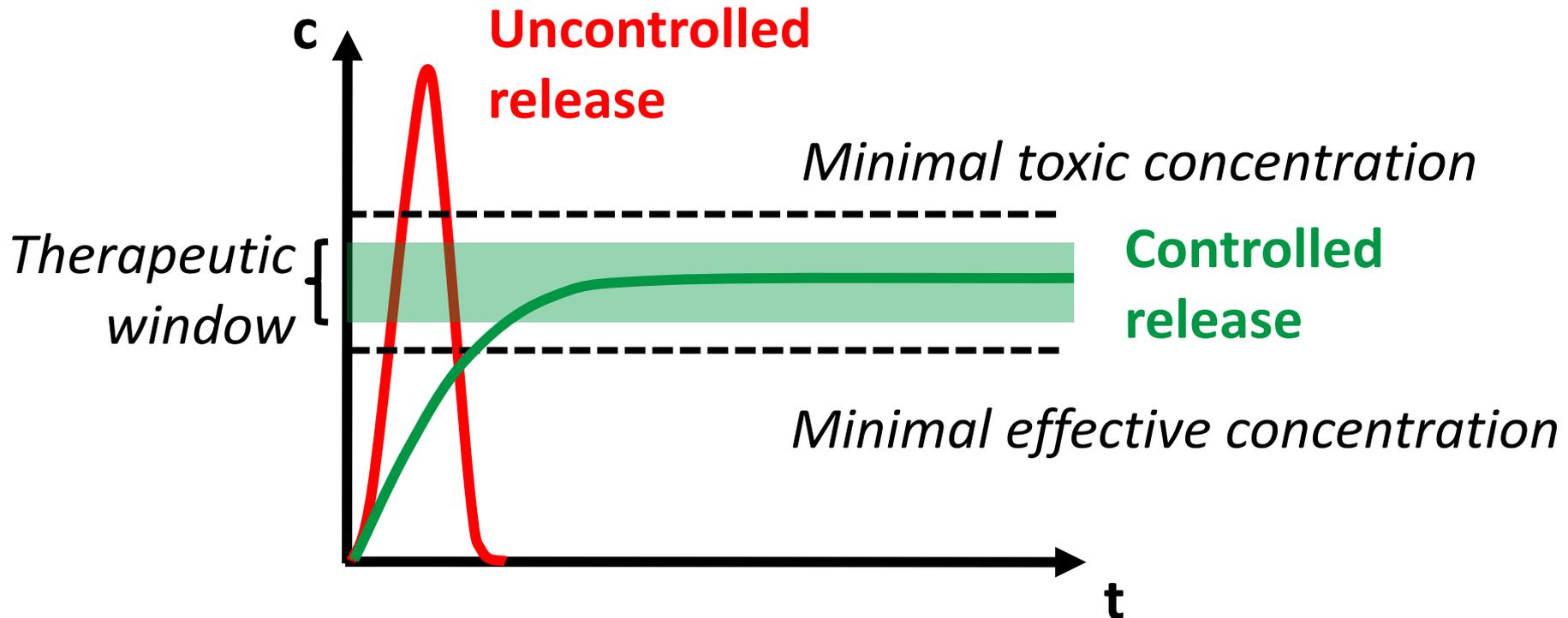
University Hospital of Lille

Inserm U1008: Controlled Drug Delivery Systems and Biomaterials

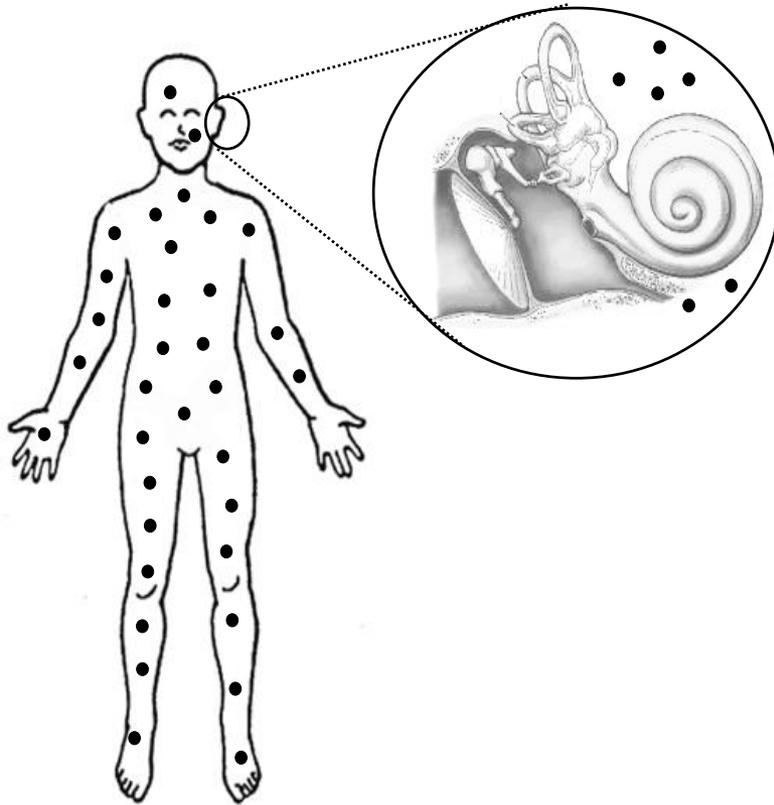


Why Controlled Drug Delivery?

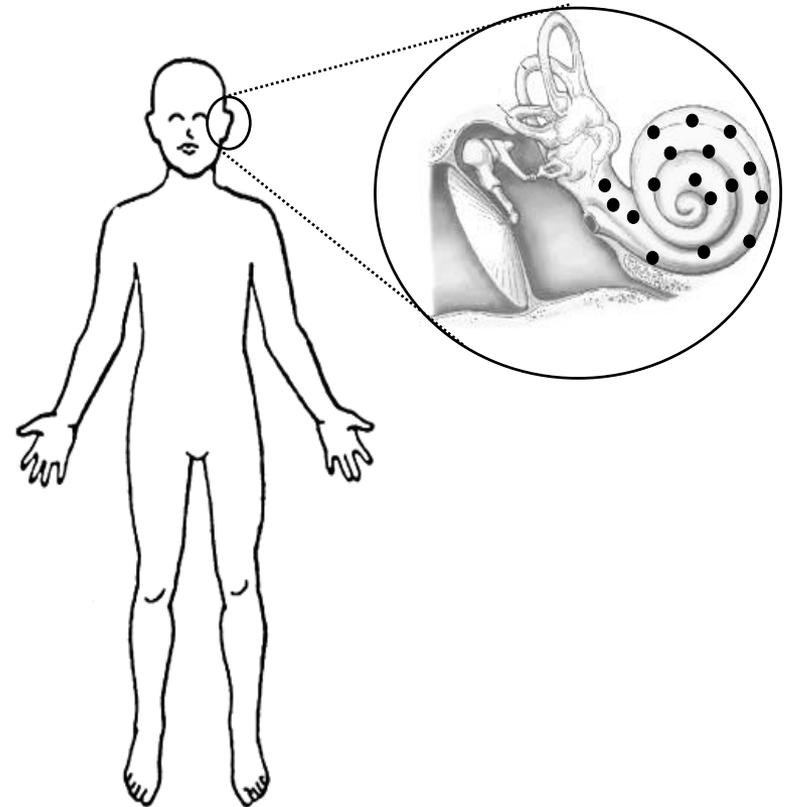
Drug concentration at the site of action  Efficacy & Safety



