Stem Cells and Healing

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THE NORTH WEST EMBRYONIC STEM CELL CENTRE (NWESCC)

Directors: Profs Sue Kimber and Daniel Brison
Marker: Fibulin-2
Cells: MEFs

DAPI  Fibulin  Merged

Isotype Control
The NWESCC Clean Laboratory is the first in the North West to derive human embryonic stem cell lines at current clinical standard. This will allow scientists to develop stem cell products for potential therapeutic use.

Situated in new Core Technology Facility, University of Manchester
Stem Cells and Healing

• Regenerative Medicine: Biblical context of healing

• Stem Cells in Medicine

• Adult (tissue) Stem cells

• Embryonic Stem Cells

• Some Current uses of Stem Cells

• Some controversies and thoughts
Regenerative medicine

Repair or replacement of diseased or damaged tissues

Clinical focus for genetic or multifactorial diseases:

• Prevention
• Leave the body to repair on its own
• Stimulate bodies own repair mechanisms / aid repair with drugs
• Transplantation of organs or cells
• Prosthesis
Biblical context for Healing

God cares about our health and welfare

**Leviticus 13-14**  Gods instructions to the Israelites included how people were to behave for healthy lives including dealing with infectious skin diseases and other infections.

God wants to bring about healing

**Jer 30:17**  I will restore you to health and heal your wounds declares the Lord

**Jer 33:6**  I will heal my people and will let them enjoy abundant peace and security

**Psa 30:2**  O Lord my God, I called to you for help and you healed me

God intends his people to work for the same goals:

Ezekiel prophesied against the leaders of Israel because ‘you have not strengthened the weak or healed the sick or bound up the injured’ **Eze 34:4**
Jesus healing ministry

About 16+ separate reported instances of Jesus healing ministry

**Luke 5:17** And the power of the Lord was present for him [Jesus] to heal the sick

**Lk 10: 8** When you enter a town and are welcomed eat what is set before you. **Heal the sick who are there** and tell them ‘The kingdom of God is near you.’
Mark 3: 1-6

• Jesus healed people’s ailments

• Healing is a good action

• More important to do what is right than to obey ritual laws

• We have to take responsibility for deciding what is the right thing to do.
Stem Cells in Medicine

What is a Stem Cell?

• Stem cells are unspecialized cells that have two defining properties;
  – The ability to undergo cell division for long periods of time in culture (**self renewal**)
  – The ability to form at least one, and often many, **different specialised cell types**
Stem Cells are present in many parts of the body:

- Present in many juvenile and adult organs and tissues:
  - Some organ systems have abundant supplies of stem cells e.g. bone marrow

- These stem cells can be harvested from the body and grown in the lab.

- Stem cells can sometimes be taken from one organ of a patient and used to treat another injured or diseased organ. They can be used autologously.
Adult Stem Cells in the body replace cells lost through wear and tear e.g. in skin and gut

**Gut lumen** (cells constantly worn away)

In the intestine, stem cells generate new cells to replace the surface cells worn away by passage of food products.

Stem cells in their special niche (environment) at the bottom of a gut crypt.
The natural function of stem cells in embryonic development and in adult repair can be exploited for cell therapies.

1) By stimulating body stem cells
2) By replacing diseased tissues with stem cells from outside the body

Stem cell therapies are happening now!
Haematopoietic (blood) Stem Cells (HSCs) are used to treat blood disorders by transferring bone marrow

Bone marrow containing HSCs removed from region of pelvis of a different (tissue matched) person

● Bone marrow transplantation is used when a patient has a disorder affecting one of the types of cells produced from the Haematopoietic (blood) Stem Cells e.g. cancer affecting the white blood cells (leukaemia)

● The patient receives high doses of drugs (chemotherapy) which kills the cancerous cells but also the patients own bone marrow stem cells

● Bone marrow from a matched donor is injected into the patient to replace the HSCs
Decellularised donor windpipe skeleton + patients own Mesenchymal Stem Cells = windpipe repair

Macchiarini et al 2008
Embryonic Stem (ES) Cells

• ES cells are generated from very early embryos that are surplus to patients’ requirement in Assisted Reproduction programmes such as In Vitro Fertilisation (IVF).
Embryonic Stem (ES) Cells

