Ethical and Moral Issues in Human Pluripotent Stem Cell (hPSC) Research

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Outline of Talk

– Moral Controversy

– Ethical Issues

– Medical Ethics in the Context of Treatment

– Clinical Trials
Human Embryonic Stem Cells

- Pluripotent potential: Can form all cell types in the body

- May, in the future, become the foundation for treating diabetes, cancer, AIDS, heart disease, tissue transplantation, and neurological disorders, such as Parkinson’s Disease & Alzheimer’s Disease

- Knowledge of hESC may also lead to use of the cells in screening for new drugs and toxins.

Therese Winslow, Regenerative Medicine, 2006:

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Somatic Cell Nuclear Transfer (SCNT)

Evan Snyder and Jeanne Loring, Beyond Fraud - Stem-Cell Research Continues, NEJM 354 (4): 321, [Figure 1]: January 26, 2006.
Moral Controversy about hESC Research?

- Does stored IVF material (embryos) represent more than discarded cells such as skin cells or biopsy material?
  - Are hESCs potential human beings?
  - Are all stored embryos potential human beings?
  - Should embryos have the same moral status as a living human being?

- Is it wrong to create an embryo (fertilization or SCNT) with the intention to destroy it?

- Is there theological disagreement?

- Objections to human/animal hybrids & human cloning
Moral Objections: Bioethics Counsel

• The moral debate: When does human life begin?

  – *Disrespect for nascent life*: Any stage of human embryonic development represents nascent human life, including stored embryos from *in vitro* fertilization (IVF). Therefore, the embryo is inviolable or entitled to the same respect and protection as living people, and therefore, should not be destroyed for research.

  – *Risk v. Benefit*: The destruction of embryos in the earliest stage of development (blastocyst) and prior to implantation in the uterus, constitutes a threat to life and cannot be justified or balanced by the promise of future research discoveries that may address human illness and suffering.

  – *Moral v. Legal Standing*: An intent to have concerns about the moral standing of the embryo impact legal standing?
Religion & Science: What is it to be a “living individual”?

**Judaism**
- No central authority
- Traditionally limited moral status of embryo before 40 days of development

**Hinduism**
- No central authority
- Indian gov’t allows hESC research but not the creation of embryos for research

**Islam**
- No central authority
- Muslim legal commentators generally accept the morality of abortion through the 40th day

**Buddhism**
- No central authority
- *Ahimsa*: principle of non-harming. Debate on whether prohibits infliction of harm on sentient beings or all living things.

**Christianity**
- Post-Reformation Protestant Traditions/Decentralized Authority
- Papal authority (canon law v. theology)
- St. Augustine: Ensoulment & Sentience after 40 days
- Thomas Aquinas: Differentiates primary matter (*potentiality*) from substantial form (*actualizing principle*).
- Pius IX (1869) declares all direct abortions homicide regardless of fetal stage of development

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Moral Perspective

• Human life is a continuum
  – Individuals of every age and condition merit the same respect for their fundamental right to life.
  – Differences in stage of development are part of the continuum, an embryo is part of that continuum.
  – Therefore, embryos are entitled to being treated with dignity like people.

• Humans are made in the divine image and likeness, and must always be treated as an end in themselves, not merely as a means to other ends.

• hESC research is immoral because it approves doing deadly harm to a member of the human species solely for the sake of potential benefit to others.

• "[The ISSCR Guideline] is worthless as an ethical guide because it is issued by scientists and entrepreneurs who have dedicated their careers to destructive human cloning and human embryo research and who will profit from the expansion of these abuses," LAT Feb 3, 07 on ISSCR Guidelines

Richard M. Doerflinger: Deputy Director of the Secretariat for Pro-Life Activities, United States Conference of Catholic Bishops
Moral Perspectives

**IVF & hESC research**
- Genetic materials outside of the uterus have no legal status
- They are not part of the human being until implanted in a uterus
- No potential to be a human being until implanted in a uterus
- During the 1st 40 days of gestation their status is “as if they were simply water” (Babylonian Talmud)

**Science**
- Technology is morally neutral
- Technology gains moral valence on the basis of how we use it

**Ethical duties of medical practitioners**
- Physicians are agents in the act of healing
  - Duty to develop and use therapies that can aid in taking care of our bodies
  - Health care is a communal responsibility

Morals & Ethics

- **Morality**: Individual or group attempt to embody in daily attitudes and actions their vision of the highest good. Typically, tied to religious traditions.
  - Respective moral authority derived from ancient texts:
    - Judaism - Laws of Moses
    - Christianity - Hebrew scriptures and teaching of Jesus
    - Islam - Message given Muhammad in the Qu’ran.
  - A “private language”: Only adherents of the same tradition can be expected to understand and accept as authoritative religious based pronouncements on morality

- **Ethics**: Employs a common language (reason) in justifying assertions about prescribed and proscribed attitudes and actions. Embraces uncertainty and ambiguity.

