A 3D Simulation of the Diffusion Profile of Brain Derived Neurotrophic Factor in the Inner Ear Using COMSOL Multiphysics®

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INTRODUCTION:

Sensorineural hearing loss can be treated in many cases by regenerating the synaptic connections between the extant Auditory Neurons (ANs) and transplanted human stem cell derived ANs. Brain-Derived Neurotrophic Factor (BDNF) plays an essential role in directing the growth of both types of AN neurites towards one another. Using COMSOL Multiphysics®, we have developed a finite element model to analyze the diffusion profile of varying initial concentrations of BDNF, released from Polyhedrin Delivery System (PODS™) (Cell Guidance System, Cambridge, U.K.), inside a 3D surface model of a murine scala tympani recreated from micro-computed tomography images.

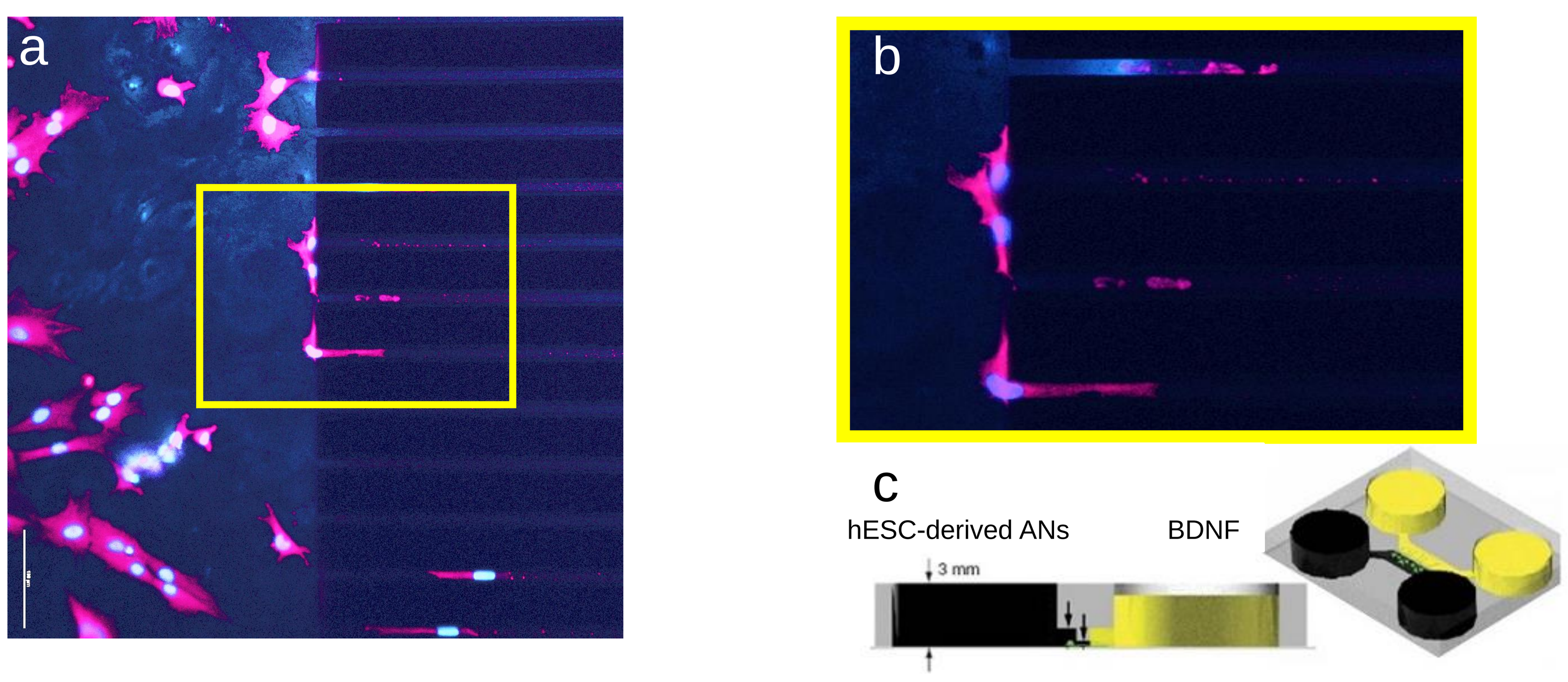

Fig. 1: a and b: Immunohistochemistry of empirical experiment showing neurite extension towards a chamber contains BDNF (10 ng/mL). c: Xona™Microfluidics device (Xona™Microfluidics, LLC, San Diego, CA).