Drug delivery to the inner ear

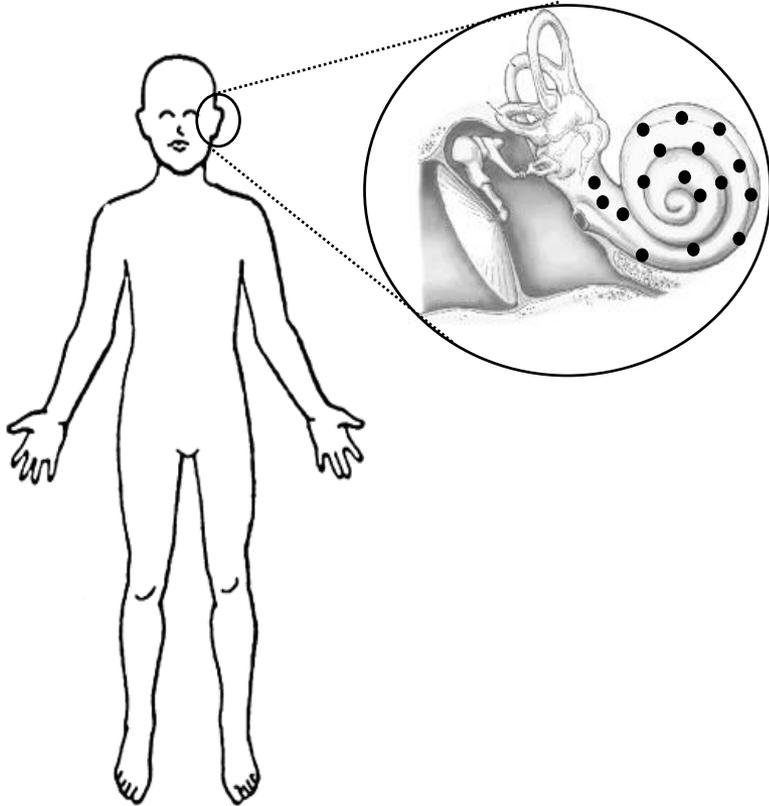


General administration



Intra-cochlear administration

Blood-Cochlear barrier



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

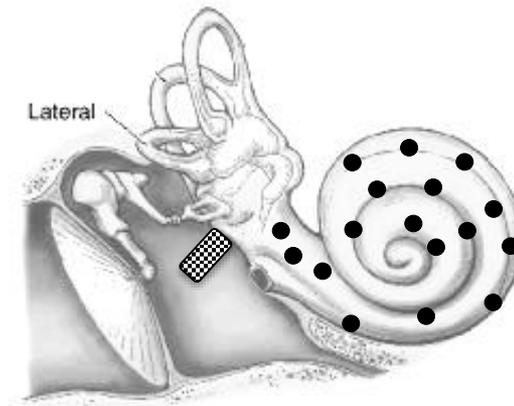
2- Cochlear injection

3- Cochlear administration with controlled diffusion: drug eluting devices

Intracochlear devices



Extracochlear devices





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International Journal of Pharmaceutics

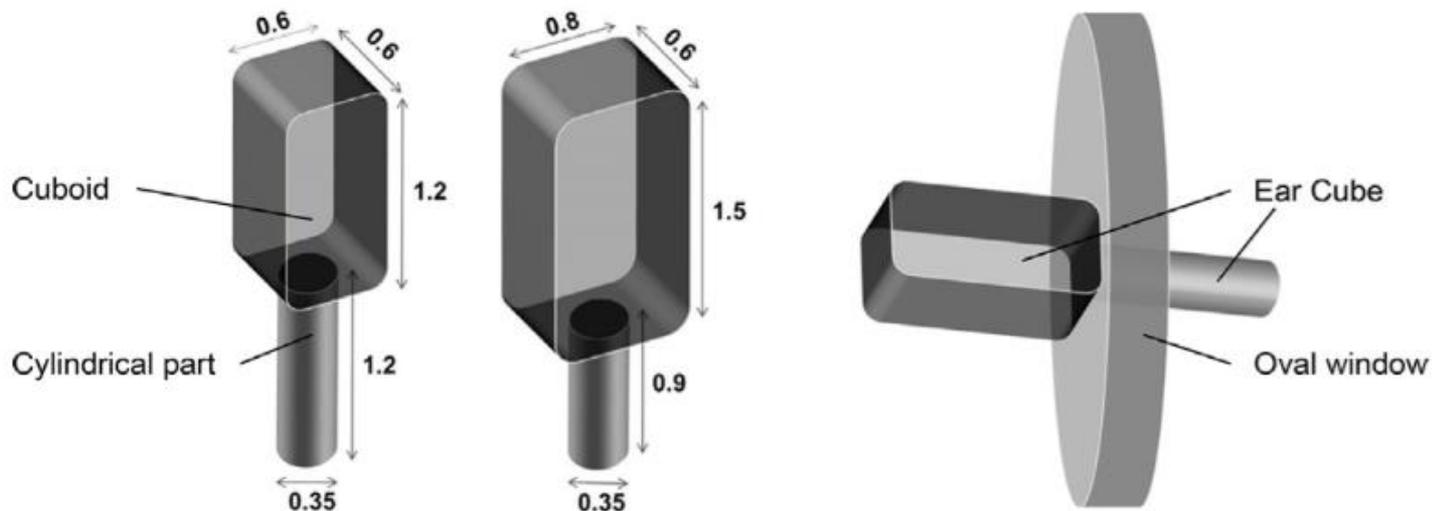
journal homepage: www.elsevier.com/locate/ijpharm



Ear Cubes for local controlled drug delivery to the inner ear



M. Gehrke^{a,b}, J. Sircoglou^{a,b,c}, D. Gnansia^d, G. Turrel^d, J.-F. Willart^{a,e}, F. Danede^{a,e},
E. Lacante^{a,b}, C. Vincent^{a,b,c}, F. Siepmann^{a,b}, J. Siepmann^{a,b,*}