*Ernlè W. D. Young, Ethical Issues: A Secular Perspective, 2001*
...a doctrine, attitude, or way of life centered on human interests or values; especially: a philosophy that usually rejects supernaturalism and stresses an individual's dignity and worth and capacity for self-realization through reason."

*Merriam Webster Dictionary*
Ethics: Immanuel Kant (1724 –1804)

• Unique human traits
  – Free will, self-ruling capacity = autonomy
  – Traits make people intrinsically valuable
  – Differentiates between things that are valued for their use or serve the ends of others

• Ethical responsibility:
  – Respect for other persons as intrinsically valuable as self-regulating beings: dignity beyond price
  – Therefore, people should be treated as ends to themselves and not a means to an end.
Ethical Principles

• Respect for persons
  – Dignity
  – Autonomy
  – Informed consent
  – Avoid coercion and undue influence

• Beneficence
  – Risks
  – Benefits

• Justice
  – Distribution of risks and benefits
Policy Options

• Permit all hESC research
• Ban all hESC Research
• Limits:
  – Permit research only on existing lines
  – Permit research only on “residual” clinical embryos
  – Permit research only on “residual” and new clinically created embryos
  – Permit research on residual/new clinical embryos and those created by SCNT
  – Permit research on all of the above and on embryos created via SCNT into non-human animal eggs
National Discussion: Political Football

• 1975-79: Department of Health, Education, & Welfare will not fund research on human embryos or IVF unless reviewed by an Ethics Advisory Board (EAB)
  – Human research regulations require EAB for same work

  1978: Birth of Louise Brown in UK, 1st IVF baby
  (EAB approves 1st research involving IVF)

  1979: EAB report concludes that federal support for IVF research is “acceptable from an ethical standpoint” provided it attempted to est. IVF safety
  – conditions are met for informed consent
  – the research includes scientific goals “not reasonably attainable by other means”
  – Not maintaining embryo in vitro beyond the stage normally associated with the completion of implantation (14 days after fertilization)

• 1980 - 93: EAB dissolved = no new funding for related research
• 1994: Human Embryo Research Panel (HERP)
• 1996: Dickey Amendment to PHS Appropriations Bill

• 1998: J Thomson isolates and patents hESC
  – 1999: WJ Clinton asks the National Bioethics Advisory Commission to report on hESC research

• 2001: GW Bush hESC research policy (patchwork of State laws)
• 2004: CA Proposition 71
• 2005: National Academy of Science hESC Guidelines
• 2009: B. Obama hESC research policy
Federal Policies & Commissions

– **Human Embryo Research Panel (HERP) report (1994)**

- Embryos do not have the same moral status as persons
  - Absence of developmental individuation in the pre-implantation embryo
  - Lack of even the possibility of sentience and most other qualities relevant to moral status of persons

- Human embryos are more than property and warrant serious moral consideration as a developing human life form

- They have an intermediate status: neither person nor property

- Demonstrate respect by limiting the time frame in which research is done on them and the purposes of the research
The Bush Policy

Criteria:
1. hESC must have been derived from an embryo that was created for reproductive purposes
2. Embryo no longer needed for such purposes
3. Informed consent must have been obtained from donors
4. No financial inducements were provided for donation of the embryo
5. Derivation process had already been initiated and the embryo from which the hESC was derived no longer had the possibility to develop into a human being

Federally funded research permitted on ~22 useable hESC lines derived prior to 8/9/01.
Federal Funding Policy at Issue

Dickey – Wicker Amendment:
PHS Appropriations Rider 1996:

SEC. 510. (a) *None of the funds made available* in this Act may be used for (1) *the creation of a human embryo or embryos for research purposes*; or

(2) *research in which a human embryo or embryos are destroyed, discarded, or knowingly subjected to risk of injury or death* greater than that allowed for research on fetuses in utero under 45 CFR 46.208(a)(2) and section 498(b) of the Public Health Service Act (42 U.S.C. 289g(b)).

