Drug Delivery to the Inner Ear

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Neurodegeneration and bionics

- Bionic devices can be used to stimulate nerves for clinical applications
  - Cochlear Implant
  - Bionic Eye

- Neurodegeneration – decreased nerve survival

- Combine therapeutic drugs with bionic devices to enhance nerve survival and improve outcomes
Sensorineural hearing loss – the clinical problem

- Major cause of hearing loss
- 278 million people world-wide (2005)
- 0.5% of Australians experience a bilateral, severe-profound SNHL

→ Cochlear Implant
The auditory system

- **Outer ear**
  - Sound collection

- **Middle ear**
  - Sound transfer
  - Couples mechanical vibration from air → fluid

- **Inner ear (cochlea)**
  - Sound transduction
  - Mechanical → electrical signal
The inner ear – normal hearing

- Sound transduction via hair cells and auditory neurons

![Diagram of the inner ear showing hair cells and auditory neurons]
The inner ear – normal hearing

- Hair cells secrete neurotrophins

→ BDNF, NT-3
The inner ear – sensorineural hearing loss

Loss of hair cells
The inner ear – sensorineural hearing loss

Loss of hair cells

↓

Loss of neurotrophins

(BDNF, NT-3)
The inner ear – sensorineural hearing loss

Loss of hair cells
↓
Loss of neurotrophins
(BDNF, NT-3)
↓
Auditory neuron degeneration
Auditory neurons and the Cochlear Implant

- Directly electrically stimulates auditory neurons
- Reduced auditory neuron population
Auditory neurons and neurotrophins

Exogenous neurotrophins

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Auditory neuron survival
Exogenous neurotrophin treatment

Deaf, BDNF-treated

Deaf, Untreated

(Shepherd et al., 2005; J Comp Neurol)
Neurotrophin delivery techniques

• Pump-based system
  o Potential risk of infection
  o Finite delivery period
Neurotrophin delivery techniques

(Gillespie et al., 2003; J Neurosci Res)
Neurotrophin delivery techniques

![Graph showing neuronal density (neurons/mm²) over time for BDNF treated and untreated groups. The graph includes data points at various time intervals: Deafening, Implant, 4 weeks, 6 weeks, and 8 weeks. The y-axis represents neuronal density, while the x-axis represents time. The graph indicates a decrease in neuronal density over time, with a significant difference between BDNF treated and untreated groups.](Gillespie et al., 2003; J Neurosci Res)
Neurotrophin delivery techniques

- Osmotic pumps
- Smart polymers

*PpyNT3 coated electrodes*
Neurotrophin delivery techniques

- Osmotic pumps
- Smart polymers
- Nanotechnology
Neurotrophin delivery techniques

- Osmotic pumps
- Smart polymers
- Nanotechnology
- Viral gene transfer
Neurotrophin delivery techniques

• Osmotic pumps
• Smart polymers
• Nanotechnology
• Viral gene transfer

• Cell-based therapies
Our research focus

Use cell-based therapies and neurotrophin-producing cells to support long-term auditory neuron survival
Cell-based neurotrophin treatment in the deaf cochlea

- BDNF-Schwann cells
  → Naturally secrete neurotrophins
  → Genetically modified to over-express BDNF

- Cell encapsulation
Cell-based neurotrophin treatment in the deaf cochlea

(Pettingill et al., 2011; PLoS One)
Cell-based neurotrophin treatment in the deaf cochlea

Auditory neuron density (neurons/mm$^2$)

Time

- 2 weeks
- 4 weeks

Pettingill et al., 2011; PLoS One
Cell-based neurotrophin treatment in the deaf cochlea

- NTCell – choroid plexus
  → naturally secrete a variety of neurotrophins

- Electrical stimulation – cochlear implant
Cell-based neurotrophin treatment in the deaf cochlea

(Treated) (Control)

(Wise et al, 2011; Neurotherapeutics)
Cell-based neurotrophin treatment in the deaf cochlea

(Treated v untreated cochlea)

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(Wise et al, 2011; Neurotherapeutics)
Summary

- Cell-based neurotrophin treatment supports auditory neuron survival in SNHL
  - in the guinea pig and cat
  - for up to 6 months
- Survival effects are enhanced with concurrent electrical stimulation from a cochlear implant

Cell-based neurotrophin treatment may be a clinically transferable method to promote auditory neuron survival in deafness.
Effects of neurotrophin delivery on the peripheral processes

Drug delivery to:
• Preserve peripheral processes
• Promote regrowth
• Can we control regrowth
• Other applications: protection of residual sensory function
Analysis of peripheral processes

Peripheral processes in the normal cochlea

50 µm
Peripheral processes and neurotrophin treatment

Treated cochlea

Control cochlea

Greater peripheral process density

![Graph showing density comparison between treated and control cochleae with statistical significance indicators.](image-url)
Neurotrophins promote process regrowth

Normal

Deaf

Neurotrophin

Regrowing peripheral processes

Wise et al (2011 unpublished)
Regrowth of peripheral processes near the electrode array
Regrowing peripheral processes travel along the electrode array.
Controlling process regrowth with localised neurotrophin delivery
Controlling process regrowth with localised neurotrophin delivery
Controlling process regrowth with localised neurotrophin delivery
Controlling process regrowth with localised neurotrophin delivery
Controlling process regrowth with localised neurotrophin delivery

Localised source of neurotrophins


20 µm
Improving nerve / electrode interface

Can we regrow processes towards an electrode?
Preserving residual sensory function

Can we deliver drugs that protect remaining sensory function following cochlear implantation?

Sensory cells
Loss of auditory function following cochlear implantation

Cat with high frequency hearing loss

Chronic electrical stimulation (6 months)
Summary: Drug delivery to the inner ear

- Clinically viable delivery techniques
- Neurotrophin delivery effective:
  - Auditory nerve survival
  - Maintain peripheral processes
- Peripheral process regrowth
  - possibly improve nerve – electrode interface
- Drug delivery to improve residual sensory function?
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Questions
Processes and glial cells growing in scala tympani

Wise, Pujol et al (2011 unpublished)

Shepherd & Colreavy, 2004
Loss of sensory function

- Sensory cells present
  - OHC
  - IHC

- Loss of sensory cells

- Good SGN survival

- Loss of SGNs

IHC

OHC