The Practical use of Stem Cell Therapy in a Clinical Setting - Concurrent Workshop

Saturday, 22 June 2013
Start 4:30pm
Duration: 60mins

Professor Richard Boyd
Monash University
Australia

Professor Martin Pera
Stem Cell Sciences
University of Melbourne
Stem Cell Therapies: The path to helping patients…

Richard Boyd
Group Leader
Stem Cells and Immune Regeneration Laboratory,
Dept Anatomy and Developmental Biology

MONASH University

Hong Kong Stem Cell bank and clinic
Knee cartilage performs essential mechanical function.

Cartilage damage and pain control are major clinical challenges.

New technologies or therapies are urgently needed.
**HOPES: Diseases for stem cell treatment.**

- Osteoarthritis “wear and tear” from aging and sport
- Neurotrauma – Alzheimers, Parkinson’s, spinal cord injury, motor neurone disease, stroke
- Cardiovascular
- Repair of Immune system
  - **Immune deficiency**
    - Cancer – chemotherapy, radiation induced immunodeficiency
    - Aging
    - Chronic infection
  - **Autoimmune disease (type 1 diabetes, MS, rheumatoid arthritis)**
  - **Transplantation tolerance**
- Skin - burns, wounds
- Lung (COPD, asthma, allergies)
- Kidney disease
- Diabetes……
- **Healthy start to life – cerebral palsy, lung, kidney**
HURDLES

• Ethical
  • Strict Government regulations now in place
  • Human ES cells can only be developed under license from NH&MRC; obtained from discard IVF embryos under strict informed consent
  • Human cloning banned
  • Creating and destroying human life solely for research or therapy banned
  • 1000+ ES lines so no new ones needed
  • iPES – also large number of lines
    – Age, environment, disease type, geographical
HURDLES

• Safety
  • Must have pre-clinical animal data, preferably large animals (more realistic models for human disease)

• Practical
  • Which stem cells to use?
  • Your own or someone else’s?
  • Stem cell banking – for one or for all in the family?
    – Is this financially justifiable
  • Commercial IP – who owns it?
Why are stem cells different?

• Perceived as the body repair kit
• Natural healers – Body’s ambulance
• Life is short
• Hurting ain’t fun
• World is small
• People are “rich”
• People are impatient

“Stem cells - The Gold Rush of medicines”

Stem cell tourism – beware the bad guys
“Good guy” – stem cell clinics

- Safety first
- Pre-clinical data
- Conduct properly sanctioned clinical trials
- Registered with TGA/FDA
- Support underlying research
- Every patient enlisted on trial
- Thorough analysis of what is injected and where and what is the outcome
- Realistic, non-opportunistic funding
- PATIENT CARE and FOLLOW-UP
Stem cell therapies: Our code of ethics

We have formed an entity “Australian Autologous Cell Therapies Group”

– Academic, clinical and commercial “clinical groups”
– make certain there is maximal patient safety; clinical rigour,
– evidence based,
– appropriate thorough patient follow-up;
– on-line data management (we are working with “Clinical Intelligence Pty Ltd. Melb)
– Peer group evaluation of data; international presentations and publications
– Everyone wins?!?!!
The Funding dilemma: A practical solution?

Alternative additional strategy to meet clinical integrity and patient needs (prevent medical tourism)

- **Phase I funded by commercial entity**
  - When clinicians satisfied….

- **Dual Phase II strategy:**
  - RCT (patients don’t pay but have 1 in 2 chance of getting “drug”
  - If it is a cross-over trial (recommended) placebo’s now get test ‘drug’ and vice versa usually after ~ 6 month

- **BUT – many patients don’t want this**
  - They are actually in pain and would rather “pay for procedure” knowing that some good may occur because of previous pre-clinical data and hope to relieve pain
The Funding dilemma: RCT and “user pays”

**SO: This becomes a Case Series** – *patients offered the option of paying for stem cell therapy*

- Companies thus receive compensation for their outlay in the RCT
  - No need for patients to travel to less regulated clinics and pay $30-50k