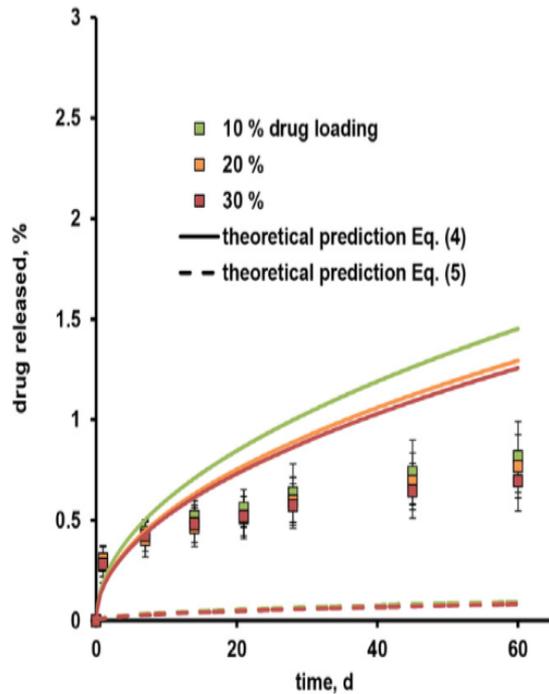
Results: DXM Release

Silicone-based implants

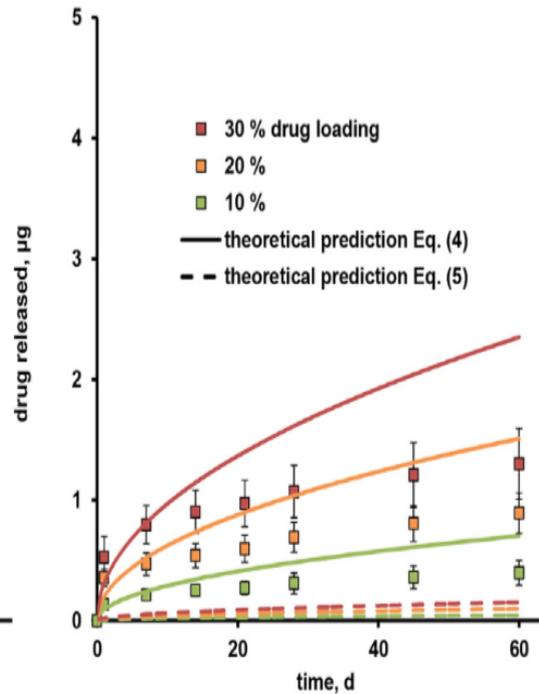
Drug release was prolonged and continuous during the observation period (90 days for implants).

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

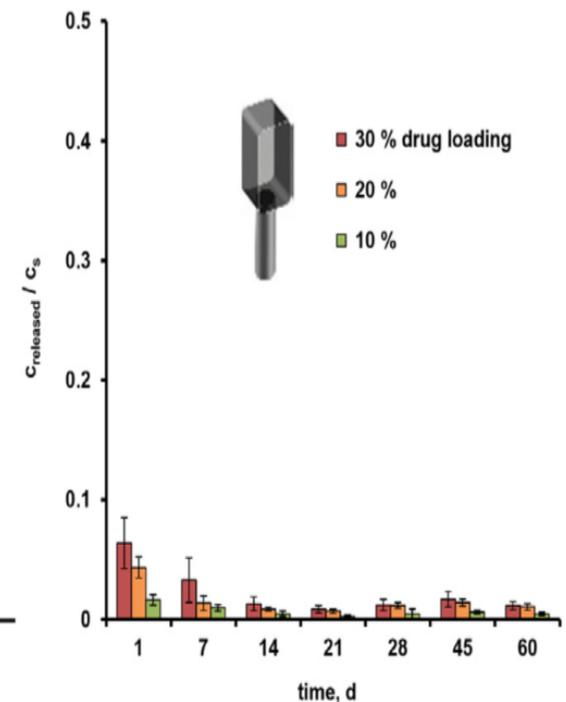
relative drug release



absolute drug release

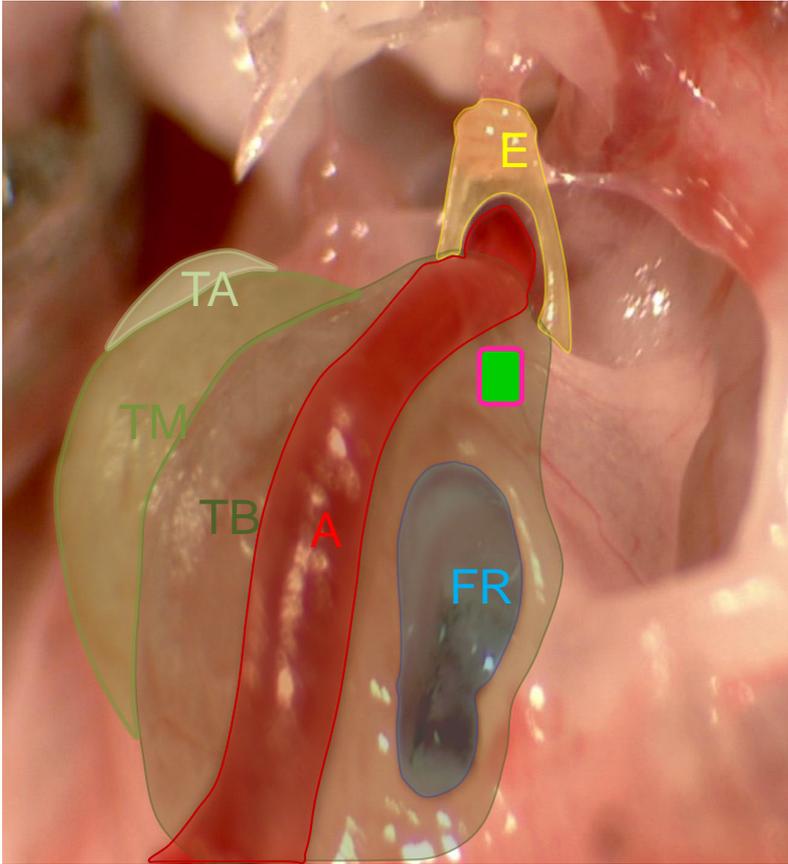
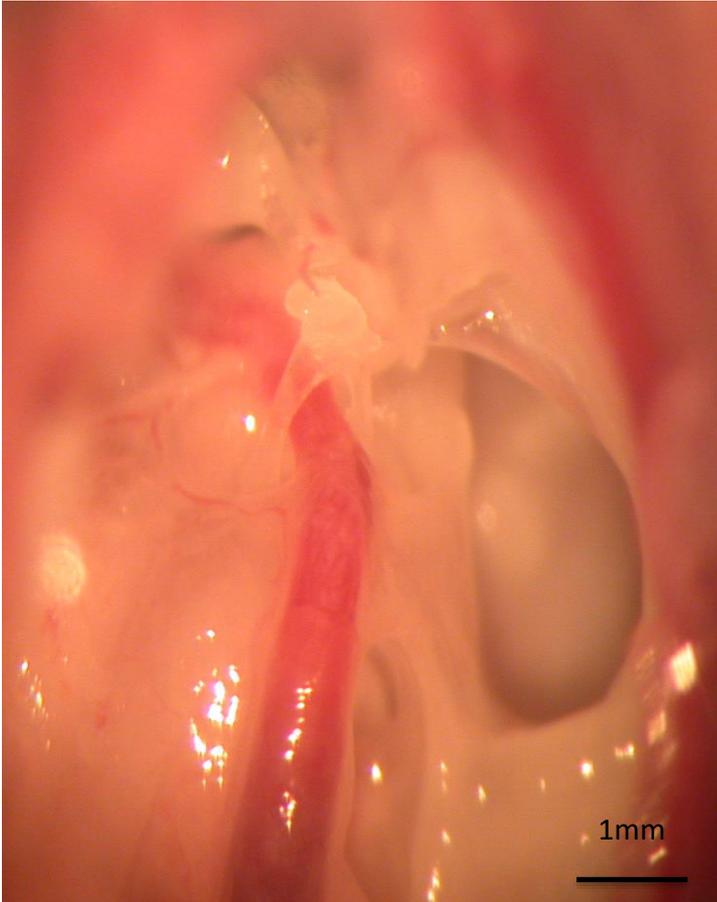