- Egg (oocyte)
- Fertilised egg
- 2 Cell Embryo
- 4 Cell Embryo
- 8 Cell Embryo
- Day 0
- Day 1
- Day 2
- Day 3
- Day 4
- Day 5: 30-120 cells
- Blastocyst
- Size = 1/10 mm
- HFEA licence, informed consent
- To use for therapy: HFEA licence and HTA/FDA clinical licence
Human Fertilisation and Embryology Authority (under Human Fertilisation and Embryology Act 2008) regulates and licences all research and stem cell generation from human preimplantation embryos;

Research must fall under one or more of following

a. to promote advances in the treatment of infertility

b. to increase knowledge about the causes of congenital disease

c. to increase knowledge about the causes of miscarriage

d. to develop more effective techniques of contraception

e. to develop methods for detecting the presence of gene or chromosome abnormalities in embryos before implantation

f. i. to increase knowledge about the development of embryos

ii. to increase knowledge about serious disease

iii. to enable any such knowledge to be applied in developing treatments for serious disease

Extended purposes 2001 includes stem cells
Advantage of Embryonic Stem cells: infinitely expandable
ES cells can give rise to all tissue types (pluripotent)

Fertilized egg has the potential to make a fetus if normal

ES cells extracted at this stage: can make all specialised cell types but can't make a fetus or baby

http://stemcells.nih.gov/info/basics/
ES cells can be instructed to make a desired cell type

Specific hormones, proteins and other molecules can make ES cells become different types of specialised cells: They can **DIFFERENTIATE**

- **ENDODERM CELLS**: e.g. gut, pancreas and liver cells
- **MESODERM CELLS**: e.g. heart muscle, kidney and blood cells
- **ECTODERM CELLS**: e.g. brain cells, skin

"Cocktail" 1

"Cocktail" 2

"Cocktail" 3

ES cells can be instructed to make a desired cell type
ES cell become specialised cells in a dish which can function in the body

Gut cells

Neurons

Beating heart muscle
Human Embryonic Stem Cells (hESc) directed through a 3 stage protocol produce an enriched population of chondrogenic cells.

- **Stage 1**: hESc/IPS day 0, Wnt/activin
- **Stage 2**: Follistatin / BMP/FGF-2
  - **Stage 2**: d5
  - **Stage 2**: d8
- **Stage 3**: BMP-2/FGF-2/ GDF-5
  - **Stage 3**: d14

**ES Hues7/Sox-9**
- 95% Sox 9 positive

**ES Hues8 /Sox9**
- 97% Sox 9 positive

Chondroitinase sensitive **Safranin O**: marker for cartilage producing cells

Oldershaw et al 2010
Since human ES cells can easily be grown to produce large cell numbers and can be coaxed to form any desired specialised cell type, they hold considerable promise for cell therapy for incurable disease and drug discovery.
ES based therapies are being trialled

Finance halts new therapy: Nov 2011 Geron pull out of all pluripotent stem cell therapies and concentrate on cancer

are safe and can enhance nerve-repair in spinal cord injury patients

‘The London vision project’: cell therapy for degeneration of the back of the eye (Macula Degeneration). Adults stem cells are not promising, but retinal pigment cells from ES cells successful. Therapy at the stage of projected phase 1 clinical trials (ACT, Morefield Eye Hospital Pfizer) at end of 2011
Some considerations and issues.....

Embryonic Stem Cells: Research and Therapy

Q?
• Is use of human IVF embryos for Embryonic Stem Cell- generation acceptable?

• Is discarding embryos **without** using them for a good (ethical) purpose acceptable?
Outcome for IVF embryos

- Transferred to patient
- Frozen
- (Perish on thawing)
- Discard (perish)
- Stem cells (perish)
- Research (perish)

- Research (perish)
- Stem cells (perish)
- Discard (perish)
- Transferred to patient
- Donated to another couple
Some considerations and issues.....

Large numbers of embryos are discarded during routine IVF

- Fresh embryos
  - highly variable by clinic, freezing policy etc.
  - 10 - 75% ???

- During freezing/thawing process
  - 10-40%

- Frozen stored embryos (10 year rule in UK): allowed to perish at couples request.

