The Current Development and Ethical Issues in Stem Cell Research and Applications

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Lecture Outline

• Clinical uses of Stem Cell
• Ethical considerations
• Regulatory issues
Hong Kong Mucopolysaccharidosis & Rare Genetic Diseases
Mutual Aid Group
Clinical Uses of Stem Cells

• Hematopoetic Stem Cell Transplantation
  – Bone marrow, peripheral or cord blood
• Ex vivo expansion of human epidermal and corneal stem cells
• Ex vivo manipulation (gene transfer) of autologous human stem cells
• Stem cell transplantation to foster tissue repair (CNS, spinal cord, cardiac, other)
Potential uses of Stem cells

http://en.wikipedia.org/wiki/Stem_cell
Structures in the brain related to Parkinson’s disease.

Focus of Human Stem Cell Debate

- Derivation of pluripotent human stem cell (hSC) lines from oocytes and embryos is fraught with disputes.
- Several other methods fewer ethical concerns. E.g. induced pluripotent stem cells (iPS cells) avoids the ethical problems specific to embryonic stem cells.
- With any hSC research, however, there are difficult dilemmas, including
  - consent to donate materials for hSC research,
  - early clinical trials of hSC therapies,
  - and oversight of hSC research.
Picture of Dolly, the cloned sheep

Ethical Issues in SC Research

Table 1. Ethical issues at different phases of stem cell research

<table>
<thead>
<tr>
<th>Phase of research</th>
<th>Ethical issues</th>
</tr>
</thead>
<tbody>
<tr>
<td>Donation of biological materials</td>
<td>Informed and voluntary consent</td>
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<tr>
<td>Research with hESCs</td>
<td>Destruction of embryos</td>
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<tr>
<td></td>
<td>Creation of embryos specifically for research purposes</td>
</tr>
<tr>
<td></td>
<td>1. Payment to oocyte donors</td>
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<tr>
<td></td>
<td>2. Medical risks of oocyte retrieval</td>
</tr>
<tr>
<td>Use of stem cell lines derived at another institution</td>
<td>3. Protecting reproductive interests of women in infertility treatment</td>
</tr>
<tr>
<td>Stem cell clinical trials</td>
<td>Conflicting legal and ethical standards</td>
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<tr>
<td></td>
<td>Risks and benefits of experimental intervention</td>
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<td></td>
<td>Informed consent</td>
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</tbody>
</table>
http://www.animaladoptions.org.uk/can-endangered-animals-be-saved-by-stem-cell-zoos
Pluripotent Stem Cells

# Regulation of iPSC Research

## Table 1 | Emerging themes in regulation of iPSC research

<table>
<thead>
<tr>
<th>Consent</th>
<th>Canada</th>
<th>California (US)</th>
<th>UK</th>
<th>Japan</th>
<th>International (ISSCR)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Requires free and informed consent, provided voluntarily and with full disclosure of all information relevant to the consent</td>
<td>Requires specific and informed consent</td>
<td>Requires free and informed consent, although standard consent allows for unrestricted use in research. Not clear if informed consent requirement can be waived when donors are unable to give consent</td>
<td>Voluntary, contemporaneous and informed consent required (with a few exceptions for stored tissue samples)</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Identity</th>
<th>Canada</th>
<th>California (US)</th>
<th>UK</th>
<th>Japan</th>
<th>International (ISSCR)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Requires anonymity (for nonautologous lines)</td>
<td>Using identifiable cells requires notification to a designated SCRO</td>
<td>Unclear, although importance of phenotype/genotype relationships, and therefore traceability, is recognized</td>
<td>Use of identifiable cells possible, but requires IRB approval</td>
<td>Use of identifiable cells requires additional and comprehensive review</td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Use: derivation of human germ cells</th>
<th>Canada</th>
<th>California (US)</th>
<th>UK</th>
<th>Japan</th>
<th>International (ISSCR)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Permitted, subject to regulation, but cannot create an embryo for research purposes; will trigger application of AHRA</td>
<td>Requires additional ethics review</td>
<td>No restrictions on derivation; can create (but not implant) an embryo, with a license; limit of 14 days in vitro</td>
<td>Permitted, subject to strict oversight; fertilization prohibited</td>
<td>Unclear or not addressed</td>
<td></td>
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</tbody>
</table>

<table>
<thead>
<tr>
<th>Use: transplantation into humans</th>
<th>Canada</th>
<th>California (US)</th>
<th>UK</th>
<th>Japan</th>
<th>International (ISSCR)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Requires SCOC approval</td>
<td>Requires additional ethics review</td>
<td>Subject to oversight, GTAC and AHRA approval</td>
<td>Requires additional ethics review and Home Office license</td>
<td>Requires approval and oversight</td>
<td>Requires additional and comprehensive review</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Use: grafting into nonhuman animals</th>
<th>Canada</th>
<th>California (US)</th>
<th>UK</th>
<th>Japan</th>
<th>International (ISSCR)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Requires SCOC approval</td>
<td>Requires additional ethics review</td>
<td>Requires local ethics review and Home Office license</td>
<td>Requires approval and oversight</td>
<td>Subject to review, approval and ongoing monitoring</td>
<td></td>
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</tbody>
</table>