COMPUTATIONAL METHODS:

The geometry for the simulation was recreated from the scanned mouse cochlea tissue samples. Fiji imaging software (NIH, Bethesda, MD) was used to convert images to binary, clean noise, and isolate the scala tympani at each cross section. The isolated cross sections were then stacked to construct a 3D surface, which was exported to Autodesk Meshmixer™ (ver. 3.5) (AUTODESK, Inc., San Rafael, CA) for modifications.

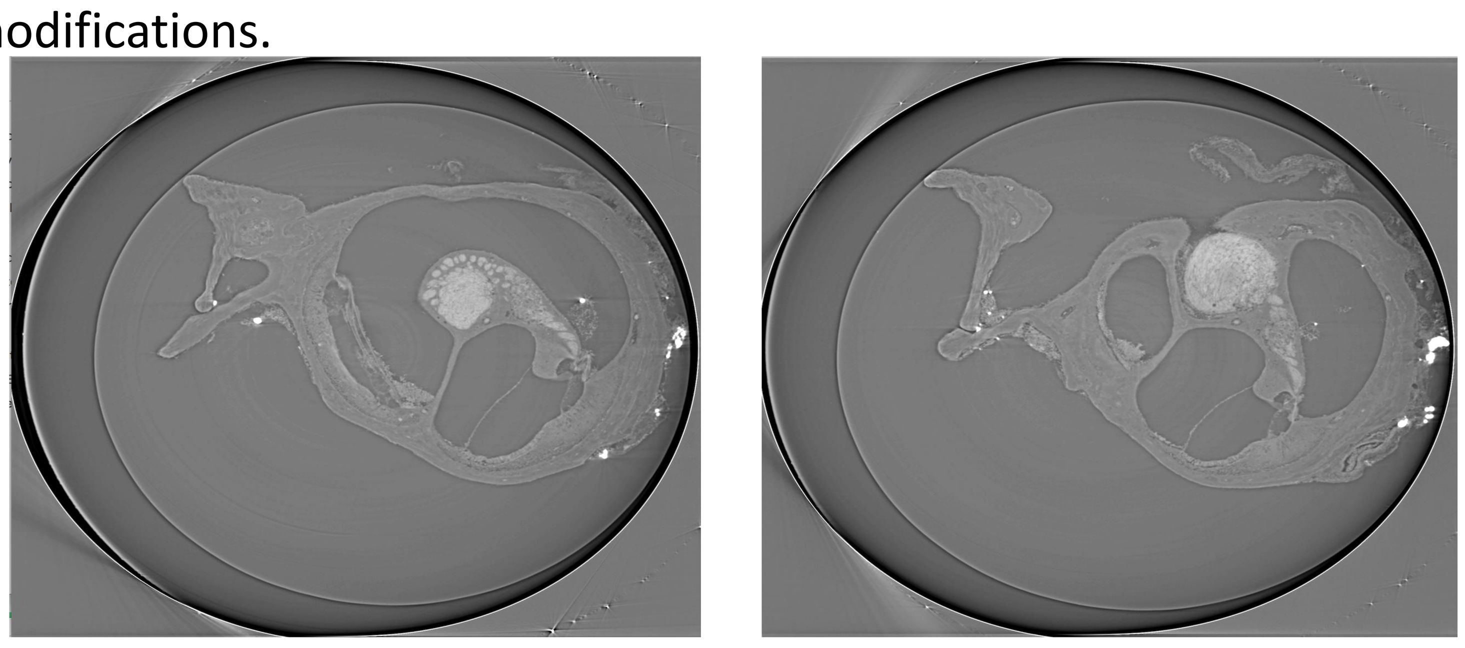

Fig 2: Mouse cochlear tissue samples were imaged using 22 keV X0rays at Argonne National Laboratory.