**CONTROL OF ROGUE CLINICS**

- Strict clinical appraisal and follow-up
- Strict analysis of what is being injected
  - Effectively multi-centre trials
  - Data (good, bad or otherwise) published in reputable journals;

**NOTE AND VIP!**

*All patients must be enrolled in a trial; this is experimental medicine!*
Which stem cells to choose..??
Many Types of Stem Cells!
Another HURDLE:
How do I know my stem cell is heading along the right pathway??
Genetic modification of embryonic stem cells. *Andrew Elefanty, Ed Stanley*

Replace one copy of a gene with a fluorescent gene

Whenever the modified gene is expressed, the cell will fluoresce

Provides ability to identify the cells of interest when they appear
ES/iPS cells can differentiate into all the cell types in the body

blood cells
liver
heart muscle
pancreas
nerve

Differentiation of ES/iPS cells provides an avenue to
• study early development

• generate tissue specific stem cells and mature end cells to study disease
to screen drugs/therapeutic agents for efficacy and toxicity for cell therapies
Human ES cells with fluorescent reporters allow visualization of multiple different cell types.

- ES/iPS
- blood cells
- thymus
- heart muscle
- pancreas
- nerve

Green fluorescent beating human cardiomyocytes
Human ES cells with fluorescent reporters allow visualization of multiple different cell types

- blood cells
- thymus
- heart muscle
- pancreas
- nerve

Green fluorescent human insulin producing cells
Human ES cells with fluorescent reporters allow visualization of multiple different cell types:

- blood cells
- thymus
- heart muscle
- pancreas
- nerve

Green fluorescent human neural cells
Neural Tissue Engineering using nanobiotechnology

1. Engineer scaffolds that promote neurite/nerve extension
2. Fabricate “smart” scaffolds that can instruct stem cells.
3. Future work towards cell replacement strategies using stem cells.

David Nisbet
John Forsythe
Monash Engineering
Tissue Engineering Scaffolds

Important Features

• Interfiber distance
• Surface functionality

Factors Controlling Nerve Growth
Interaction of Stem Cells with Nanofibrous Scaffolds


Unmodified nanofibrous scaffold

PCL nanofibrous scaffold surface modified

A HURDLE

Stem Cell are very exciting but
back to the BIGGEST PRACTICAL PROBLEM…. 

• How can we find a source of our own multipotential/pluripotential stem cells, that are safe, ethical and effective in treating a wide range of diseases?
Worry!

Relief...
Miracles in motion...
A once in a lifetime chance

Frozen blood from this baby’s umbilical cord could one day save its life.
A medical revolution revealed: NEWS 8

Picture: SIMON O’DWYER
Sources of stem cells in new born...

www.healthystarttolife.monash.org/

- **Umbilical Cord**
  - Haemopoietic stem cells (HSC)
  - "Wharton’s Jelly"
  - Mesenchymal Stem Cells (MSC)
Capabilities of MSC

MESENCHYMAL STEM CELLS

Endothelium

Adipose

Myocardium

Liver

Bone

Cartilage

Pancreas

Neuron
Mode(s) of action

- Cell differentiation
- Anti inflammatory
- Immunomodulatory
MSC Anti-inflammatory & immunomodulatory effects

Cytokine mediated:

- MSCs
  - IL-1ra (Volarrvic et al, Autoimmunity, 2010)
  - Down regulate pro-inflammatory IFN, IL-12 and TNF-Alpha (Abdi et al, Diabetes, 2008)
  - Promote reparatory M2 macrophages (Kim, Exp Haematol, 2009)
  - HGF, IL-10 and TGF-beta (Puissant et al, Br J Haematol, 2005)
- MSC act on Macrophages
  - IL-1ra (Danis, Clin Exp Immunol, 1995)
Amnion Stem Cells

Made by the baby for the baby.

