Stem cells, regenerative medicine and gene therapy

Dr Mike Doran | Stem Cell Therapies Laboratory - Group leader
Institute of Health & Biomedical Innovation (IHBI) | Faculty of Health | Queensland University of Technology
Translational Research Institute (TRI) | 37 Kent St, Woolloongabba, 4102 | Brisbane, QLD, Australia

Honorary Research Fellow | Mater Medical Research Institute

Tel: (617) 3443 7348 | E: michael.doran@qut.edu.au

Where are we?

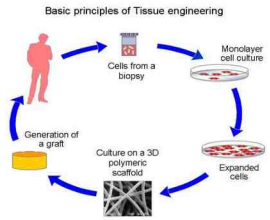
Translational Research Institute (TRI) – PA Hospital.

Today's discussion points
(stem cells in 2-hours!):

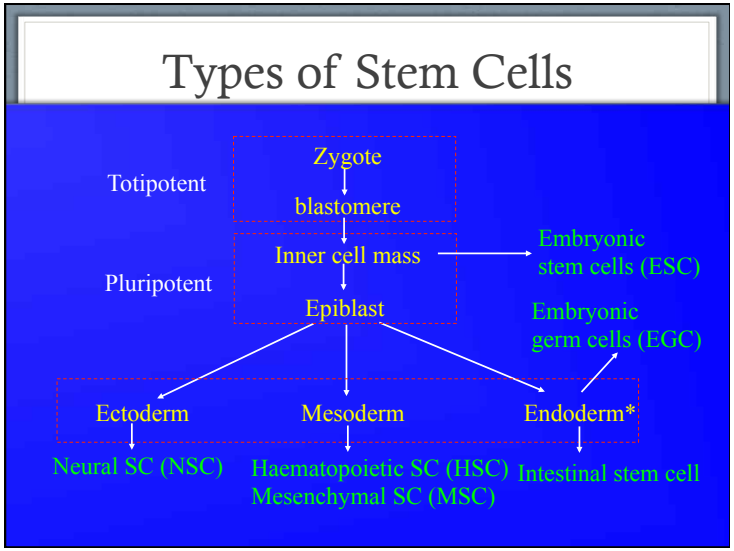
- Types of stem cells.
- Embryonic stem cells.
- Haematopoietic stem cell transplants (HSC).
- Mesenchymal stem/stromal cells (MSC).
  - *MSC differentiation and direct repair of tissue.*
  - *MSC paracrine signaling and indirect repair of tissue.*
  - ***Gene therapy and enhanced MSC repair of tissue.***

Why are we interested in stem cells?

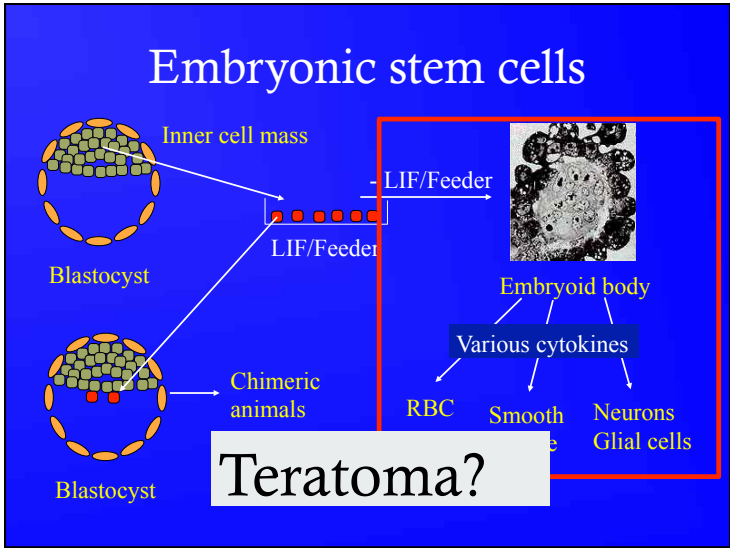
- **Stem cells** are:
  biological cells found in all multicellular organisms, that can divide (through mitosis) and differentiate into diverse specialized cell types and can self-renew to produce more stem cells.



Types of Stem Cells



Embryonic stem cells



Embryonic stem cells

1. Are there any embryonic stem cell therapies?
2. Are there any embryonic stem cell clinical trials?
3. Who/what is Geron?
4. What are the limitations? What is the future?