(b) For purposes of this section, *the term `human embryo or embryos' includes any organism, not protected as a human subject* under 45 CFR 46 as of the date of the enactment of this Act, that is derived by fertilization, parthenogenesis, cloning, or any other means from one or more human gametes or human diploid cells.
National Academy of Science (NAS) 2005 Guidelines

- **Special Status of the Human Embryo**
  - Acknowledged questions about the extent to which it is justifiable to use human embryos to expand knowledge and ameliorate human suffering
  - Outlined the conditions under which the goals may be pursued

- **Considered the position of moral equivalence: Are human embryos morally equivalent to born human persons?**
  - Is the identity of a future born person present in the embryo?
  - Evaluate the moral equivalence of the human embryo to the born human person with the embryos potentiality
  - Is human dignity undermined by excessive manipulation of the human embryo regardless of the purpose?
  - Could lead to the abuse and exploitation of human persons more generally
National Academy of Science (NAS)

- **Cultural Practice**
  - Natural loss of embryo in normal reproduction is not recognized as a death that requires a funeral
  - Disposal of stored embryos after completion of IVF is not murder
  - The embryo may have greater moral status than other collections of cells but not so much that its cells may not be respectfully applied toward other goals to which the faithful are committed.

- **Balance of Human Dignity**
  The use or creation of human embryos in research, or even genetics/molecular biology = manipulations of life that undermine dignity

  **versus**

  Healing the sick as a profound moral obligation and the restoration of health and natural functions as the promotion of human dignity = not squandering undifferentiated blastocysts
National Academy of Science (NAS)

2005-10 Guidelines for hESC Research

– Supports hESC research
  • Addresses blastocysts made for reproductive purposes and later obtained for research from IVF clinics
  • Blastocysts made specifically for research using IVF
  • Somatic Cell Nuclear Transfer (SCNT)/Therapeutic Cloning
  • Concerns about chimeras

– Institutional Oversight of research through Embryonic Stem Cell Research Oversight (ESCRO) Committees

– National Policy Review (three revisions since 2005)

– Did not address translational research
**NAS: Why perform chimeric hPSC research?**

### Contribute to repair or regenerative processes

<table>
<thead>
<tr>
<th>Purpose</th>
<th>Considerations:</th>
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<tbody>
<tr>
<td>1. Production of:</td>
<td>1. Number of hPSC or progenitors transferred</td>
</tr>
<tr>
<td>a. motor neurons</td>
<td>2. Areas of body to be involved</td>
</tr>
<tr>
<td>b. sensory neurons</td>
<td>3. Migration of cells through the body</td>
</tr>
<tr>
<td>c. neurons that secrete mediators, such as dopamine</td>
<td>4. Affect on organs and/or animal functioning</td>
</tr>
<tr>
<td>2. Important to understand if the cells WILL contribute in the context of treatment</td>
<td></td>
</tr>
<tr>
<td>3. Possibility of contribution is difficult to evaluate</td>
<td>5. Whether some valued human characteristics might be exhibited, including physical characteristics</td>
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2008 NAS Chimera Policies:

If there is a significant possibility that the implanted hPSC could give rise to neural or gametic cells or tissues, particular attention should be paid to at least three factors:

1. Extent to which the implanted cells colonize & integrate into the animal tissue
2. Degree of differentiation Proof of principle using human cells is desirable
3. The possible effects of the implanted cells on the function of the animal tissue

It is also relevant to note that neural stem cells, although not pluripotent, are multipotent and may have the potential to contribute to neural tissue in chimeric animals.
Respect for Persons: Informed Consent

- Unlimited research use: Is it ethical to ask donors to provide permission for unspecified use of somatic cells & IVF material for research?

- Ownership of resulting products: *Moore v. University of California Regents*
Withdrawal from the Research

• “...the subject may discontinue participation at any time without penalty or loss of benefits to which the subject is otherwise entitled.” 45 CFR 46.116(a)(8)

• What does it mean to withdraw from hPSC research?
  – Withdraw embryo, gametes, somatic cells?
  – What if the material is destroyed in order to derive the hPSC?
  – Withdraw the embryo/materials prior to destruction?

*Should be informed that they retain the right to withdraw consent until the blastocysts are actually used in cell line derivation.* - NAS
SCNT: Oocyte Donation & Commodification

- Undue influence
- Commodification
- Utilitarianism: Is there such a thing as too much payment?
- Oocytes from miscarried or aborted fetuses (*Public Law 103-43: Research on Fetal Tissue*)
- Oopherectomy

**CA DPH:** “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. For purposes of this section, ‘valuable consideration’ does not include reasonable payment for the removal, processing, disposal, preservation, quality control, and storage of oocytes or embryos.” (CA H&S Code 125350)
Risks of Oocyte Donation:

Ovarian Hyperstimulation Syndrome (.5-5%)

**Hormones**
- Commonly use Lupron off label
- Ovarian torsion
- Liver dysfunction
- Renal failure
- Blood clots
- Memory loss
- Neurological dysfunction
- Cardiac disorders
- Death

**Procedure**
- Rupture of ovaries
- Cysts
- Cancer
Science overcoming ethical issues?
Induced Pluripotent Stem Cells (iPSC)

The New York Times

Scientists Bypass Need for Embryo to Get Stem Cells

By GINA KOLATA
Published: November 21, 2007
Derivation of human embryonic stem cells (hESC)

Derivation of induced pluripotent stem cells (iPSC)

ES cell culture  iPS cell culture

Pluripotent stem cells

Skin cell  Pancreatic cell  Nerve cell

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Justice: Distribution of risks & benefits

Prop 71 = Public Investment

1/05: Authorized issuance of general obligation bonds to Finance Institute activities up to $3 Billion subject to annual limit of $350M.