Towards a cure

Sean Murphy
Placental tissue Stem Cells

**Placenta:** Placenta derived stem cells

**Chorion:** Mesenchymal Stem Cells

**Umbilical Cord:**
- Hematopoietic Stem Cells
- Mesenchymal Stem Cells

**Amnion membrane:**
- Mesenchymal Stem Cells
- Amnion Epithelial Cells

**Amniotic sac**

**Umbilical cord**

**Placenta (villous chorion)**

**Yolk sac remi**

**Chorionic sac** (smooth chorion)
Isolation of amnion epithelial cells

Baby delivered by Caeserian section

Amnion is peeled from chorion and cut into pieces

Washed several times to remove blood/blood clots; Membrane digested in trypsin

Cells are collected by filtration

Trypsin is inhibited

Cells cryopreserved, cultured or used for experiments
AEC formed from the Epiblast - multipotent stem cells
AEC can differentiate into mesodermal, endodermal and ectodermal derived tissues

Neurons

Lung Epithelium

Hepatocytes

Osteocytes

Hair and skin

Cardiomyocytes

Pancreatic cells

Adipocytes

Fliniaux, 2004, Miki et al. 2005, Murphy et al. 2010
Breast milk – natures “jewel” for health
The Value of **Maternal** Stem Cells at birth

**Placental, chorion, decidual tissue**
- Maternal Mesenchymal Stem Cells for maternal use!
- Females have higher incidence of autoimmune disease!

**Breast milk!**
- Contains \( \sim 1 \) million cells/ml
- Mixture of:
  - **Immunity** - Type II macrophages, T regulatory cells
    -> key elements in preventing maternal-fetal rejection
  - also Ab and T cell based immunity
  - **Stem Cells** - breast duct -derived **pluripotential**
    “epithelial” stem cells; Mesenchymal Stem Cells
- **Present as long as lactating; increased with feeding**
These newborn stem cells are so valuable! - should be banked

- Nature’s whole body repair kit
- ProStemCell Pty Ltd Hong Kong
- State of the art stem cell bank!
  - World’s first comprehensive stem cell bank
  - Sponsored research with our lab; $500k
    - 3 research programs
    - Optimising cryopreservation
    - Amnion for skin wounds
    - Cord MSC and amnion for immune system repair
  - Partner for ARC Linkage grant ~$600k
The Value of Stem Cell Family Banking

Cord blood
HSC - compatible for parent or sibling transplant (haplo – ‘close’); even blood relative

Cord Tissue
MSC from Wharton’s jelly for regenerative medicine and inhibiting inflammatory diseases – autoimmunity, asthma, allergies, arthritis
MSC can be expanded in culture

Amnion
Pluripotential epithelial stem cells for potential repair of “all” tissues and organs

Placental, chorion, decidual tissue
HSC
Maternal MSC for maternal and sibling use
Females have higher incidence of autoimmune disease!

Breast milk
• Stem cells and immunity for mother and child
New Born Stem Cell Banking – a logical choice

Bank it

Donate it

BUT don’t discard it.

It just makes sense!
HOPES
Can stem cells fix diseases - safely?
Multiple Sclerosis (Claude Bernard Group)

Current Research

Endogenous Neural Stem Cell Mobilisation

Thymic Regeneration – Reprogramming the Immune system

Stem Cell Therapy and CNS Repair

Tolerance Induction and Immune Regulation
MSC and AMNION-DERIVED STEM CELLS SUPPRESS THE MULTIPLE SCLEROSIS-LIKE DISEASE IN MICE

C. McDonald, G. Jenkin, C.C.A. Bernard
Lung disease optimal for MSC treatment

Tracy Heng

95% cleared from blood < 5 mins

Half-life = 24hr in lungs

IV hMSCs in adult mice (10⁴ to 10⁶)

>90% trapped in lung as emboli

<5% in circulation

Injured organs

Secreted factors?

Cell contacts?

Differentiation

↓ Inflammation
↓ Immune responses
↓ Apoptosis
↑ Endogenous stem/progenitor cells
...other effects?