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<thead>
<tr>
<th>Clinical trials with humans</th>
<th>Canada</th>
<th>California (US)</th>
<th>UK</th>
<th>Japan</th>
<th>International (ISSCR)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Requires overwhelming evidence from preclinical models for safety and efficacy</td>
<td>Requires approval and oversight</td>
<td>Requires approval and oversight and overwhelming evidence from preclinical models for safety and efficacy</td>
<td>Requires approval and oversight and additional and comprehensive review</td>
<td>Requires approval and oversight and additional and comprehensive review</td>
<td></td>
</tr>
</tbody>
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1. The wording for each jurisdiction is not standardized but is instead meant to paraphrase the relevant regulation or guideline, in order to capture subtle variations.

2. Would make autologous clinical trials a challenge.

Evolving Debate

• “While issues regarding the moral status of embryos remain relevant, the field is evolving and extending its consideration to current and emerging issues including patenting, policy approaches, procurement of embryos, stem cell tourism and new sources of stem cells, among others.”

ISSCR Guidelines for Responsible Translational HSC Research

Major Principles

• Independent Review and Oversight
• Voluntary Informed Consent
• Patient Monitoring/Adverse-Event Reporting
• Medical Innovation
• Social Justice and Other Aspirational Goals

Independent Review and Oversight

• “Individuals with stem-cell-specific expertise [must] be involved in the scientific and ethical review at each step along the translational research process.”

• Such “individuals… are best able to assist investigators and human research review committees to assess the scientific underpinnings of the clinical trial protocol; the in vitro and in vivo preclinical studies that form the basis for proceeding to the clinical study; and the risks of abnormal product function, proliferation, and/or tumor development.”

• “Rigorous preclinical testing in animal models - whenever possible for the clinical condition and the tissue physiology being studied - is especially important.”

Voluntary Informed Consent

• “Special emphasis [should] be placed on the unique risks of stem-cell-based clinical research; …include sensitivities surrounding the source of cellular products, tumor formation, immunological reactions, unexpected behavior of the cells, and unknown long-term health effects.”

• “Research volunteers must be educated about the realistic potential for therapeutic benefit as they may have recourse to…therapeutic alternatives and…[have] misconceptions about the potential for therapeutic efficacy.”

• “Research subjects’ comprehension of relevant information - especially of the risks and uncertainties – [should] be evaluated at the time of obtaining consent.”

“Exceptional circumstances [may] allow clinicians to attempt medically innovative care in a very small number of seriously ill patients, subject to stringent oversight.”

- independent peer review, institutional accountability, rigorous informed consent, close patient monitoring, transparency, timely adverse-event reporting, and a commitment to move to a formal clinical trial in a timely manner after, at most, a few patients.

“Holding some current SC clinics to [ISSCR guidelines] would identify significant shortcomings and… question the legitimacy of… attempts at providing ‘innovative care’.”

Opinion: The default position should be to conduct clinical trials of stem cell transplantation under an IND.

Summary of stem cell regulation in overseas countries

- No legislation specific for stem cell therapy or research
- Regulated under the same regulatory framework as for other human tissues and cells
  - A risk-based regulatory
  - Level of regulatory control is commensurate with the level of risk
- Ethical considerations relating to the use of human embryos are addressed separately
- Stem cells derived from non-human animal tissues or cells, US and EU—same regulatory framework as for high-risk human tissues and cells
General principles

A risk-based approach to regulation of human tissues and cells is adopted:

• For low risk group, the focuses of the regulation are preventing disease transmission from donors to recipients and ensuring the safety and quality of human tissues and cells procured, processed, stored and distributed for use in human.

• For high risk group, it is also required to demonstrate to the regulatory authority the clinical safety and efficacy of human tissues and cells for use in human before marketing. Investigational use of high-risk human tissues and cells in human requires authorisation by the regulatory authority.
Risk assessment of stem cell-based products

Regulatory framework

- Low risk group is regulated solely under the legislation for human cells, tissues, and cellular and tissue-based products (HCT/Ps).
- High risk group is also regulated under the legislation for biological products, drugs and/or devices.
Regulatory authority & legal instrument

Low risk group

Regulated by the US Food and Drug Administration (FDA) as HCT/Ps under section 361 of the Public Health Service (PHS) Act/ part 1271, title 21 of the Code of Federal Regulation (CFR) – also known as “361 HCT/Ps”
High risk group
Regulated by FDA as biological drugs or devices under the Federal Food, Drug and Cosmetic (FD&C) Act and section 351 of PHS Act/ relevant parts of 21 CFR e.g. 600-680 for biologics, 201 for drug labelling, 210-211 for drug cGMP, 312 for investigational new drugs (IND), 800s for devices, etc
Scope