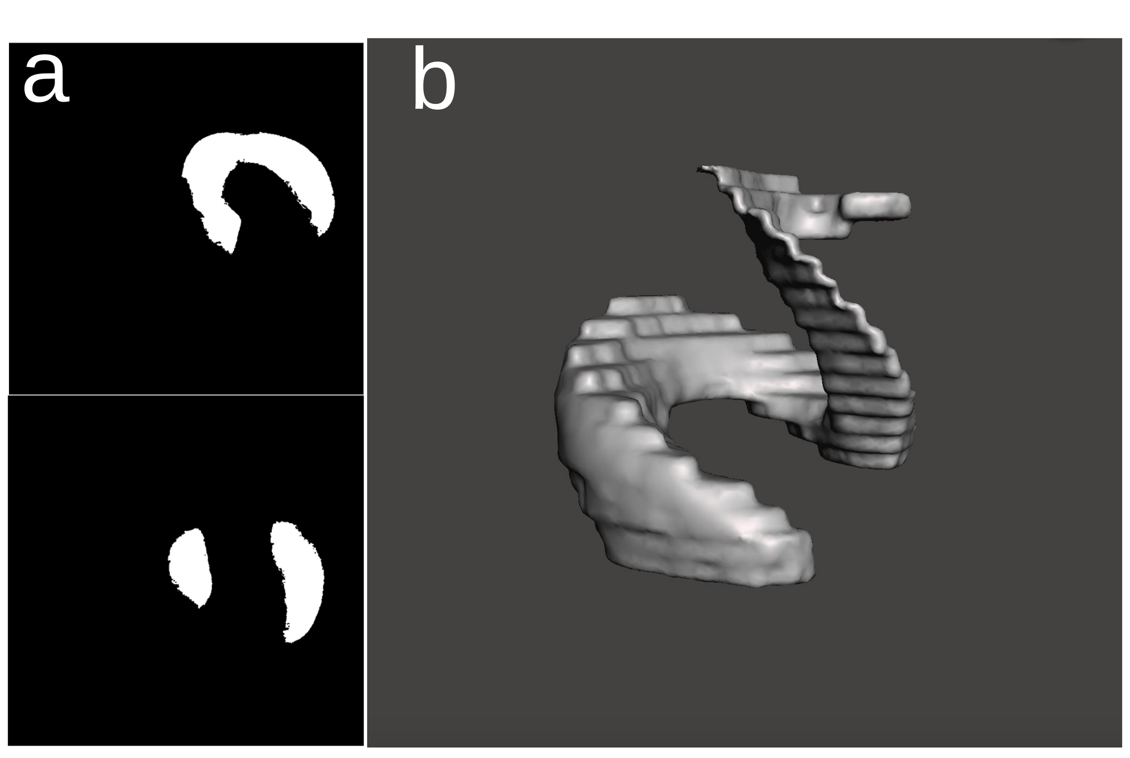

Fig 3: (a): Isolated scala tympani at each cross section, after conversion to binary and cleaning of noise. (b): 3D reconstructed surface of scala tympani constructed from stack of cross sections.

The Coefficient Form PDE interface of COMSOL Multiphysics® was used:

$$\mathrm{Da}\left(\frac{\partial u}{\partial t}\right) + \nabla \cdot (-c\nabla u - \alpha u + \gamma)\ \beta \cdot \nabla u + au = f \qquad (1)$$

where Damping factor (da) = 1, diffusion coefficient c = 6.76 mm^2/day (diffusion coefficient was estimated from diffusivity of β-Lactoglobulin) [1]. Here, we assumed the diffusivity is constant. Conservative flux convection (α), convection (β), and conservative flux source (γ) = 0 (they were not taken into account). Absorption coefficient (a) was estimated from reaction kinetics data of Leukemia Inhibitory Factor (LIF) and was set to 0.2148/day [1]. Source term expression (f) was created from estimate of reaction kinetics data of release of LIF from PODS™ and from crystal equivalence estimate of standard recombinant protein; kindly provided by Cell Guidance Systems, Cambridge, UK. Source term expression f was thus defined as 1.146/day * 3.3 μg/mL* $* \ e^{-\frac{1.146}{day} * t}$. Finally, zero flux boundary conditions were used on all walls of scala tympani.

