CELL-BASED NEUROTROPHIN DELIVERY FOR AUDITORY NEURON SURVIVAL IN DEAFNESS

Dr Lisa Gillespie
Prof Rob Shepherd
Dr Mark Zanin
Sensorineural hearing loss

{SNHL}

Hair cells
\downarrow
Auditory neurons
\downarrow
Hearing
Sensorineural hearing loss

{SNHL}

Hair cells

↓

Auditory neurons

↓

Hearing
Sensorineural hearing loss

\{SNHL\}

Cochlear Implant

↓

Auditory neurons

↓

Hearing
Auditory neurons and sensorineural hearing loss

{SNHL}

- Loss of sensory hair cells
- Loss of peripheral processes
- Loss of auditory neurons
- Elevated EABR thresholds
Auditory neuron degeneration: Implications for the cochlear implant

- Decreased neuronal population
- Elevated thresholds

- Preservation of auditory neurons in deafness may enhance cochlear implant efficacy
Auditory neuron degeneration: The role of neurotrophins

Loss of hair cells $\rightarrow$ Loss of neurotrophins (BDNF, NT-3) $\rightarrow$ Auditory neuron degeneration

Deaf

Exogenous neurotrophins $\rightarrow$ Auditory neuron survival

Deaf, BDNF-treated

(Shepherd et al., J. Comp. Neurol. 2005)
Neurotrophins: Delivery mechanisms

- Clinically applicable delivery methods are required

- Key requirements
  - Efficacy
  - Longevity
  - Safety

- Pump-based systems
- Nanotechnology
- Viral gene transfer
- Cell-based therapies

→ To protect auditory neurons from deafness-induced degeneration using cell-based delivery of neurotrophins
Cell-based neurotrophin treatment: 
*In vitro* methods

- Neurotrophin-expressing cells
  - Fibroblasts, Schwann cells
  - Lipofection, nucleofection
  - BDNF, NT-3
Cell-based neurotrophin treatment: 
*In vitro* results

- Neurotrophin-expressing cells
  - **Fibroblasts**, Schwann cells
  - Lipofection, nucleofection
  - **BDNF**, NT-3

![Control fibroblasts](image1.png)  ![BDNF-fibroblasts](image2.png)

![Graph](Graph.png)

*(Gillespie et al., unpublished; 2013)*
Cell-based neurotrophin treatment: 
*In vivo* methods

- Encapsulation in alginate microcapsules
  - Semi-permeable; biocompatible; ~500 µm diameter
- Immune protection
- Prevent dispersal
Cell-based neurotrophin treatment: *In vivo* methods

- Bilaterally, ototoxically deafened
  - Hair cell destruction
  - Auditory neuron degeneration
Cell-based neurotrophin treatment: *In vivo* methods

- *In vivo* implantation of encapsulated BDNF-fibroblasts
  - 10 capsules per cochlea
  - Basal turn, scala tympani

- Long-term survival effects
  - Bilateral implants
    - Left = encapsulated BDNF-fibroblasts
    - Right = empty capsules
  - 1 and 6 month survival
Cell-based neurotrophin treatment: 
*In vivo* methods

- *In vivo* implantation of encapsulated BDNF-fibroblasts
  - 10 capsules per cochlea
  - Basal turn, scala tympani

- With a cochlear implant
  - Unilateral implants
    - Left = encapsulated BDNF-fibroblasts + CI
  - 1 month survival
  - EABRs
Cell-based neurotrophin treatment: 
*In vivo* results

- **eBDNF-fibroblasts (1 month)**

  - Enhanced auditory neuron survival

  *(Gillespie et al., unpublished; 2013)*
Cell-based neurotrophin treatment: *In vivo* results

- eBDNF-fibroblasts + electrical stimulation (1 month)
- Enhanced auditory neuron survival
- Functional benefits

(Gillespie et al., unpublished; 2013)
Cell-based neurotrophin treatment: *In vivo* results

- eBDNF-fibroblasts (6 months)
- Enhanced auditory neuron survival

(Gillespie et al., unpublished; 2013)
Cell-based neurotrophin treatment: 
*In vivo* results

- Inflammatory response

(Gillespie et al., unpublished; 2013)
Implantation of encapsulated BDNF-expressing fibroblasts into the deaf guinea pig cochlea supports auditory neuron survival for at least six months

- Long-term BDNF expression
- Auditory neuron survival
- Functional effects
- Minimal inflammatory response
Cell-based neurotrophin treatment is a potential clinically transferable method for long-term auditory neuron survival.

Cell-based neurotrophin treatment + Cochlear implant ↓ ↑ long-term auditory neuron survival ↓ ↑ efficacy of cochlear implant
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