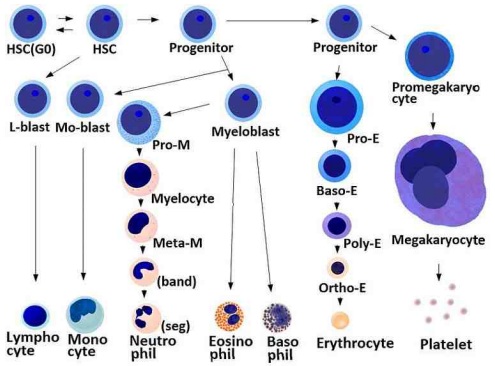
Embryonic stem cells - challenges

- Human ESC derived from excess blastocyst in 1998 (also EGC from aborted fetus)
- Pluripotent but incapable of morphogenesis (need blastocyst)
- Difficult to differentiate into desired cell types
- Does not resolve immunological problem, if derived from anything but identical twin!
  - May be able to derive HLA specific ES covering most matches

What is the future of embryonic stem cells?

- Therapies? Cloning? Induced Pluripotent Stem Cells (IPS)? - routes to self! Is cancer going to be a problem?
- Model systems?
  - These topics require another lecture and hopefully I am invited to speak with you about these interesting challenges.

Haematopoietic stem cells (HSC)



http://en.wikipedia.org/wiki/File:Blood_cells_differentiation_chart.jpg

Haematopoietic stem cells (HSC)

1. Are there any haematopoietic stem cell therapies?
2. How do these therapies work? What is the basis?
3. Are there any haematopoietic stem cell clinical trials?
4. What are the limitations? What is the future?

HSC Transplants

- First efforts were with Yugoslavian nuclear workers in 1959 – these failed.
- In 1968 the first successful transplant was performed in Minnesota by Dr Robert Good.
- Now greater than **50,000** allogeneic have been performed world wide.
- *What is Allogeneic? What is Autologous?*

HSC Transplant limitations

- Allogeneic – first challenge is finding a match.
  - Solutions are/is umbilical cord blood to provide match and HSC *ex vivo* expansion to increase cell number.
- Autologous – the challenge is mobilizing sufficient cells
  - Solution is better drugs, and possibly HSC *ex vivo* expansion to increase cell number.

HSC Transplant Summary

- HSC transplants are routine and life saving.
- This is the only routine (clinical) stem cell transplant procedure.
- There is considerable opportunity to improve clinical outcomes and to make this process saver.

I would be happy to come back and chat about these topics as well.

Mesenchymal Stem/Stromal Cells (MSC)

- What are MSC?
- What is their role in the body?
- Are they used in the clinic?
- Are their any clinical trials with MSC?

Mesenchymal Stem/Stromal Cells (MSC)

There are really two stories for MSC

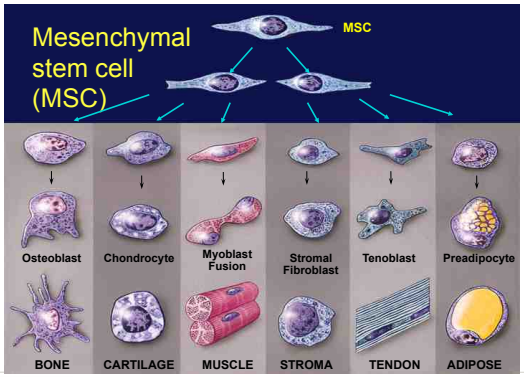
1. Direct differentiation into tissues.
2. Indirect paracrine signaling and tissue regeneration (and control over inflammation?).