(D. Prockop 2009 Mol Ther)
Ovalbumin-induced asthma model

Tracy Heng

Days

0

OVA/alum

8 9 10

Intranasal OVA

Analysis

11 12

DAYS
OVA-sensitised mice develop cellular infiltration of the airways
MSC treatment decreased OVA-specific T cell proliferation and cytokine production.
... MSC reduce eosinophils in asthma lungs

(T.Heng)
MSC treatment dramatically improved lung function

Airway Resistance (RI)

Dynamic Compliance (Cdyn)
Veterinary applications

- to improve animal health; pre-clinical model for humans

- **Adipose-derived cells:**
  - *(A) Stromal vascular fraction (SVF)*
    - MSC, Tregs, type II Macrophages
    - Pre-adipocytes, fibroblasts, endothelium
  - *(B) In vitro expanded MSC*
    - Immunosuppressive; pro-repairing

- Horses with bowed tendons, ligament injuries, and fractures,
- Dogs with osteoarthritis
- More than 5,000 horses treated since 2003
- More than 4,500 dogs treated since 2006
- More than 350 dogs, cats, horses in Australia

*(Australian Veterinary Stem Cells, Vet Stem)*
Veterinary applications -

**SVF**
- >70% of all animals responded
- No serious adverse effects
- Strong evidence of pain reduction and return of capacity

**Expanded MSC**
- >70% of all animals responded
- 100% of younger dogs

*Osteoarthritis (most)*

*Chronic kidney failure*

*Cardiovascular disease (dilated cardiomyopathy)*

*(Australian Veterinary Stem Cells, Vet Stem)*
Clinical Cases- “Sophie”

- NSAIDs and Cartrophen gave only mild relief, and “Sophie” had difficulty with steps, trotting, and getting in and out of the car.
- Now, 1 month after treatment, her owner says “I have my old dog back again!”
- “Sophie” can now jump into the car, and trots and runs with a new lease on life.
- THE FAMILY PET CAT ISN’T HAPPY!
<table>
<thead>
<tr>
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<th>Pre-treatment</th>
<th>Day 30</th>
<th>Day 60</th>
<th>Day 90</th>
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Clinical Cases- “Cooper”

- “Cooper” was treated with allogeneic adult MSC
- injected into both hip joints
- great improvement within a month
- Owners comment “A dramatic improvement in climbing stairs and now playing with other dogs.”
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Solving Osteoarthritis

Dr Dan Bates (BSc (Hons), B.Med)
How?

OA Clinics

Pain relief

Wt loss

Exercise

Inject

ACS

Cells

Oral

HA

Research

TGA

Data

Business

Halving joint replacements
Osteoarthritis

- NSAIDS
  - Panadol

- Increase Exercise

- Decrease weight

Decrease pain
Osteoarthritis

NSAIDS

panadol

Increase Exercise

Decrease weight

Decrease pain
Osteoarthritis

- NSAIDS
- Panadol

- Increase Exercise

- Decrease weight

Decrease pain
Osteoarthritis

- NSAIDS
  - Panadol

- Increase Exercise

- Decrease Weight

Decrease pain
Decrease Pain → Increase Exercise → Decrease Weight

1kg = 2kg/step = 16 tons/day
Stem cells in osteoarthritis
Osteoarthritis

Stem Cells

Slow degeneration

Decrease Pain

Increase Exercise

Decrease Weight

Regenerate
Are they safe?

11,687 horses and dogs
AE rate 1.28%
50+ animal studies

Multiple case series
503 published patients
Multiple diseases
Multiple injection sites

Gimble 2010
11687 horses and dogs
AE rate 1.28%
50+ animal studies

Garcia olmo, 2009/2012

Wakitani 2011

Riodean 2009

Centeno 2010

Garcia olmo, 2009/2012

Mesimaki 2009

Lendeke 2004

Rodriguez 2012

Yoshimura 2007

Yoshimura 2010

Yoshimura 2008

Rigotti 2007
Are they safe?

- Decrease pain

4 animal studies showing decreased pain
6 human OA studies, 9 human cartilage defect studies
Individualised care
Decreased central sensitisation
Are they safe?

