Repair of the adult brain and spinal cord

The development of the CNS in the fetus involves the proliferation, migration and then differentiation of billions and billions of cells.

There is an enormous diversity of neuronal types in the CNS – morphologically and chemically.

Each neuron must then integrate into appropriate local and distant neural circuits.

The development of different cell types, and the interactive circuits between them, requires very complex interactions over space and time.

Neurons come in many shapes and sizes, and also have different biochemical properties.

Traumatic and vascular accidents

There is considerable plasticity in the circuits of the CNS – hence learning and memory – but after injury or after degenerative changes the mature CNS has little inherent capacity for large-scale repair.

Any loss or disruption of brain circuitry will have a profound effect on mental health.
Adult central nervous system (CNS) lacks effective spontaneous regeneration

**Contributing Factors:**
- Little if any neuronal replacement
- Inhibitory CNS environment:
  - Inhibitory molecules on oligodendrocytes and central myelin
  - Glial/meningeal scar
- Lack of trophic support
- Intrinsic change in neuronal responsiveness

After injury or stroke it is vitally important to minimise initial injury effects and prevent further secondary degeneration.

In neurodegenerative diseases ways must be found of diagnosing the illness much earlier and preventing any further deterioration.

**IF ALL ELSE FAILS……….**

Repair strategies focus on two basic issues:
- Cell replacement, pathway reconstruction

**Cell protection or replacement**

Various strategies may be used to protect injured or compromised neurons.

Cell replacement involves the transplantation of new cells to replace neurons or glial cells that have already been lost after trauma, stroke or as a result of some degenerative disease.

**Pathway reconstruction**

In pathway reconstruction the neurons may not be significantly affected but the circuits between them may be damaged – eg after spinal cord injury or after certain types of stroke.

Thus the aim here is to re-establish functional connections between different parts of the CNS. These regenerated connections must be appropriately organised and reflect the circuitry that was set up during development.

**Neuro-protection**

- Degenerative disease – earlier diagnosis
- Stroke, trauma – acute phase

Growth factors
- Cell death inhibitors
- Gene therapy - viral vectors
- Activate endogenous neural precursors
How to deliver therapeutic proteins to the nervous system?

- systemic injection
- local injection
- minipump
- fibronectin or collagen matrix
  - genetically engineered cells
  - viral vector
  - non-viral vector

A viral vector is an *attenuated, replication-deficient virus* carrying a foreign gene.

Principles of gene therapy

1. in vivo method
   - episome
   - cell
   - nucleus
   - altered chromosome

2. ex vivo method
   - therapeutic protein
   - gene
   - axotomized neuron
   - implant

Transplantation and cell replacement in the CNS

**Transplantation is a last resort**

Stroke, Alzheimer's disease, Parkinson's disease, Huntington's disease, Motor neuron disease, Multiple Sclerosis (glial disease).

For neuronal replacement to be effective it is important that transplanted cells acquire the appropriate phenotype and then integrate into the appropriate circuitry. Immunological rejection of the transplanted cells must be prevented.

The difficulty is that this rejuvenation of specific developmental processes has to be carried out in the adult brain.

Early diagnosis and neuroprotection, or cell replacement?

Parkinson's Disease
Fetal neural (mesencephalic) grafts and Parkinson's disease

Potential sources of cells for neural transplantation and cell replacement

- Fetal neural tissue/fetal neurons
- Adult neural stem cells
- Bone marrow
- Umbilical cord blood
- Fetal neural stem cells
- Embryonic stem cells
- Engineered stem cell lines
- Somatic cell nuclear transfer – ‘therapeutic’ cloning
- Xenografts

Tract damage, pathway repair

- Minimise secondary injury – remyelination
- Peripheral nerve grafts – Schwann cells
- Reconstructed nerve bridges
- Genetic modification of bridges
- Olfactory ensheathing glia
- Fetal neural tissue
- Stem cells
- Cell/polymer hybrid structures

Spinal Cord Injury
Transplantation research – spinal cord

Genetic modification of peripheral nerve bridges

Retinal ganglion cell counts in retinal wholemounts

Where to from here???

Improved methods for early diagnosis and early intervention, protecting adult nerve cells and enhancing their growth potential

Transplantation: which cells to use and under which circumstances:

Cell replacement versus tract repair

Acute versus chronic injury

Combined genetic engineering/manipulation of damaged neurons and the implantation of bridging substrates to enhance regeneration at the injury site.

Rehabilitation therapies, training