drug saturation



Materials and methods: Implantation

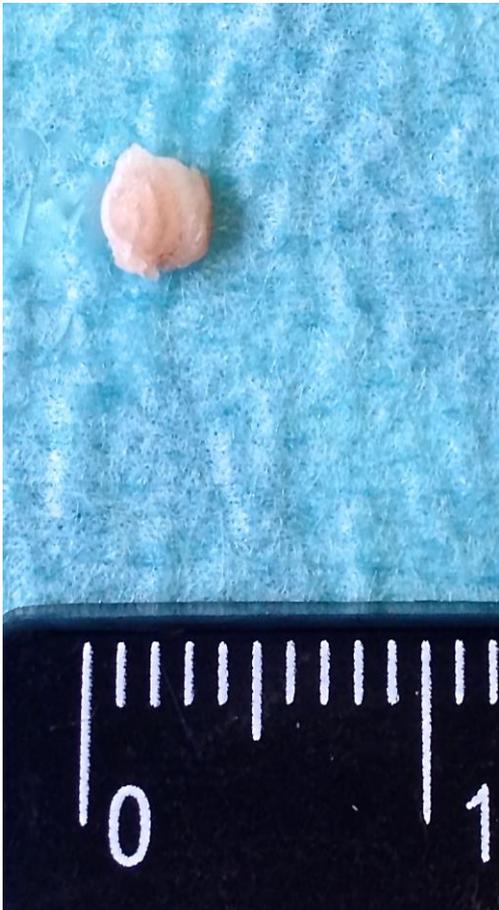
12 Mongolian gerbils implanted bilaterally



