Stem cells – from biology to clinic

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WHY MAMMALS DO NOT REGENERATE TISSUES?

• Altered genetic differentiation?

• Danger of tumor development?

• Not enough stem cells?
A STEM CELL HERE, A STEM CELL THERE...
STEM CELLS

• cells that can divide indefinitely,

and,

can develop into different tissue types
Stem cells history

- 1959 – First bone marrow transplantation
- 1981 – First mouse embryonic stem cells isolated
- 1998 – First human ES cells isolated
- 2002 – First adipose stem cells described
- 2006 – First mouse IPS cells created
- 2007 – First human IPS cells created
- 2009 – Nobel prize for mouse ES cells
- 2012 – Nobel prize for IPS cells
Self-Renewal

Stem Cell

Differentiation

Mature Cell
fertilised egg

> Totipotent

totipotent stem cells

> Pluripotent

blastocyst containing pluripotent stem cells

> Multipotent

hematopoietic SCs

neural SCs

mesenchymal SCs

tissue-specific SCs

blood cells

cells of nervous system

connective tissue, bones, cartilage, etc.
Embryonic stem cells
Embryonic stem cells (ES)

- Pluripotent
- Destruction of embryo
- Heterologous (allogeneic) transplantations
- No clinical data about efficacy and safety
- Potential for teratomas
Somatic cell nuclear transfer cells
Induced pluripotent stem cells (IPS cells)
IPS cells

2012 Nobel Prize in Physiology or Medicine

Sox2 Oct3/4 Klf4

Target genes

c-Myc

Transcription factors

Epigenetic modifiers

Shinya Yamanaka
University of Kyoto, Japan

John B. Gurdon
Gurdon Institute in Cambridge, UK
Creating iPS cells

1. Isolate cells from patient (skin or fibroblasts); grow in a dish

2. Treat cells with “reprogramming” factors

3. Wait a few weeks

4. Pluripotent stem cells

5. Change culture conditions to stimulate cells to differentiate into a variety of cell types

- Blood cells
- Gut cells
- Cardiac muscle cells
Adult stem cells
Testicular stem Cells
Muscle stem cells

“Noggin” inhibits BMPs and allows the stem cells to develop into muscle cells.

BMPs replenish the supply of muscle stem cells.
Lab grown meat
Lab grown meat
Mesenchymal stem cells

- Bone marrow
- Adipose tissue
Mesenchymal stem cells

- Differentiation into different cell types
- Easy to obtain
- Easy to grow and maintain
- No ethical concerns
- Lower transdifferentiation potential
<table>
<thead>
<tr>
<th>ESCs</th>
<th>Adult SCs</th>
<th>iPSCs</th>
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<tbody>
<tr>
<td><strong>Isolate from the inner cell mass of the blastocyst</strong></td>
<td><strong>Circulating precursors</strong></td>
<td><strong>Isolate and amplify somatic cells</strong></td>
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<tr>
<td><strong>Endoderm</strong></td>
<td><strong>Bone marrow derived</strong></td>
<td><strong>Retroviral transfection</strong></td>
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<tr>
<td><strong>Mesoderm</strong></td>
<td><strong>Vascular integration and pro-angiogenic paracrine factors</strong></td>
<td><strong>Pluripotency induction</strong></td>
</tr>
<tr>
<td><strong>Ectoderm</strong></td>
<td><strong>Tissue derived</strong></td>
<td><strong>Endoderm</strong></td>
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<td><strong>Enhanced perfusion and tissue function</strong></td>
<td><strong>Mesoderm</strong></td>
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<td><strong>Ectoderm</strong></td>
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</tbody>
</table>

**Origin:**
- ESCs: Blastocyst of embryo
- Adult SCs: Bone marrow, circulation or resident tissue
- iPSCs: Reprogramming of somatic cells

**Strengths:**
- ESCs: Pluripotent (3 germ layers), Self-renewal and high replicative capacity
- Adult SCs: Autologous, Clinical safety and efficacy data
- iPSCs: Totipotent (3 germ layers and trophoblast)

**Weaknesses:**
- ESCs: Immunological concerns, Subject to ethical debate, Potential for teratoma and teratocarcinoma
- Adult SCs: Limited number, Limited replicative capacity
- iPSCs: Potential for teratoma and teratocarcinoma, No clinical data
Potential uses of Stem cells

- Stroke
- Baldness
- Traumatic brain injury
- Blindness
- Learning defects
- Deafness
- Alzheimer's disease
- Amyotrophic lateral-sclerosis
- Parkinson's disease
- Myocardial infarction
- Missing teeth
- Muscular dystrophy
- Wound healing
- Diabetes
- Bone marrow transplantation (currently established)
- Multiple sites: Cancers
- Spinal cord injury
- Osteoarthritis
- Crohn's disease
- Rheumatoid arthritis
Look! Stem cells!
Stem cells in veterinary medicine
Use of adult stem cells in veterinary medicine

- Stem cells from white adipose tissue
- Treatment of problems with locomotor apparatus
- Horses, dogs
Stem cell treatments

• 2009 – 2011 – Development and experimental treatments

• 2011 Introduction into clinical veterinary medicine at Veterinary faculty in Ljubljana

• 2012 Spin-out company Animacel established

• 2012 – 2014 Clinical study
Adipose derived stem cells

- Enzymatic digestion of tissue
- Seeding and expansion of cells
- Cell harvest
Chondrocytes; alcian blue

Osteocytes; alizarin red
• Over 300 dogs treated
• More than 90% owners report improvement
• Clinical examination confirmed improvement
• No side effects
Treatments performed

- OA knee: 22%
- OA elbow: 16%
- OA hip: 14%
- Hip dysplasia: 17%
- Ruptured l. cruciata: 17%
- Cartilage damage: 6%
- Other: 6%

Total number of dogs: > 300
Limping in individual dogs 1 year after treatment

Before treatment

1 year after treatment

Limping according to Brummberg
MSC

- HGF, EGF, IL-6, SCF, TNF-α, collagen type I, Fibronectin, LRP -> Supportive function
- IL-1, IL-10, TNF-α, HGF, TGF, FGF, EGF -> Suppress inflammation
- SDF-1, VEGF, IGF-1 -> Inhibit apoptosis
- IL-10, TNF-α, HGF, MMP-9 -> Anti-fibrosis
- HGF, FGF, EGF, TNF-α, IL-3, IGF, SCF -> Differentiation