Recent Developments in the *Stem Cell Century*: Implications for Embryo Research, Egg Donor Compensation, and Stem Cell Patents

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### Stem Cell Technology

#### Technology:
- **hESC**: Human embryonic stem cells
  - Harvested from 5-day old embryos
  - Can create all cell types
  - Proliferate rapidly in culture
  - Stable over long periods

- **SCNT**: Somatic cell nuclear transfer (therapeutic cloning)
  - Cloned adult cells
  - Harvested from 5-day old embryos
  - Disease-specific cell lines
  - Patient-specific treatments

- **iPSC**: Induced pluripotent stem cells
  - Reprogrammed adult cells
  - Retroviruses used
  - No embryos used
  - Patient-specific treatments
Which of the following views about the moral value of 5-day old human embryos (blastocysts) most closely reflect your own?

a) Blastocysts have the same moral value as persons. We should not do anything to a blastocyst that we would not do to a person.

b) Blastocysts have no more moral value than any other clump of human cells. Anything we would be comfortable doing to a clump of skin cells we should be comfortable doing to blastocysts.

c) Blastocysts have an intermediate amount of moral value. They are less valuable than persons, but more valuable than other clumps of cells.
## The Moral Value of Embryos

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iPSC technology requires a careful reassessment of intermediate value position
Which of the following views about the sale of human eggs most closely reflect your own?

a) The law should permit women to sell their eggs to anyone at whatever price the market will bear.

b) The law should prohibit women from selling their eggs for any purpose. (Reimbursement for expenses incurred might be permissible).

c) The law should permit women to sell their eggs to infertile couples (or individuals) who wish to use the eggs for fertility treatment but prohibit such sales for the purpose of conducting biomedical research.
Arguments for Permitting Compensation

(1) Enable market to clear
    Avoid shortages of necessary tissues

(2) Protect decisional autonomy of donors
Arguments for Prohibiting Compensation

Payment undermines voluntariness of donation; can be "coercive"

Problems:

- Payment does not undermine free will
- If paternalistic protection is necessary, it should extend to altruists
- Risk of true coercion minimized if there are no shortages
- Reflects wishful thinking that scarcity should not constrain choices
Arguments for Prohibiting Compensation

Treating tissues as marketable commodity undermines human dignity

Problems:

- Disembodied tissues do not possess attributes of personhood
- Research sales likely to have small marginal affect on social meaning
- Prohibitions can be seen as undermining respect for personhood
## The Law of Tissue Sales

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<td>- National Organ Transplant Act</td>
<td>- 9 prohibit tissue sales for research</td>
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<tr>
<td>- Uniform Anatomical Gift Act</td>
<td>- 13 prohibit embryo sales for research</td>
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<td>- NIH Revitalization Act of 1993</td>
<td>- Only Louisiana prohibits sales of ova for all purposes</td>
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It is legal to buy or sell for research purposes most types of tissues in most jurisdictions.
Policy Proposition:

No Cash or In-Kind Payments Should Be Made to Tissue Donors

[T]he Secretary shall conduct and support research that utilizes human embryonic stem cells...

...[provided]

(3) The individuals seeking fertility treatment donated the embryos ...without receiving any financial or other inducements...

- Stem Cell Research Enhancement Act of 2005
Policy Proposition:

No Cash or In-Kind Payments Should Be Made to Tissue Donors

The ICOC shall establish…standards prohibiting compensation to research donors or participants, while permitting reimbursement of expenses.

No Cash or In-Kind Payments Should Be Made to Tissue Donors

No human oocyte or embryo shall be acquired, sold, offered for sale, received, or otherwise transferred for valuable consideration for the purposes of medical research or development of medical therapies.

Policy Proposition:

No Cash or In-Kind Payments Should Be Made to Tissue Donors

No cash or in kind payments may be provided for donating blastocysts in excess of clinical need for research purposes.

No cash or in kind payments should be provided for donating oocytes for research purposes. Similarly no payments should be made for donations of sperm for research purposes or of somatic cells for use in nuclear transfer.

- National Research Council (2005)
Compensation of Egg Donors

Donations for fertility

- Compensation legal in 49 states

Donations for research

- “No compensation” laws
  - CA, MA, NJ, CT
  - NRC Ethical Recommendations

- Justifications:
  - Coercion
  - Anti-Commodification

Stemagen strategy . . .