Risoud et al, Hear res, 2016

Materials and Methods

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

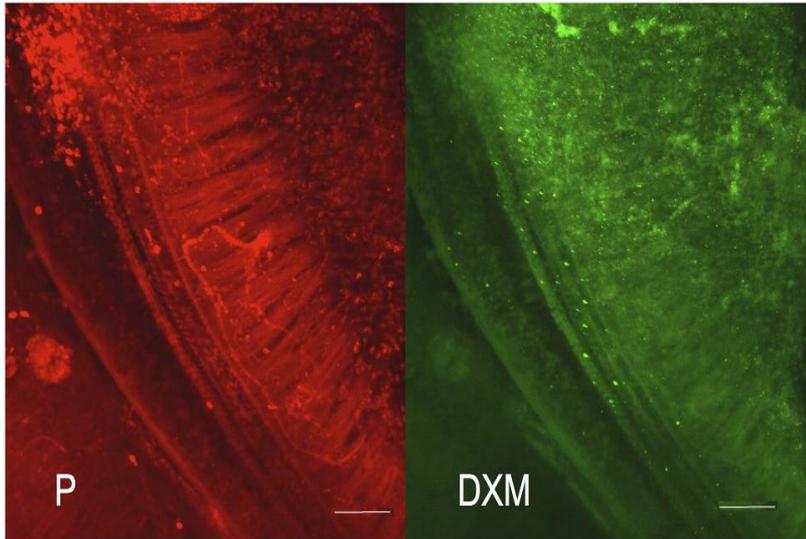


organ of Corti

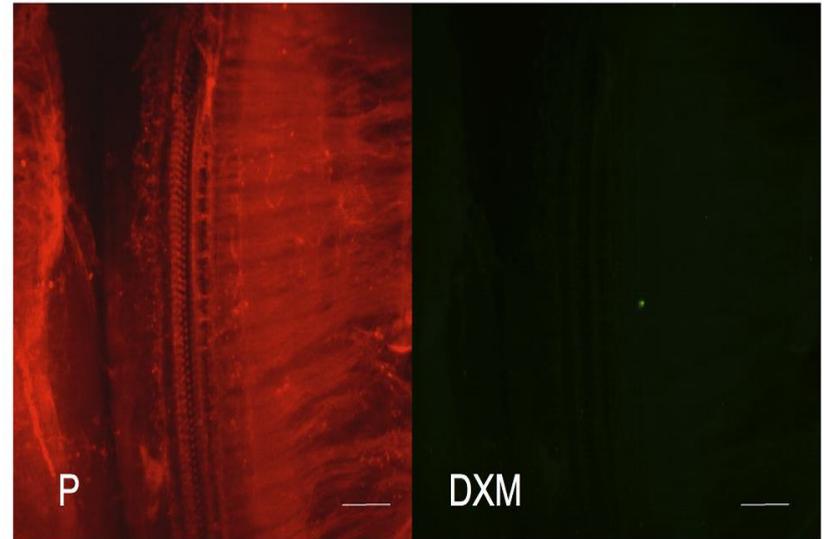


whole transparent cochlea

Controls



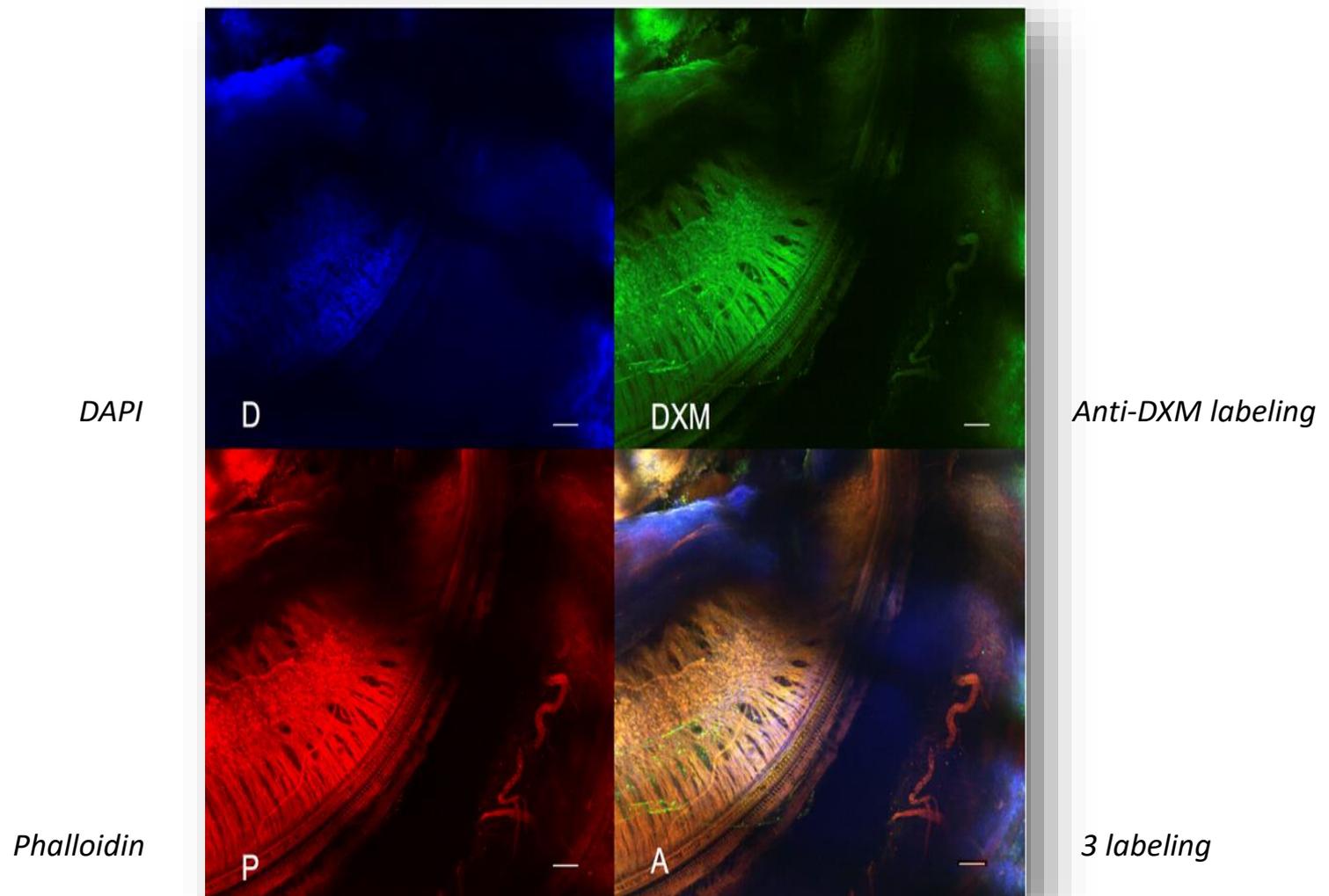
Positive: DXM intratympanic injection



Negative: saline & unloaded ear cube

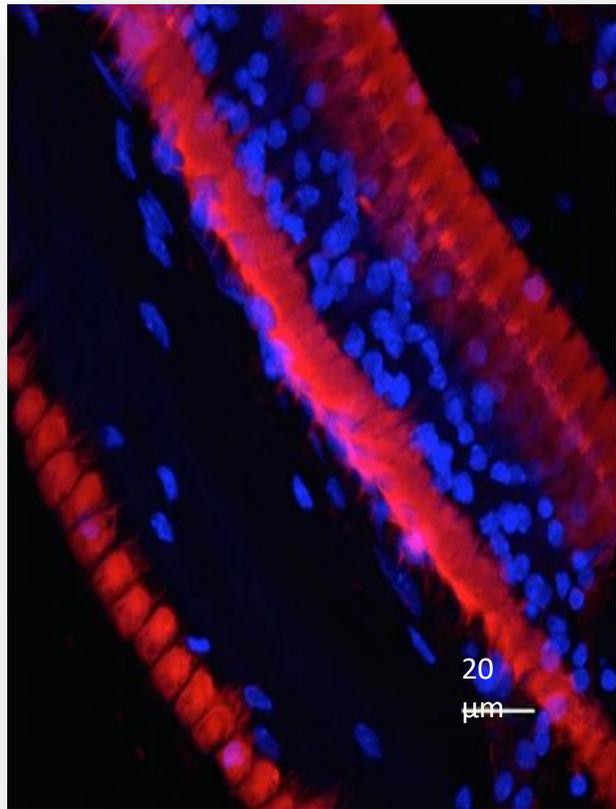
Results: Confocal Microscopy with DXM cube

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

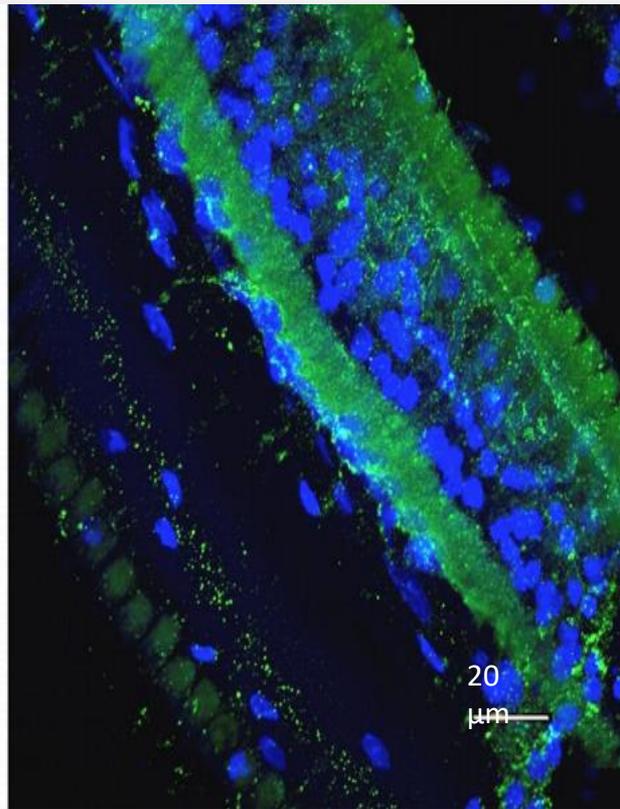


Results: Specific labeling

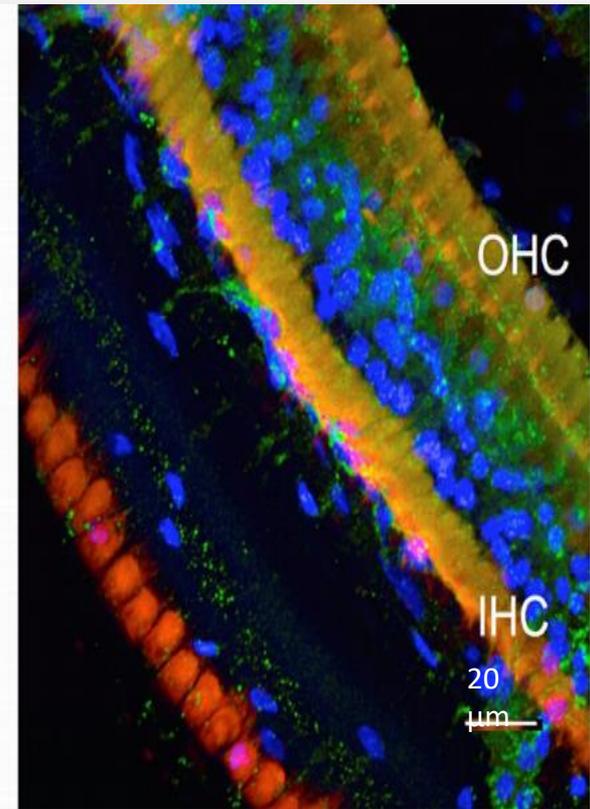
Location of anti-DXM labeling in inner hair cells and outer hair cells of organ of corti



