Therapeutic Use of Stem Cells

Practical Hurdles & Ethical Issues

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Stem cells in Development

- Blastocyst
- Cord blood

Pluripotent Stem Cells

- Pluripotent
  - to describe stem cells that can give rise to
cells derived from all 3 embryonic germ
  layers
  - Mesoderm
  - Endoderm
  - Ectoderm
  - layers are embryonic source of all cells of the
  body

Stem Cells © Dr Mark Hill 2006 Slide
What is a stem cell- Definition

• Stem cell is a cell that has the ability to divide (self replicate) for indefinite periods
  – throughout life of organism
• Under the right conditions, or given the right signals, stem cells can differentiate to the many different cell types that make up the organism

Amplifying Cells

• Stem cells in many tissues divide only rarely
  – give rise to transit amplifying cells
  – daughters committed to differentiation that go through a limited series of more rapid divisions before completing the process.
  – each stem cell division gives rise in this way to eight terminally differentiated progeny

(Ab)Normal Stem Cell Production

• (A) normal strategy for producing new differentiated cells
• (B and C) 2 types of derangement that can give rise to unbridled proliferation characteristic of cancer

Stem Cell Daughter Fates

• environmental asymmetry
  – daughters are initially similar
  – directed into different pathways according to environmental influences that act on them after they are born
  – number of stem cells can be increased or reduced to fit niche available
• divisional asymmetry
  – stem cell has an internal asymmetry
  – divides in such a way that its two daughters are already endowed with different determinants at time of their birth
Possible Therapeutic Uses

• Neural
  – Parkinson’s, ALS, spinal cord injury……..
  – Cell Replacement
    • cell death, loss of function
  – Grafting
    • where host-graft rejection normally requires substantial ongoing immunosuppression
  – Repair
    • Spinal cord and brain injury

• Other Diseases
  – Diabetes, muscular dystrophies, cardiac, vital organs…..

Current research on stem cells

• How to:
  – Isolate
  – Grow
  – Maintain, store
  – Differentiate
  – Therapeutic uses

Stem Cell Therapy: Current Limitations on Cell Transplantation

- Cell Type?
- Cell Number?
- Route of Delivery?

Enhancing Muscle Stem Cell Transplantation using Chemotherapeutic Drug Selection

• Alkylating Chemotherapy + Drug Resistant Donor Cells -
  based on mechanisms established for Bone Marrow Transplantation
  - Efficient Elimination of Endogenous Cells
  - Creating Receptive & Favourable Niche for Donor Cells
  - Selective in vivo Expansion of the Protected Donor Cells
  - Feasibility in the Skeletal Muscle as a Solid Organ?
**Skeletal Muscle Biology**

- Normal Muscle
  - Muscle fibers and myonuclei are post-mitotic
  - Muscle stem / satellite cells remain quiescent

- Injured Muscle
  - Muscle stem / satellite cells are activated and rapidly proliferate
  - Differentiated cells align and fuse to form new muscle fibres

**Muscle Stem Cell Transplantation - Improved Strategy**

- Wild-Type cell
  - Alkylates DNA
  - BCNU
  - Cell survives

- MGMT-P140K Expressing Cell
  - Alkylates DNA
  - BCNU
  - Cell survives

**Selective Enrichment: The Mechanism**

- Wild-Type cell
  - Alkylates DNA
  - BCNU
  - Cell death

- MGMT-P140K Expressing Cell
  - Alkylates DNA
  - BCNU
  - Cell survives

* Anthony Pegg
Selective Enrichment: The Mechanism

Muscle Stem Cell Transplantation: Protocol

Higher Engraftment of MGMT(P140K) Donors in Chemo-Ablated Recipient Muscle Bed

De Novo Muscle Formation by MGMT(P140K) Donors
Absence of Dystrophin in the Duchenne Muscular Dystrophy (DMD) Patients and mdx Mice

- Duchenne Muscular Dystrophy (DMD)
  - X-linked disorder with defects in Dystrophin gene
  - 1:3500 live Male Birth (20,000 babies / year)
  - Confined to wheelchair by 12 yrs and death by 30 yrs
  - Several mouse models exist including mdx mice
    (Dystrophin KO)

Restored Dystrophin Expression by Engrafted MGMT(P140K)+ve Donors in the Recipient mdx Muscle

Dystrophin - Wildtype EDL

Dystrophin - Treated with BRU

Dystrophin - Treated with O6BG

Dystrophin - Engrafted with MGMT-P140K+ve