RESULTS:

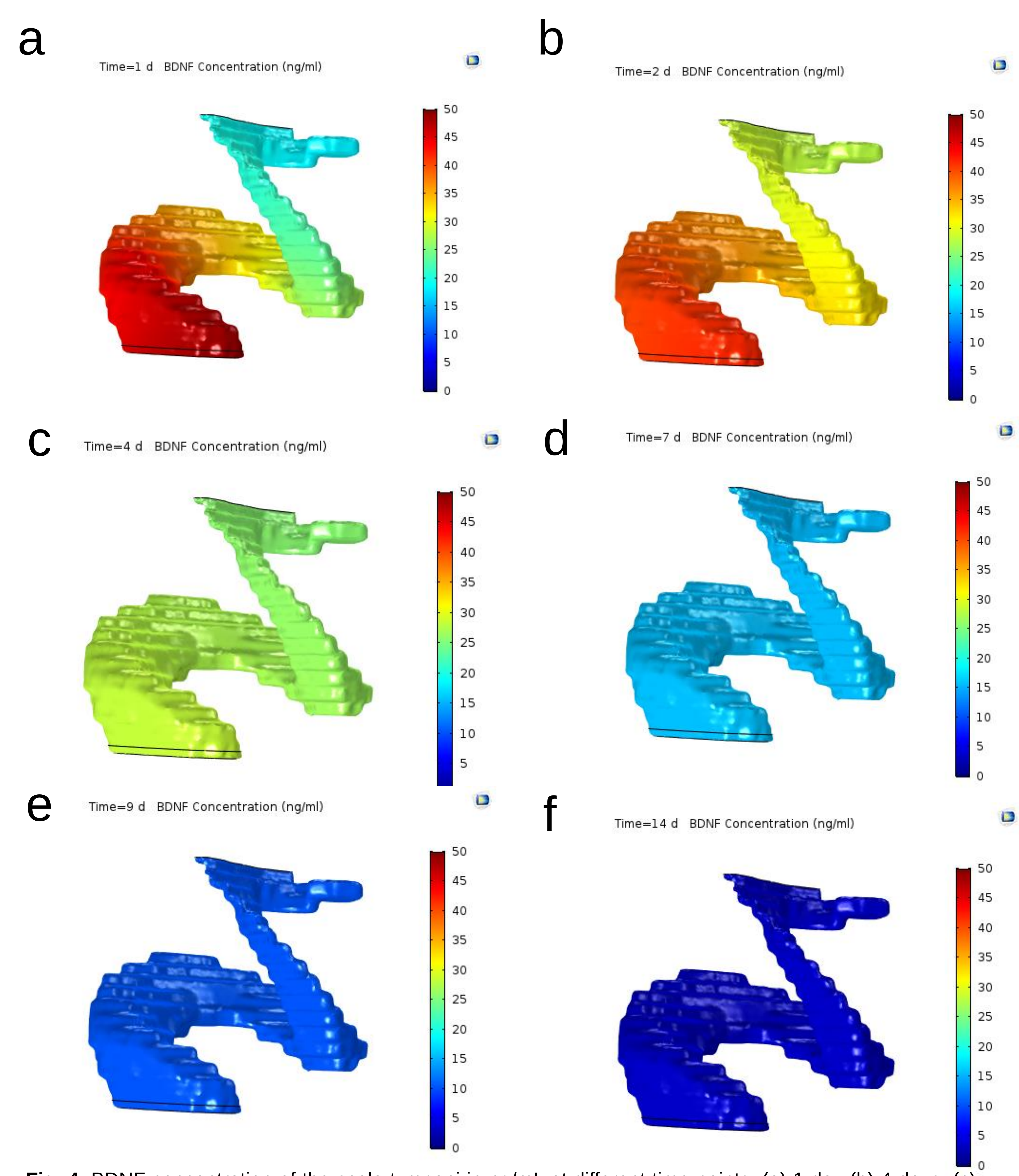

Fig. 4: BDNF concentration of the scala tympani in ng/mL at different time points: (a) 1 day (b) 4 days, (c) 6 days, (d) 9 days, (e) , (f) 14 days. 5.0 x 10^7 PODS crystals added.