Phalloidin, DAPI



DAPI, anti-DXM labeling

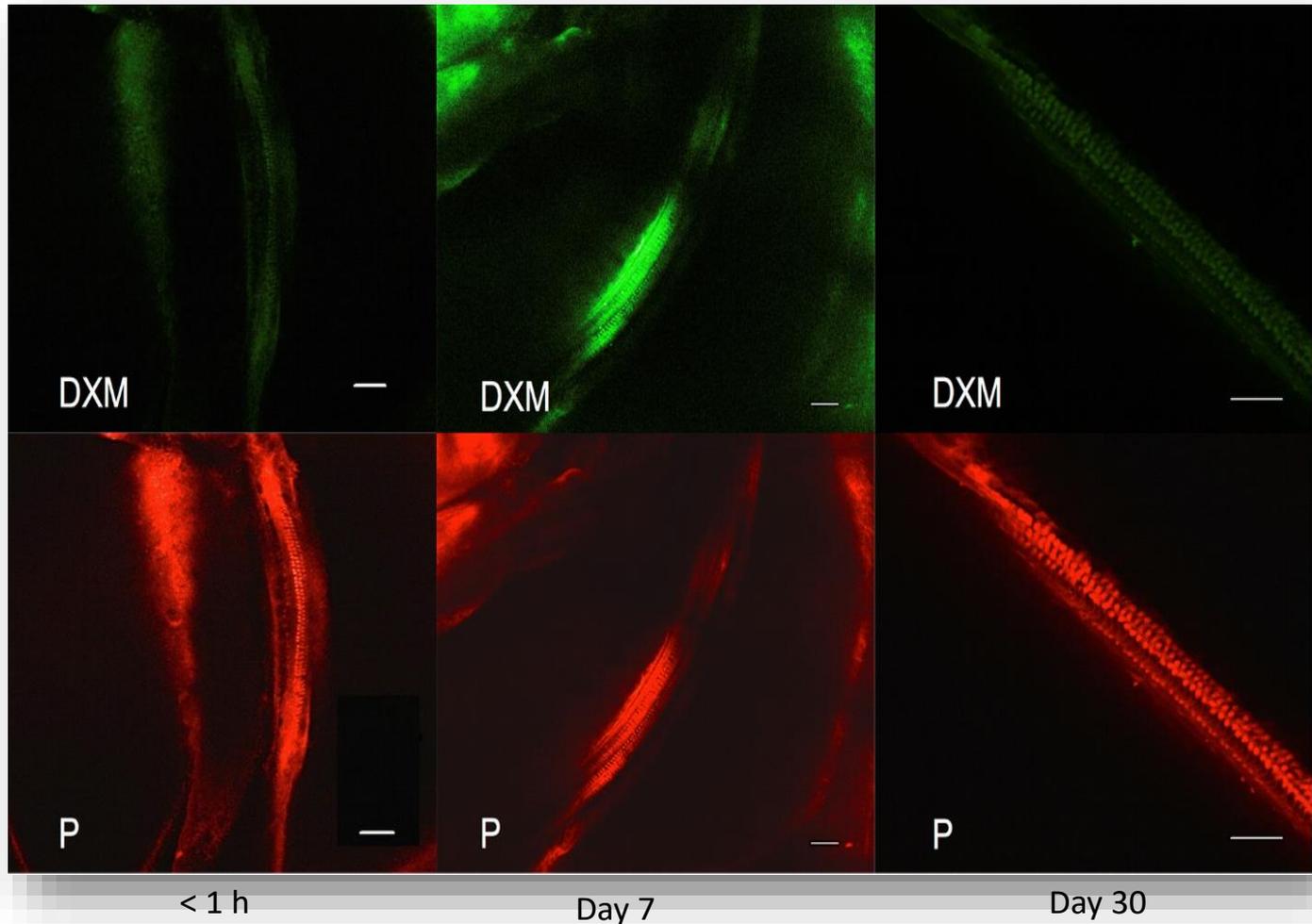


Phalloidin, DAPI, anti-DXM labeling

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

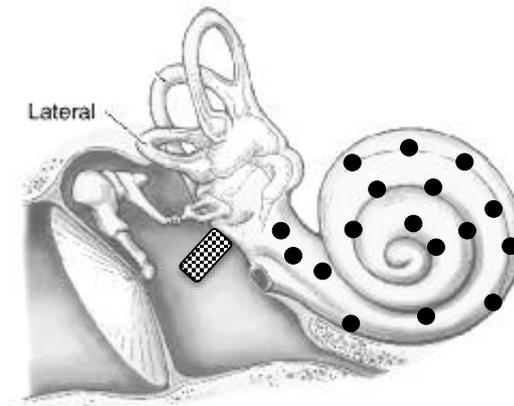
Conclusion

- 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...).