2/06: CIRM indicates Universities and non-profits that receive Prop 71 awards must return 25% of royalties on discoveries that yield $500K+
Justice: What is owed to the public?

• Public funding & Public Responsibility:
  – Publication of results
    • Scientific peer review journals
    • Negative findings
  – Ensuring diversity of cells and approaches to clinical care
  – Equitable distribution of research benefits/access to discoveries
    • Access to products and therapies developed from Prop 71 hESC
    • Boutique therapies at public cost?
  – Acknowledge US health care system limits just distribution of benefits
Clinical Trials

FDA Approves a Stem Cell Trial

By Andrew Pollack
Published: January 23, 2009
Clinical Trials

• Informed consent
  • What should subjects be told about the origin of the drug/biologic?

• Long term follow-up?
Medical Ethics: Pseudo-Stem Cell Medicine

**Hype**

- Desperate patients and their families
- Available locally or in other countries
- Claims based on patient testimonials
Medical Ethics: Pseudo-Stem Cell Medicine

Overly optimistic claims

• Unsubstantiated by evidence based research

• Not published in legitimate scientific peer reviewed journals
Medical Ethics: Pseudo-Stem Cell Medicine

Non-FDA Approved

• Lack of demonstrated safety or efficacy through rigorous evidence based clinical trials

• Exposes patients to unknown risks
Is there public support?

2005:
Johns Hopkins Genetics & Policy Center

- 81%: Heard of hESC research prior to the survey
- 67%: Support stem cell research
- 67%: "It would be terrible if cures were delayed because of policies that make hESC research difficult."
- 59%: Support policies that are more permissive toward hESC research than the current policy

- 66%+: Catholics approve of hESC research
- 50%: Fundamentalist/Evangelical Christians support hESC research

“Values in Conflict: Public Attitudes on Embryonic Stem Cell Research,” October 2005:

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Harris Poll: October 2010

“Stem cell research should be forbidden because it is unethical and immoral.”

Base: All Adults

<table>
<thead>
<tr>
<th></th>
<th>Tend to Agree</th>
<th>Tend to Disagree</th>
<th>Not Sure</th>
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<td><strong>All Adults</strong></td>
<td>17%</td>
<td>62%</td>
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<td><strong>Catholic</strong></td>
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<td>61%</td>
<td>19%</td>
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<tr>
<td><strong>Protestant</strong></td>
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<td>66%</td>
<td>20%</td>
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<tr>
<td>“Born-Again Christians”</td>
<td>23%</td>
<td>51%</td>
<td>27%</td>
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</table>
“Using cells from human embryos for research comes too close to allowing scientists to play God.”

<table>
<thead>
<tr>
<th>Year</th>
<th>Tend to Agree</th>
<th>Tend to Disagree</th>
<th>Not Sure</th>
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<tr>
<td>2001</td>
<td>40%</td>
<td>53%</td>
<td>7%</td>
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<td>2004</td>
<td>19%</td>
<td>57%</td>
<td>24%</td>
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<tr>
<td>2005</td>
<td>23%</td>
<td>58%</td>
<td>20%</td>
</tr>
<tr>
<td>2010</td>
<td>20%</td>
<td>60%</td>
<td>20%</td>
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“Stem cells come from embryos, left over from in vitro fertilization, which are not used and normally destroyed. Many medical researchers want to use them to develop treatments or to prevent diseases such as diabetes, Alzheimer’s or Parkinson’s disease. On balance, do you think this research should be allowed or not be allowed?”

Base: All Adults

<table>
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<th>Should Be Allowed</th>
<th>Should Not Be Allowed</th>
<th>Not Sure</th>
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<td>All Adults</td>
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<td>12%</td>
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<tr>
<td>Catholic</td>
<td>69%</td>
<td>16%</td>
<td>16%</td>
</tr>
<tr>
<td>Protestant</td>
<td>74%</td>
<td>11%</td>
<td>14%</td>
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<td>“Born-Again Christians”</td>
<td>58%</td>
<td>22%</td>
<td>20%</td>
</tr>
</tbody>
</table>
What is now proved was once, only imagin’d.

- William Blake, 1790

Karumbayaram, Lowry, et.al: 2010