Slowed Degeneration

- Animal studies
- Multiple mechanisms of joint damage
- Slowed degeneration
- No human evidence

Matsumoto 2009

Mifume 2012

Mokbel 2011b

Deikman 2012

Tograhie 2012

Mokbel 2011a

Sato 2012

Murphy 2003

- 27 Animals
- Group-1 3W
- Group-2 6W
- 6M
- 1M
- 2M
- 6M
- 12M
Are they safe?

Regenerate

Wakitani 1994

IM 2001

Lee 2007

Olivera 2010

Gou 2004

Mokbel 2011

MSC + HA

Control

HA

Multiple animal studies
Cartilage defects
Macroscopic + histological regeneration of cartilage

Regenerate
Regenerate

9 Human studies
Cartilage defects
286 patients
“Cartilage” regeneration

Centeno 2008
Amgad 2010
Nadiadnik 2010
Kasemkijw-attana 2010
Wakitani 2002
Wakitani 2004
Wakitani 2007
Koruda 2007
Saw 2011
### Human Evidence – MSC Safety

<table>
<thead>
<tr>
<th>Author</th>
<th>Patients</th>
<th>Disease</th>
<th>Injection</th>
<th>Follow-up</th>
<th>Study</th>
<th>Symptom Improvement</th>
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<tbody>
<tr>
<td>Wakitani 2010</td>
<td>41</td>
<td>Knee Osteoarthritis</td>
<td>IA</td>
<td>11 years</td>
<td>Safety Study</td>
<td>No Cancer, No infections</td>
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<tr>
<td>Centeno 2010/2011</td>
<td>339</td>
<td>Knee, Back, Hips</td>
<td>IA, Paraspinal</td>
<td>2 years</td>
<td>Safety study</td>
<td>No Cancer, No infections</td>
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<tr>
<td>Rodrigueuz 2012</td>
<td>13</td>
<td>Rheumatoid Arthritis</td>
<td>IV and IA</td>
<td>13 months</td>
<td>Safety study</td>
<td>One episode of fever &amp; myalgia</td>
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<tr>
<td>Guadalajada 2012</td>
<td>50</td>
<td>Perianal fistulas</td>
<td>Local</td>
<td>3 years</td>
<td>Safety and efficacy</td>
<td>No Cancer No injection</td>
</tr>
</tbody>
</table>
• Adipose derived stromal vascular fraction
  – 1 patient with cartilage defect
    • 4 years of pain
    • Refused surgery
    • Healthy
    • Competent
    • Fully informed and consented
  – 12 months follow up
Human Chondral Defects, OA

Dr DAN BATES

- 12% of the population will suffer chondral lesions

- These progress to osteoarthritis

- 15% of the Australian population suffer Osteoarthritis

- Costs 23 billion dollars per year to Australian economy
MRI – Left Knee 43 yo male
Left Lateral Femoral Condyle – Pre-treatment

Chondral Defect
12 Months post treatment

Defect Coverage at 12 months (Grey Line)
3 osteoarthritis patients

- Three patients - 4 Knees osteoarthritis
  - One Grade 4
  - One Grade 3
  - Two patellofemoral joint arthritis – same patient
Osteoarthritis Knee – WOMAC*

WOMAC
24 Questions on pain, disability, joint stiffness

Grade 4 OA
• Need multiple injections
• Combination cell therapy
Summary:

• Cell and animal data support cell medicine in osteoarthritis

• Early human studies have shown
  – Cartilage regeneration
  – Improved pain and function

• Regulators have supported the development of cell medicine
I’ll believe in stem cells when Panda’s can fly
WE CAN REBUILD HIM

We have the technology.
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Neonatal stem cells
Immune Regeneration
MSC & AEC in Wound Repair
Standard Operating Procedures for isolation of AECs
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Asthma
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How do stem cells really work?

• Do they directly repair?
• Do they instruct endogenous cells to begin repair?
• Do they function by release of cytokines and growth factors?
  – DOES it really matter to the patients?
  – They just want to become healthy again!
  – IT DOES matter to us, because we need to be able to provide best possible care NOT near enough is good enough
How do stem cells really work?

• Will the ‘disease” environment influence the outcome
  – Inflammatory cytokines may switch off, dampen or even kill stem cells
  – In autoimmune disease – the same aggressive immune factors (cells, Abs) which triggered disease will attack stem cells of that same tissue type

• Age, general health
How do stem cells really work?