Intracochlear devices



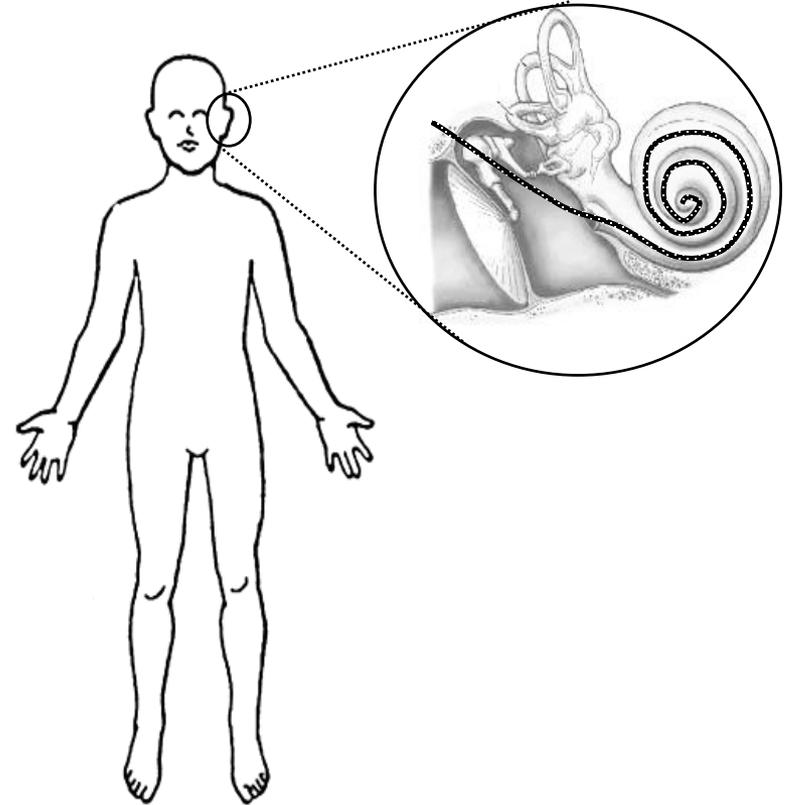
Extracochlear devices



Modified electrode: Drug is added to the silicone matrix

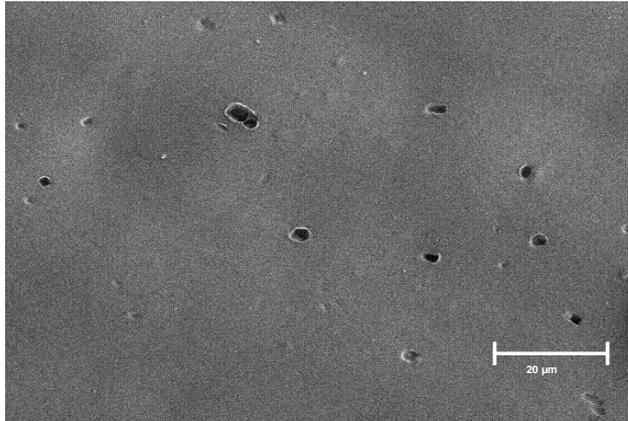


5 mm

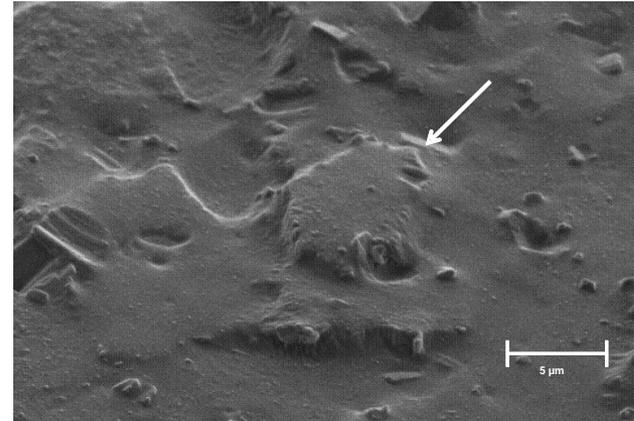


Intra-cochlear implants

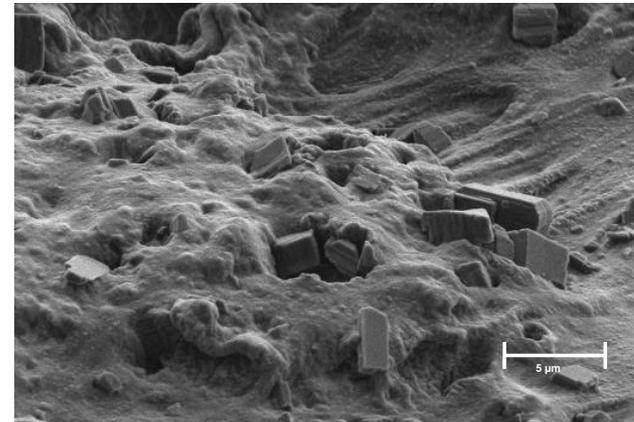
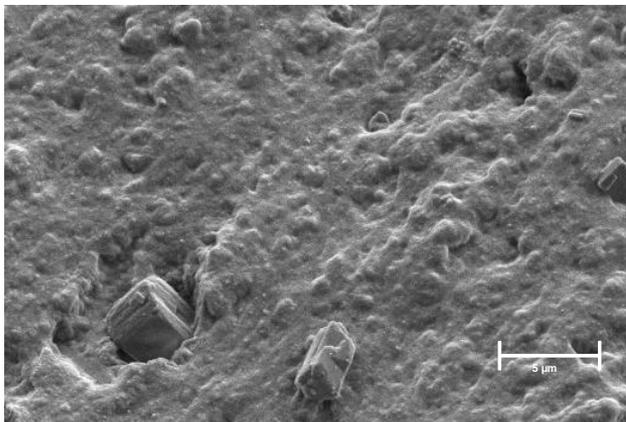
Physical state of the drug: SEM of cross sections



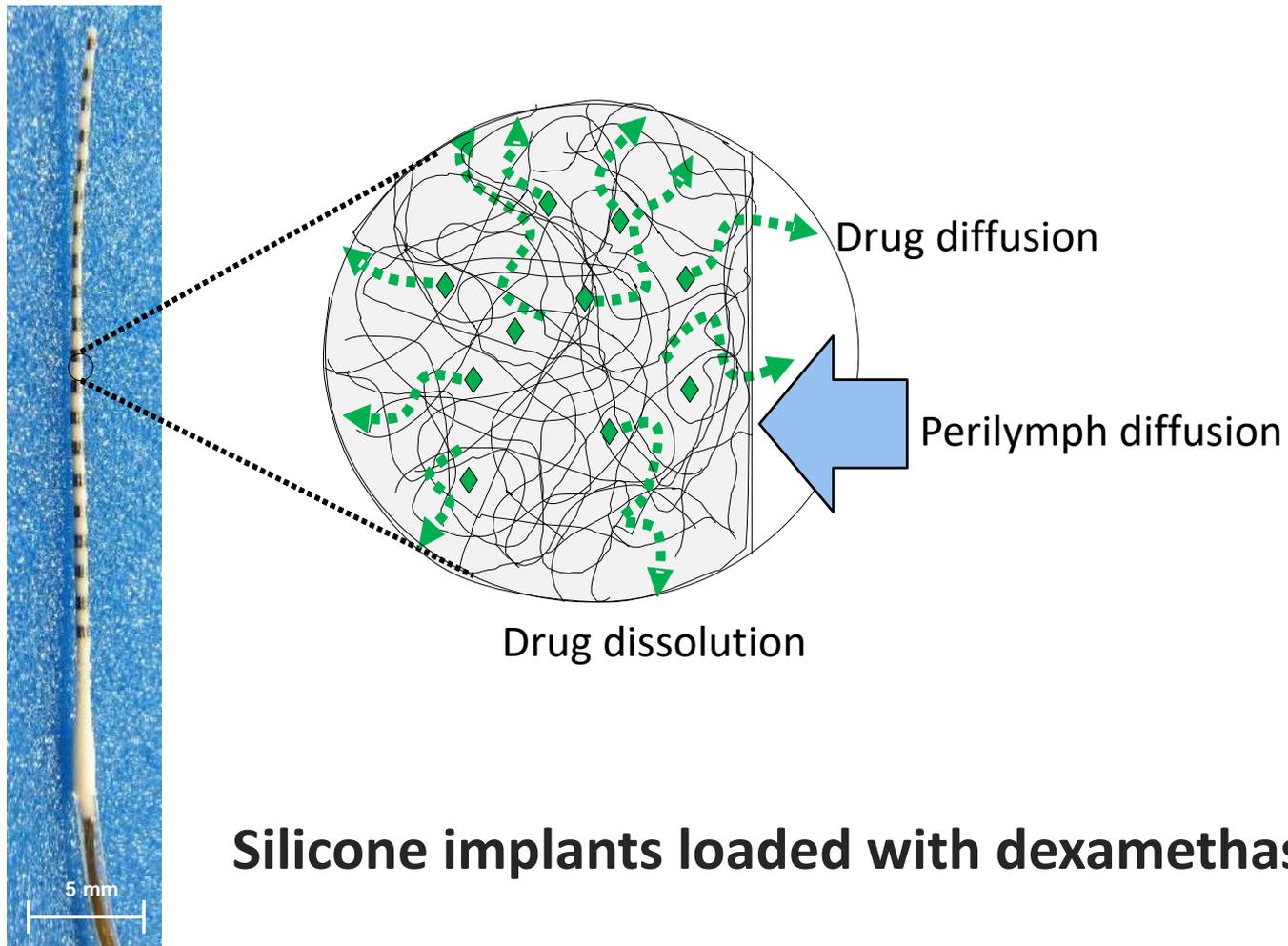
surface of a polymeric film loaded with 10 % DXM,
cross section of an extrudate loaded with 1 % DXM