CONCLUSIONS: Our computational models can help predict the optimal parameters needed to achieve SGN neurite growth *in vivo.* Standard estimates state that 10 ng/mL of BDNF is needed for sustained neurite growth, so the parameters in our simulation experiment would work with that. Future directions of the work following these simulations involve three branches:

1). Replicating simulations in scala tympani of other animals, including humans, for comparison of diffusion profiles.

2). Conducting empirical experiments and immunohistochemistry to verify simulation results and modify any estimated parameters.

3). Simulating different sources of BDNF, such as a neurotrophic ribbon that runs along the scala tympani.

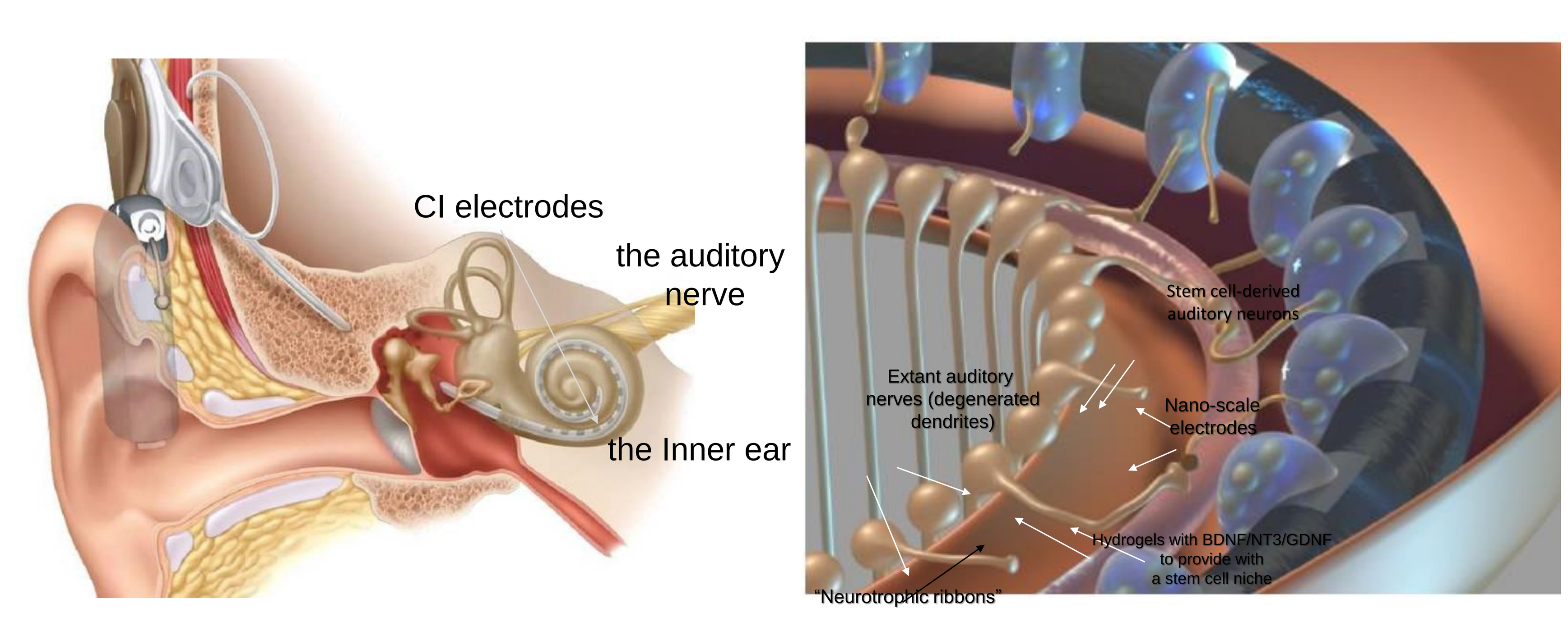

Fig 5: (a): Conventional cochlear implant (Cochlear, LTD). (b): Possible design of next generation biohybrid cochlear implant with neurotrophic ribbon as source of BDNF/NT3/GDNF.

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