Among others, the followings are excluded from the human tissues and cells regulation:

• Organs
• Blood and blood components
• Minimally manipulated bone marrow for homologous use and not combined with another article except for water, crystalloids, or a sterilising, preserving, or storage agent
• Reproductive cells and tissues that are immediately transferred into a sexually intimate partner of the cell or tissue donor
• Tissues and cells used as autografts within the same surgical operation
Examples

Low risk group

* Tissues and cells
  * Freeze dried bone and milled bone as allografts
  * Demineralised bone [US, EU but not Australia]
  * Amniotic membrane for ocular repair [US, EU but not Australia]
  * Acellular skin material [e.g. US, EU]

* Stem cells:
  * Cord blood haematopoietic stem/progenitor cells (HSC/HPC) for haematopoietic reconstitution [EU and Australia, and US if for autologous or related allogeneic use]
  * Banked dental pulp, including stem cells, for tooth regeneration [e.g. Australia]
Examples

High risk group

Tissues and cells

- Demineralised bone [Australia only]
- Demineralised bone combined with handling agent [US and Australia only]
- Autologous cultured fibroblasts for skin repair
- Autologous cultured chondrocytes for cartilage repair
- Autologous dendritic cells for cancer immunotherapy
Examples

High risk group

**Stem cells**

- Minimally manipulated, unrelated allogeneic cord blood HSC/HPC for haematopoietic reconstitution [US only]
- Mesenchymal stem cells (MSC) for treatment of graft-versus-host disease (homologous use – natural immunosuppressive function of MSC)
- MSC for the repair of myocardial ischaemia
- Differentiated MSC for cardiac muscular repair
Key regulatory requirements

Low risk group

Premises
- Establishment registration and product listing with FDA (notification only)
- Site inspection by FDA on need basis

Premarket review/authorisation by regulatory authority
- No

Donor screening and testing
- Yes, for communicable diseases only

Good practice/standards for processing human tissues and cells
- Compliance with the current good tissue practice (cGTP) regulations to prevent the introduction, transmission, or spread of communicable diseases by HCT/Ps throughout the manufacture (from recovery to distribution)
Key Regulatory Elements

**Reporting**
- Reporting of serious adverse reactions and HCT/P deviations to FDA

**Others**
- Maintaining a tracking system to enable the tracking of HCT/Ps from the donor to the consignee or final disposition and vice versa
- Retaining of records pertaining to a particular HCT/P at least 10 years after the date of its administration, or if the date of administration is not known, then at least 10 years after the date of the HCT/Ps distribution, disposition, or expiration, whichever is latest
Key Regulatory Elements

High risk group

• Regulatory requirements for “361 HCT/Ps” including
  – establishment registration and product listing,
  – compliance with donor eligibility determination,
  – tracking requirements

• Other requirements applicable to biological products, drugs and/or devices as appropriate,
  – Premarket review of product Compliance with cGMP for drugs or quality system regulation for devices
  – Investigational use for drugs or Investigational Device Exemption (IDE) for devices

• Labelling requirements, etc
Hong Kong Stem-cell trial shows promise for spinal cord injuries

June 27, 2013
By NEHARIKA SABHARWAL

Press Release

Strategic Research Development in Stem Cell and Regenerative Medicine in HKU

The use of stem cells in regenerative medicine and bioengineering has brought new hopes to the treatment in diseases of bone, diabetes, heart, brain and nervous system. The Li Ka Shing Faculty of Medicine of The University of Hong Kong has continued to strengthen stem cell research that would translate into clinical use and bring treatments for diseases which would otherwise be unavailable. For the first time, the Faculty has brought together internationally recognized and pre-eminent experts in the fields of stem cell and regenerative medicine to share with us their cutting edge research discoveries and novel developments on stem cell therapies in the Inaugural Symposium on Stem Cell and Regenerative Medicine Program held today.
Summary of stem cell regulation in Hong Kong

- There is no legislation in Hong Kong similar to overseas regulatory framework to govern the safety and quality of human tissues and cells for use in human.
Hong Kong

- Ordinance (Cap. 465) only provides for an exemption mechanism to allow using processed commercial human tissue products for transplant, which is otherwise prohibited.
Hong Kong

• Human Reproductive Technology (HRT) Ordinance (Cap.561) regulates, *inter alia*, embryo research. Derivation of hESC from human embryos requires a research licence granted by the Council on HRT.
Hong Kong

- Under the Pharmacy and Poisons (P&P) Ordinance (Cap. 138), substances satisfying the definition of “pharmaceutical products” (PP) require registration with P&P Board before marketing where the safety, quality and efficacy of PP under application are assessed.
Hong Kong

- Ethical aspects relating to human tissue/cell donation are not covered in P&P Ordinance. There are safety & quality issues specific to stem cells need to be addressed in assessing the products and manufacturing facilities if certain stem cell products are regarded as PP (e.g. highly/industrially processed ones).
Working Group on Regulation of Premises processing Health Products for Advanced Therapies