. . . Demonstrates the distinction is untenable
Patent Law Basics

Patent provides 20-year monopoly
  - Prevent others from using invention
  - Does not provide affirmative right to market

Requirements of patentability
  - Invention
  - Utility
  - Novelty
  - Nonobviousness
  - Enablement

Issued patents are presumptively valid
  - Can be overturned by PTO or federal courts
WARF Patent Background

- James Thomson's group first to produce primate ESC lines
  - Monkeys: 1994
  - Humans: 1998

- 3 patents for "Primate Embryonic Stem Cells"
  - "Composition of matter" claims
    - hESCs that remain stable, undifferentiated for at least 1 year
  - "Process" claims

- WARF claims ownership over all hESC lines
  - Regardless of genotype
  - Regardless of method or culture medium used
  - Regardless of who produces the line
iclicker Question #3

Which of the following views about the patenting of human embryonic stem cells most closely reflects your own?

a) The creators of the first human embryonic stem cell lines should not be entitled to patent protection. The technology should be freely available to everyone.

b) The creators of the first human embryonic stem cell lines should be entitled to patent their specific method of creating them, but other scientists should be permitted to create other human embryonic stem cell lines as long as they use a different process.

c) The creators of the first human embryonic stem cell lines should be entitled to patent all human embryonic stem cell lines, such that no other scientists may create such cell lines without negotiating permission from the creators.
Patent Theory

Pros of patents:
- Incentive to innovate
- Incentive to commercialize

Cons:
- Patents can deter secondary inventions
  - In theory, market should avoid this result
  - In practice, markets can fail due to:
    - Transaction costs
    - Risk aversion
    - Differential estimates of patent value

Happy medium:
- Adjust patent breadth to incent technological improvements
WARF hESC Patents

• WARF obtains 3 patents on primate/human embryonic stem cell lines
• Problem: Broad primary patents impede follow-on research
• Routes of challenge under patent law:
  – Product of nature
  – Overbreadth
  – Hatch-Waxman Safe Harbor
  – Nonobviousness Requirement

Reexamination sought by Public Patent Foundation
Invention

- "Products of nature" are not patentable

- **Diamond v. Chakrabarty** (1980)
  - "Anything under the sun that is made by man"

- Question: How do you characterize Thomson's innovation?
  (a) hESCs are found in nature
  (b) Purified, stable hESC lines are not found in nature

- Likely outcome?
  - Federal Circuit court precedents suggest WARF patents are valid
    - 4200 patents issued for human genes
  - Supreme Court ruling in **LabCorp. v. Metabolite** raises questions
- European Patent Convention has "ordre public" provision
  - EPC panel has ruled unmodified hESCs unpatentable

- U.S. "moral utility" doctrine
  - Dates to early 19th century
  - 1987, PTO suggests doctrine might apply to inventions:
    "injurious to the well-being, good policy, or good morals of society"

- Likely outcome?
  - 1999, Federal Circuit rules doctrine is unsupported by the Patent Act
Enablement

- Patent description must "enable" a skilled practitioner to reproduce product

- Problem: How much protection should be given around the enabled invention?
  - Example 1: A washing machine with one additional bolt added
  - Example 2: Samuel Morse claims:
    "use of motive power of electric current for printing intelligible characters"

- What exactly do WARF patents enable?
  - hESC lines
  - A product containing hESCs and a particular mix of ingredients
  - hESC lines with 5 particular genomes

- Likely outcome?
  ???
"Safe Harbor" from Infringement Suits

1984, Hatch-Waxman Act provides:
"it shall not be an act of infringement to make, use or sell a patented invention…
solely for uses reasonably related to the development and
submission of information under a Federal law which regulates the
manufacture, sale or use of drugs..."

- Purpose: allow generic makers to submit proof of bioequivalence before
  patent expires

- Merck v. Integra Lifesciences (2005) interprets statute broadly
  - Supreme Court holds use of RGD peptides in research is protected

- Likely outcome?
  - Courts unlikely to permit all uses of hESCs
Nonobviousness

- “Obvious if "prior art" would have allowed ordinarily skilled practitioner to make advance

- Public interest groups filed a "Request for Reexamination" with the PTO

- Argument: Thomson merely used “mouse method” on primate embryos

- USPTO upholds patents (February/March 2008):
  “Obvious to try” not sufficient to demonstrate obviousness
  “Reasonable likelihood of success” standard not met

- Questions raised:
  - Legal: Is ruling consistent with *KSR v. Teleflex (S.Ct. 2007)*?
  - Policy: Is this the type of advance for which patents should be granted?
WARF hESC Patents

- Reexamination limited to nonobviousness claim

- Argument: (1) Thomson used “mouse method” on primate embryos
  (2) This was “obvious” to ordinarily skilled researcher

- Patent office upholds WARF patents, Feb.-March 2008
  - Uncertainty of the art
  - Failures with other species
    No reasonable expectation of success

- Broader issue: How strictly should obviousness requirement be interpreted?
  - KSR v. Teleflex: would not occur “in the ordinary course”