• Should we inject:
  • Stem cells
    – GOOD will self renew, live a long time but
    – BAD may not actually fix the problem because they are still multipotential and not instructed to therapeutic need
  • Progenitor cells
    – GOOD destined to become a defined cell type
    – BAD – won’t self renew; may need multiple injections
How do stem cells really work?

• Therapeutic stem cell products
  – GOOD – should form into desired therapeutic cell
  – BAD – won’t self renew
  (but if repair sufficient might be OK)
HURDLES

• Funding – this is biggest problem
  • Government – who are we trying to kid?
  • Industry – do they own the IP?
    • Will the trials be successful?
    • Will the Govt’s give rebates?
    • Will patients pay large sums (~$10k per treatment)
• IP and “definition” world is messy
  • eg what is a mesenchymal stem cell versus stromal cell?
  • are the rules of stem cells being obeyed?
  • what are people really injecting?
Must do clinical trials
The Funding dilemma

• Normally:
  • A drug company develops a therapeutic product
  • Has Patent/IP
  • Files for a Phase I – safety, dose escalation trial
  • Leads to Phase II Open label or better a
  • Randomised, placebo controlled, double blind efficacy trial (neither patient nor Doc know what is being injected)
  • Leads to “Licensing” Phase III trial (many 100’s patients)
Must do clinical trials

The Funding dilemma

- Costs? $500m - $1b!
- Time 10 - 15 years
- It is the ideal but this is an insurmountable hurdle for patients and in reality patients may suffer because therapies won’t be developed!
- People won’t wait – but TRIALS are the key – otherwise how do we know the medicine works?
- Without trials and clinical proof we are just in the world of snake oil
- Can there be a compromise?
- A new practical solution to developing therapies?
Developing new stem cell treatments: The Funding dilemma:

Take mesenchymal stem cells as an example:
Treatment of musculoskeletal /osteoarthritis
>11,000 large animals; pre-clinical
~1000 humans in “clinical treatment” studies, some random controlled trials (RCT)

• Company X has some form of IP - usually on the source of the cells or method of “manufacture” – composition of matter Patent

• begins an Open label trial – case series ~15-30 patients

• Establishes proof of concept (don’t do a trial you don’t have a very good idea of the outcome!)

• Files for new IND (Investigative New Drug)
Developing new stem cell treatments: The Funding dilemma:

- Enrols patients (usually 50-100) in a randomised double-blind trial
  - What is the control?? Must be current best medical practice, standard of care; placebo probably saline
- When trial fully enrolled it is closed off till last patient through
  - Ethics 3-6 months
  - Usually at least 12 months of treatment analysis
  - Trial duration ~ 18 months to 2 years
  - If successful, leads to Phase III, 100-300+ patients
- No further enrolments; patients have to wait…
The Funding dilemma: A practical solution?

- In Australia such treatments can be conducted under the TGA “Biological Exemption”
  - Basically states “Clinician takes full responsibility for what the patient receives, for one clinical treatment (can be multiple procedures but only for one treatment
- No need for Phase I, II, III to get a TGA registered product
- For “minimally manipulated procedures (cells not basically altered, no need for GMP
- For enzymically released cells and in vitro expanded, GMP conditions are also not mandatory but we have advised the TGA they should be!
Stem cell therapies: A practical solution?

- AUTOLOGOUS ! Safety first; no immune rejection
- ALLOGENEIC – may be desirable in the elderly, genetic disorders, evidence of disease susceptibility; immune rejection always an issue
- CODE OF ETHICS
  » We have formed an entity “Australian Autologous Cell Therapies Group”
  » Academic, clinical and commercial “clinical groups”
  » Developing our own code of ethics to make certain there is maximal patient safety; clinical rigour, evidence based, appropriate thorough patient follow-up; on-line data management (we are working with “Clinical Intelligence Pty Ltd; Melb)
  » peer group evaluation of data; international presentations and publications
- Everyone wins?!?!?