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

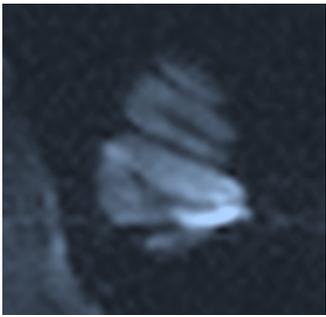


Drug release mechanisms



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



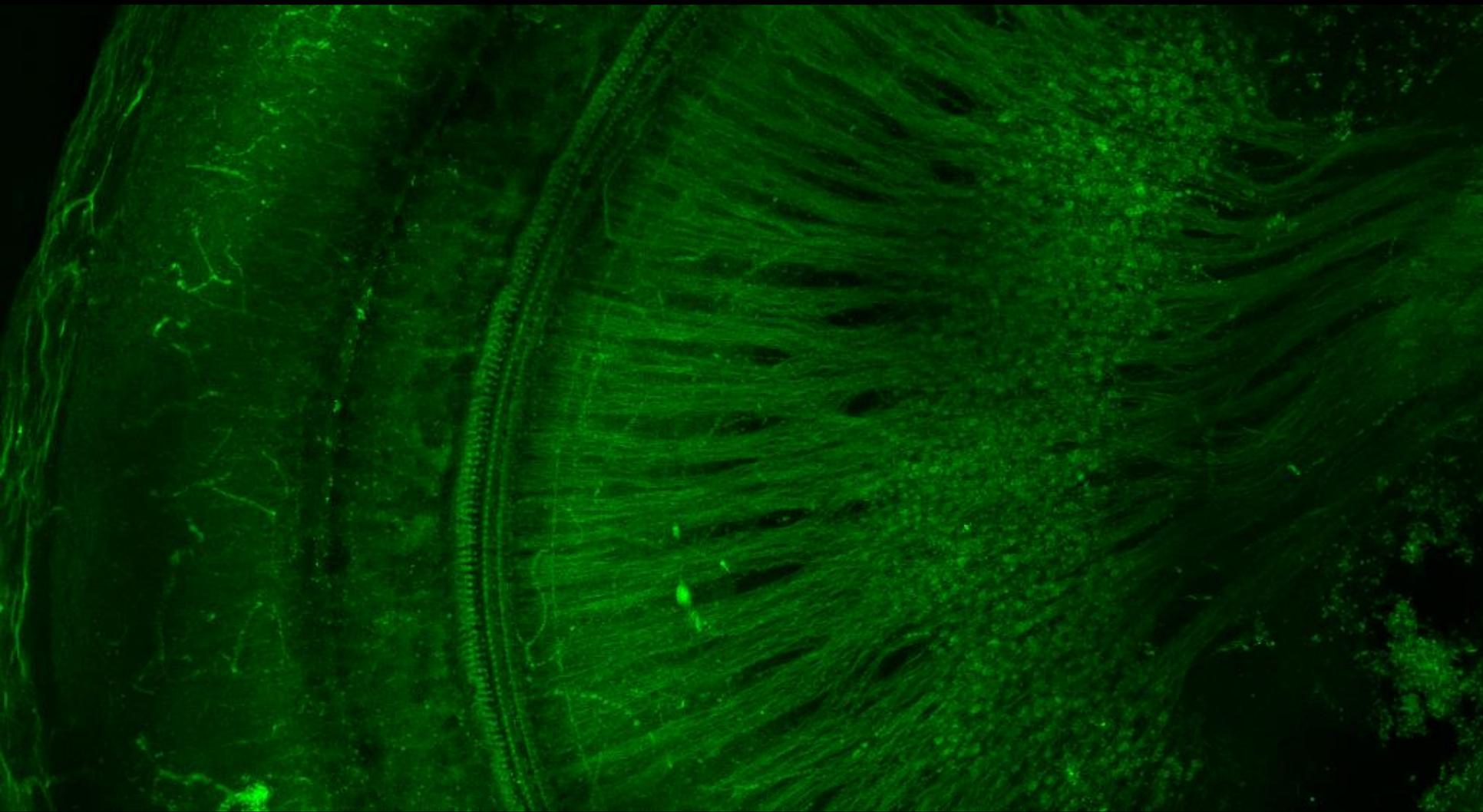
- Active dexamethasone electrode array with controlled release allows a better conservation of hearing thresholds at 1 month for 500, 1000, 2000, 4000 and 16000 Hz and at 1 year for 16000 Hz in our gerbil model.

Krenzlin et al, J Control Release (2012)

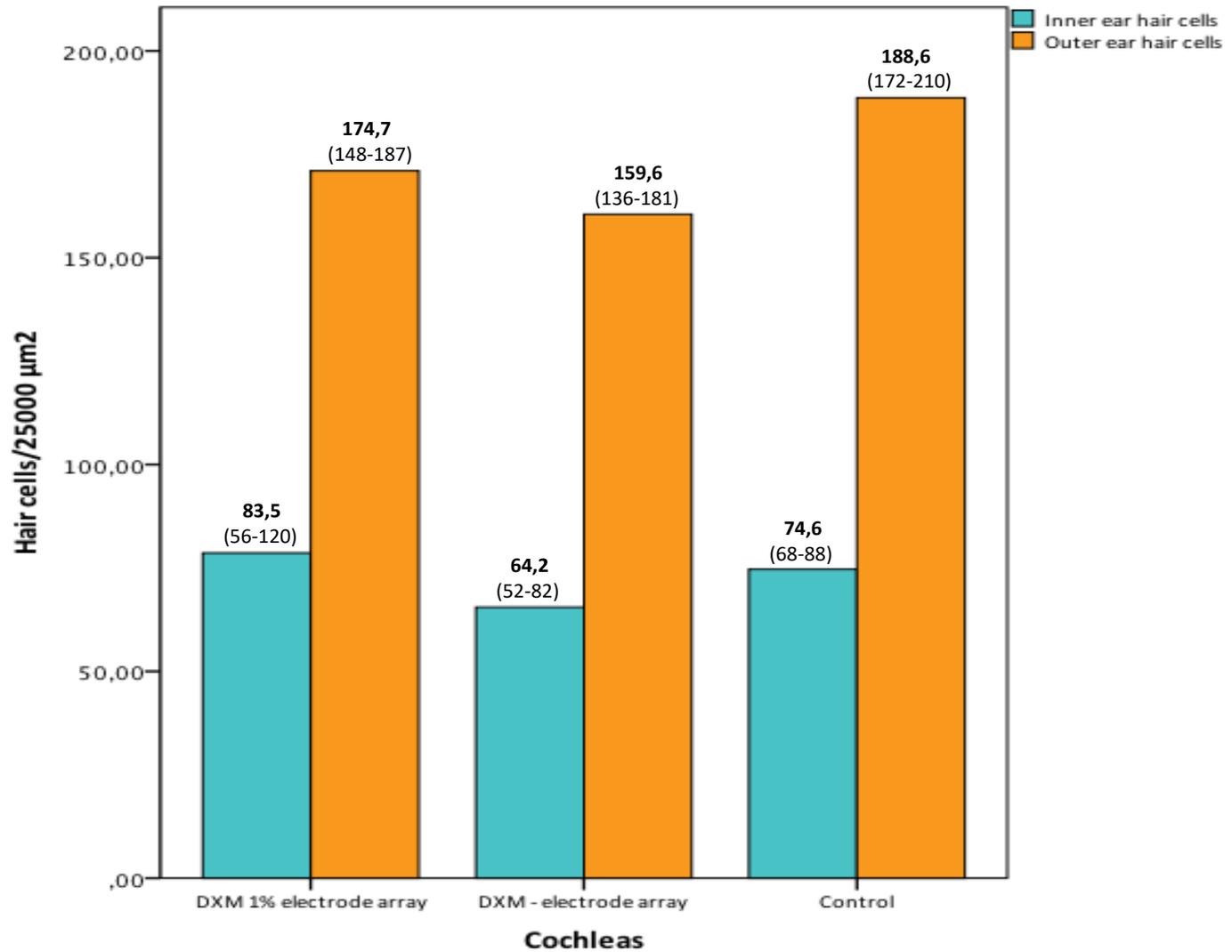
Douchement et al, Cochlear Implants Int (2014)

Cochlear implants: long term safety ?





Cell population



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 on a long term basis!)
 - 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



Inserm U1008: Controlled Drug Delivery Systems and Biomaterials: J. Siepmann, C. Vincent

PE Lemesre

D. Douchement,

G. Dedieu,

J. Lamblin,

A. Terranti,

S. Krenzlin,

F. Siepmann

M. Risoud

NX Bonne

M Tardivel

J. Sircoglou,

M. Gerkhe

NX Bonne

M. Ting

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