400,000 human embryos are stored frozen in US; 50% of these are not used and discarded
How should we view this?  
Status of the Human Preimplantation Embryo

When does the embryo become a person?

For you have created my inmost being; you knit me together in my mother’s womb. **Psalm 139: 13**
Before I formed you in the womb I knew you **Jer 1:5**

• Does a new person begin on incorporation of a sperm into an egg or later in the womb?
A preimplantation embryo is a ball of cells <1/10mm across.

It lacks recognisable structures and is non sentient (no nervous system or other tissues).

Potential: Not every embryo will form a person: Naturally, around 50% of human embryos perish in the reproductive tract at this early stage.
Status of the Human Preimplantation Embryo

- Potential: Some embryos that develop beyond the pre-implantation period may give rise to twins, so can't say will form a single person during pre-implantation period

Different positions within the Christian churches

- Gradual increase in protection
- Increasing development
- Full protection equivalent to a person from day of fertilisation
Ethics of use of Human Preimplantation Embryos and Stem cell generation

**Equal value argument:**

Is the preimplantation embryo of equal value to a 4 month old baby?

Once hESc are isolated they can no longer (even together) make a fetus

**Saving life argument**

If stem cells can give rise to a cure for an incurable or fatal disease is it ethical **not** to use them to save a life?

**Slippery slope argument**
Should embryos be generated specifically with the intention of making stem cells?

• Article 18 of the European Convention on Human Rights and Biomedicine forbids the creation of embryos for all research purposes (Council of Europe 1996)

• Risks to woman
• ‘Instrumental’ goal in embryo generation
What are the Alternatives?

• Adult stem cells?
  Not ethics free and often will not be effective

• Induced pluripotent Stem Cells?
  ES-like cells but not suitable for clinical use

• Status quo?
  Patients will continue to suffer, new medical research advances rejected.
Adult cells be reprogrammed to an embryonic stem cell-like state

Refutes previous dogma that differentiation is irreversible
Mixture of retrovirus containing constructs for oct-4, sox-2, c-myc, klf-4

Several weeks on fibroblast feeders in ES cell medium

Select e.g. for Nanog-GFP or morphology

Pluripotent cell marker expression

Contribution to blastocyst and adult including gametes

Chimeras

Teratomas

In vitro multilineage differentiation

Success 0.01-0.1%
# ES Cell versus AS Cell

<table>
<thead>
<tr>
<th></th>
<th>ES cells</th>
<th>AS Cells</th>
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<tbody>
<tr>
<td><strong>Therapeutic potential</strong></td>
<td>ES cells differentiate into <strong>more</strong> types of specialised cells than AS cells</td>
<td>AS cells tend to have a <strong>restricted</strong> ability to generate specialised cells</td>
</tr>
<tr>
<td><strong>Culture</strong></td>
<td>Easy to grow for long periods of time</td>
<td>Difficult to expand (tend to stop dividing) and poor function in patient</td>
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<tr>
<td><strong>Immune response</strong></td>
<td>Risk of immune rejection if used for tissue regeneration so need to tissue match</td>
<td>No rejection if patient’s own AS cells can be used (not always possible)</td>
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<tr>
<td><strong>Surgery</strong></td>
<td>One operation</td>
<td>Need two operations if from same patient, or risky operation for donor</td>
</tr>
<tr>
<td><strong>Ethical considerations</strong></td>
<td>Can be controversial</td>
<td>Non-controversial if patient is donating own stem cells, or consenting adult donor</td>
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<tr>
<td><strong>Safety</strong></td>
<td>Danger of dividing undifferentiated stem cells remaining? (cancer?)</td>
<td>Less danger of cancer. Can give unwanted specialised cell types</td>
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So is it ethically acceptable to generate stem cells from preimplantation embryos for therapeutic use and research?

**But also**

Is it ethically acceptable to discard embryos **without** generating stem cells which can be used to understand serious disease or develop new therapies?
So we have to decide

ES cells, a precious resource to develop treatments for saving life & understanding incurable diseases

Stem cells from human pre-implantation embryos unacceptable. Use only adult stem cells/ try to develop new drugs?
Thank you for listening

Any Questions?