2012 NIH definition for MSC?

The classical view -

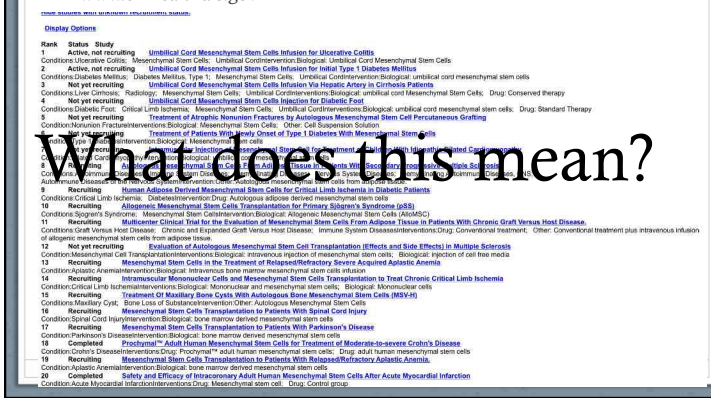
- Mesenchymal stem cells give rise to a variety of cell types: bone cells (osteocytes), cartilage cells (chondrocytes), fat cells (adipocytes), and other kinds of connective tissue cells such as those in tendons.

Classical view - Mesenchymal Stem/Stromal Cells



The MSC story seems to be more complex…

www.clinicaltrials.gov



What does this mean?

Cell Stem Cell

Perspective

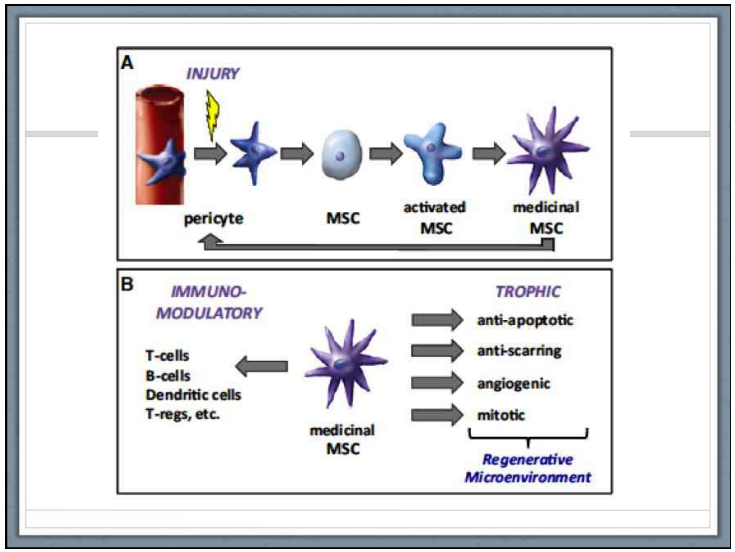
Cell PRESS

The MSC: An Injury Drugstore

Arnold I. Caplan[1,*] and Diego Correa[1]
[1]Skeletal Research Center, Department of Biology, Case Western Reserve University, 10900 Euclid Avenue, Cleveland, OH 44106-7080, USA
*Correspondence: arnold.caplan@case.edu
DOI 10.1016/j.stem.2011.06.008

Now that mesenchymal stem cells (MSCs) have been shown to be perivascular in vivo, the existing traditional view that focuses on the multipotent differentiation capacity of these cells should be expanded to include their equally interesting role as cellular modulators that brings them into a broader therapeutic scenario. We discuss existing evidence that leads us to propose that during local injury, MSCs are released from their perivascular location, become activated, and establish a regenerative microenvironment by secreting bioactive molecules and regulating the local immune response. These trophic and immunomodulatory activities suggest that MSCs may serve as site-regulated "drugstores" in vivo.

Caplan is ALSO credited with the original MSC definition.



MSC are Injury Drug Stores!

- EGF
- KGF
- IGF-1
- GDNF
- PDGF-BI
- VEGF-1
- Ang-1
- EPO
- TPO
- MIP-1
- Collagen type 1

Immune modulation and allogeneic potential.

This is so important!

The potential of MSC!

- Not just bone and cartilage repair –

6 Not yet recruiting Treatment of Patients With Newly Onset of Type 1 Diabetes With Mesenchymal Stem Cells

Condition:Type 1 Diabetesintervention:Biological: Mesenchymal stem cells

Condition:Aplastic AnemiaIntervention:Biological: bone marrow derived mesenchymal stem cells
20 Completed Safety and Efficacy of Intracoronary Adult Human Mesenchymal Stem Cells After Acute Myocardial Infarction
Condition:Acute Myocardial InfarctionInterventions:Drug: Mesenchymal stem cell; Drug: Control group

www.clinicaltrials.gov

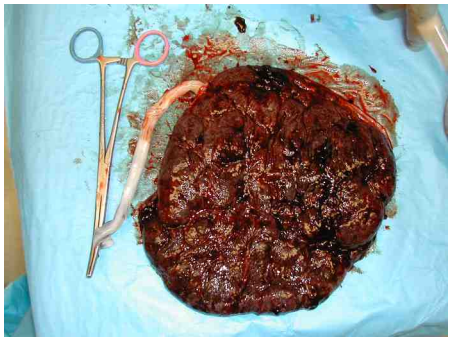
Our own team is looking at tendon repair, bone repair, repair of diabetic foot ulcers and the growth of blood stem cells (HSC) using MSC.

