Stem Cell Ethics and IP: An Introduction

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Nomenclature

• CIRM: California Institute for Regenerative Medicine

• SCRO: Stem Cell Research Oversight Committee

• IRB: Institutional Review Board
  – Ethics oversight mechanism for enforcing federal regulations for the protection of human subjects in research
Prop. 71 & CIRM

- CIRM – policies posted for public comment at <http://www.cirm.ca.gov/>
  - Proposed medical and ethical standards regs
  - Intellectual property policy for non profit orgs
  - Proposed modification to COI policy
Research Ethics Overview
After Prop. 71

• Beyond the “moral status of the embryo”

• Protection of human participants in research

• Research animal protections

• Democratization in the governance of science
Beyond moral status questions

• **WHICH EMBRYOS CAN BE USED IN RESEARCH?**
  
  – Only those left over from IVF?
  
  – Is it morally permissible to make embryos purely for research purposes?
  
  – Is there a time limit beyond which in vitro embryos acquire properties that place limits on research?
Proposed Ethics Regulations

• not eligible for CIRM funding:
  – Culture of an intact human embryo or product of SCNT after the appearance of the primitive streak or 12 days, whichever is earlier
    • Implies that the point at which individuation occurs is morally significant and my impose limits
    • Easy political compromise

• CIRM-funded research will include derivation of stem cell lines, and the regulations include protections for oocyte donors
  • Implies that creation of embryos for research is ethically permissible
Human Participant Protections

• Some covered by existing federal regulations and institutional oversight mechanisms
  • People into whom stem cells might be injected
  • Under current interp of federal regulations: Oocyte donors when oocytes are being retrieved for research
  • CIRM proposed guidelines require IRB review when appropriate

• Some might fall through the cracks of existing regulations
  • DONORS OF OOCYTES, SPERM, EMBRYOS, CORD BLOOD, OR SOMATIC CELLS FOR SNCT
Protecting Donors

• May not have provider-pt relationship with health care professionals who retrieve gametes or with scientists who create embryos

• May not ever interact with CIRM-funded researchers and may not fit the regulatory definition of a “human subject”

• May have provided cells previously for banking or for a clinical intervention with a vague permission allowing undescribed future research

• Who has legal duties to protect and respect their interests???
Oocyte Donors

• Special concerns bcs of potential serious physical harms:
  – Procedure is burdensome, often extremely unpleasant and causes morbidity
  – Moderate probability ovarian hyperstimulation syndrome (medium and long-term risk)
    • Abdominal pain, occasionally leading to renal failure and hospitalization
    • Potential future infertility
    • Low probability of death
  – Long-term consequences not well known → uncertainty
Consent For Donation

• Help oocyte donors weigh risks against benefits and their motives/values

• Ensure that all donors who contribute to stem cell research are engaged in an activity that is consistent with their deeply held beliefs and their values.
CIRM proposed consent rules

• Donors of all cells have given **VOLUNTARY AND INFORMED** consent.

• Minimize conflicts of interest for those offering the opportunity to donate bio materials
  • generally, the donor’s treating physician cannot be the CIRM-funded researcher
  • physician performing oocyte retrieval shall not have a financial interest in the outcome of the CIRM-funded research.

• Donor’s preferences re. the uses of their material must be documented and CIRM-funded research cannot violate these preferences
Special Rules for Oocyte Donors

• Enhance the standard consent PROCESS:
  – Must provide an adequate period of time for deliberation (adequate to be determined by the IRB)

  – The researcher shall take steps to ascertain that donors have understood the essential aspects of the proposed research

  – Other???
Informed Consent Summary

• Are the CIRM proposed regs repeating the mistakes of the federal regulations
  – Too much specificity about content
  – Not enough specificity about process

• Create a record-keeping emphasis but still do much research with less-than-adequate informed consent and less-than-adequate protection from real risks?
Animal Safety Concerns…

• Injecting human stem cells into animals could create a variety of chimeras
  – Yuck factor!!! But…
    • We already make a variety of human – non-human chimeras during research
    • Beyond the yuck factor: “What is actually wrong with making chimeras???”

– One possible problem
  • Create an organism that has human-like cognitive or emotional qualities. It’s existence could constitute a harm, or we could inadvertently harm it in research by failing to recognize its interests or rights
Democratization of Science

• Given that US science has been quite productive with governance largely left in expert hands, what could we or should we change?
  • Greater transparency and accountability
  • Priority setting that includes a broader range of interests and perspectives

• Trade-offs
  • Impede progress and create gridlock
  • Create disincentives that chase the best and brightest out of stem cell research or out of biomedical research altogether
  • Create disincentives for investors, diminish the number of treatments and products brought to market
"We're here to help with your stem cell research. I'm a philosopher and he's a politician."
IP and Licensing Policy
Why Worry About IP and Licensing

• Getting the most bang for Californian’s bucks
  – Maximize knowledge production and diffusion
  – Maximize the number and rate of new products and treatments
    • Distributive justice: want tx to be affordable and available to those who need them
Patentable and Patented

- Human stem cells, and a method of making them, are patentable and already patented
  - James Thomson inventor, WiCel (U. of Wisconsin) assignee: US patent nos. 6,200,806 and 5,843,780 (the ‘806 & ‘780 patents)
  - Terms probably expire in 2015

- SNCT patented by Campbell & Wilmut
  - US patent no. 6,147,276
  - US patent only covers non-human mammals
  - Expires 2020
What is a Patent?

• **RIGHT TO EXCLUDE** others from making, using, selling, offering for sale, or importing the patented item or process
  - Not a positive right to make, do, etc.
  - A patent does not necessarily confer a monopoly

• Quid pro quo between the citizens and the inventor:
  - citizens obtain new, useful knowledge/products
  - inventor obtains exclusionary rights for a limited term of years.
Patentability

• Is it patentable subject matter?
• Is it useful as defined by law (utility)?
• Is it new as defined by law (novelty)?
• Is it non-obvious to one of ordinary skill in the art; is this enough of a contribution to knowledge to justify the patent right (non-obviousness)?
• Is the scope of the exclusionary right sought commensurate with the inventor’s contribution to knowledge (112 requirements)?
Patent “property” is defined by the patent’s claims

- Thomson patents claim:
  - Purified preparations of embryonic stem cells from humans and other primates
    - Pluripotent
    - Proliferate in vitro for over 1 yr while maintaining a stable, euploid karyotype
    - Have the potential to differentiate into “derivatives of” the three germ layers that represent the earliest developmental stages of an embryo (endoderm, mesoderm, ectoderm)
    - Defined by the presence and absence of certain cell surface proteins and enzyme activities
Scope of Thomson Patents

• What counts as “embryonic”?  
  – Thomson recently filed a continuation in which claims do not use the term embryo or embryonic any more. Potentially, much wider claims.

• Others can still patent new stem cell inventions!  
  – These new inventions must meet the requirements for patentability
  
  – New stem cell patents may or may not require cross-licensing with Thomson patents
Power of Owning Patent Rights

• Can exclude others from using something covered by a claim, even when their use is not commercial
  • Can prevent others from doing research without the patent holder’s authorization (license)

• Patent rights are enforceable even if the owner is not making or using anything covered by the patent claims

• Need not enforce the right to keep it

• RIGHT COVERS INDEPENDENT INVENTION OF THINGS COVERED BY A CLAIM, AND AFTER-DEVELOPED TECHNOLOGY
  
  – WiCel can exert rights over new stem cell lines derived by CIRM-funded scientists
  – Recent MOU between WiCel and NIH
Patent Licensing

• Patentees have wide leeway in licensing:
  – Can license exclusively or non-exclusively
  – Can license only some of the rights
    • for instance, can put restrictions on types and numbers of uses
  – Field of use restrictions are permissible
  – Geographic restrictions are permissible
Other relevant licensing considerations

• Data Use Agreements
  – Transfer of data among non-profit researchers or between non-profit researcher and for-profit institutions (biotech or pharma)

• Material Transfer Agreements (MTAs)
  – Transfer among researchers of stem cells and other reagents

• Patent licenses, data use agreements and MTAs concern different rights
  – Authorization for research or product development can involve one, two or all three
Proposed CIRM Policy for Non-Profit Research Organizations

- Policy goals:
  - Achieve academic openness and bring scientific advances to the public via commercialization
    - May be some tension between these goals, need to figure out how to maximally advance both
  - A primary goal is to promote sharing of all types of IP
  - Promote collaboration between for-profit and non-profit entities so that basic science is translated into products efficiently
  - Provide financial benefit for the State of CA
Some Highlights

• CIRM-funded grantees must share materials described in publications
  • Within 60 days of receipt of a request and without bias as to the affiliation of the requester
  • Alternatively, authors may provide requestors with info re how to reconstruct or obtain the material
  • Sharing “without cost or at cost”
Highlights Continued…

• Grantees can patent
  – Grantee institutions bear the costs of patenting
  – Grantee orgs shall report filing of patent apps on an annual basis
  – Must submit a patent licensing activity report annually
  – Grantees agree that CA research institutions have a no-cost, non-exclusive license for CIRM-funded, patented inventions
• **GRNATEES SHALL NEGOTIATE NON-EXCLUSIVE LICENSES WHENEVER POSSIBLE**
  
  – Must document the commercialization capabilities of the intended licensee when granting an exclusive license

  – When exclusive licenses are granted the license will include benchmarks/milestones by which progress towards commercialization can be measured
Highlights Continued

• March-in Rights: CIRM can require licensing by a grantee or licensee, or CIRM can grant a license itself, if:
  • Grantee org has not made reasonable efforts, in reasonable time, to achieve practical application of a CIRM-funded patented invention
  • Bcs licensee has not adhered to an agreed upon plan to make therapies accessible
  • To alleviate public health and safety needs that are not reasonably satisfied by the grantee or its licensee and which needs constitute a public health emergency
When you were just a twinkle in your parents' eyes...