Limitations of MSC?

- The cost of ex vivo expansion
- Generation of sufficient MSC numbers – efficacy requires millions of cells.
- Solutions
  - *Bioreactor expansion*
  - *Placental derived MSC – assuming mechanism is paracrine.*

QUT ihbi Institute of Health and Biomedical Innovation

Placental-derived MSC



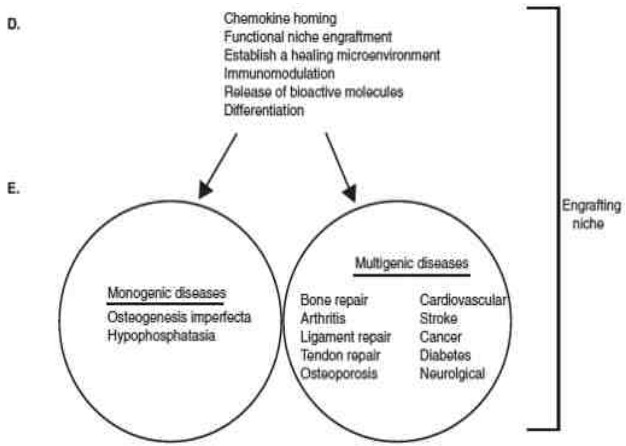
Lataillade, J.J., et al., *Regen Med*, 2007. **2(5): p. 785-94.**

Finally – Gene therapy…

If the therapeutic benefit of MSC is via paracrine signaling, then maybe we can enhance this through genetic modification?!

MSC and gene therapy?

- Why would you want to do this?
- If you know what protein you want to upregulate why don't you just manufacture recombinant protein?
- What are the weaknesses in this concept?



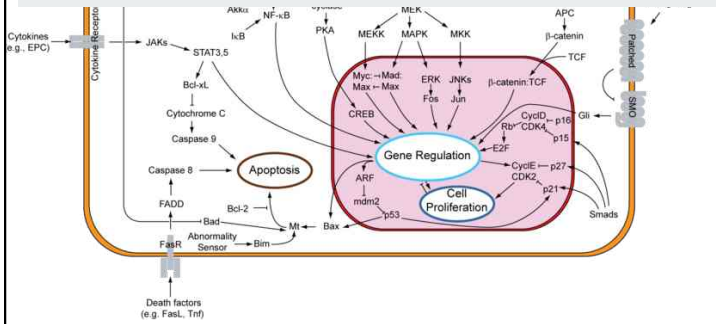
MSC summary

- MSC differentiate into various mesenchymal tissue, but this differentiation potential appears to be limited depending on the tissue from which the MSC were derived.
- MSC secrete a range of factors that may contribute to tissue regeneration.
- These factors can also make MSC a "generic" allogeneic transplant cell source.
- There are >250 clinical trials involving MSC.
- We may be able to make MSC therapies more potent through gene therapy.

The 2012 Nobel Prize

- This is the ultimate in "gene therapy"!

Induced Pluripotent Stem Cells



Induced pluripotent stem cells

- Induced pluripotent stem cells, commonly abbreviated as iPS cells or iPSCs, are a type of pluripotent stem cell artificially derived from a non-pluripotent cell, typically an adult somatic cell, by inducing a "forced" expression of certain genes.
- Yamanaka Factors: Oct3/4, Sox2, Klf4, and c-Myc

Assignment

- What is the difference between embryonic stem cells and adult stem cells?
- What are the limitations of embryonic stem cells?
- What therapies are adult stem cells used in?
- Why (from a regenerative medicine perspective) are we interested in stem cells and paracrine signaling?
- How might stem cells and gene therapy converge to enable tissue regeneration?