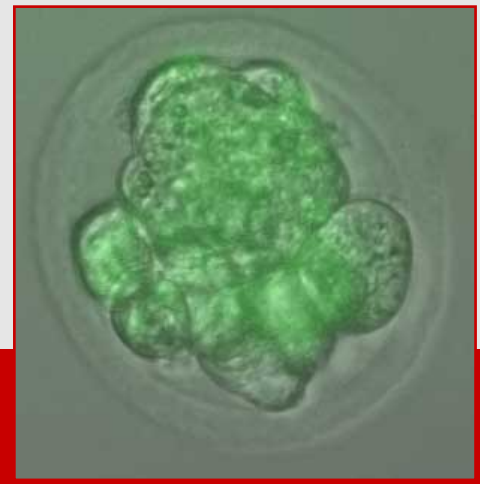

Understanding Differences in Stem Cell Governance

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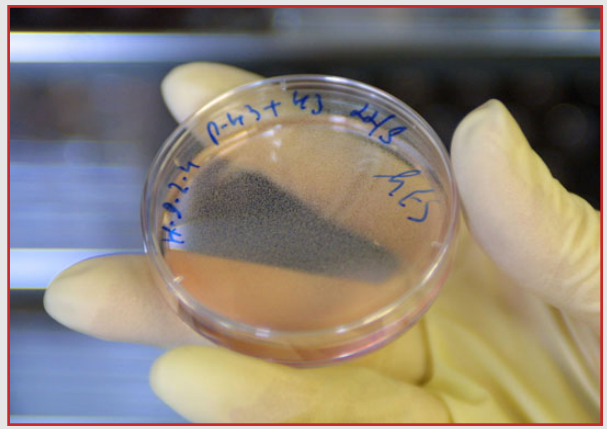
Life Science Governance Institute (LSGi)

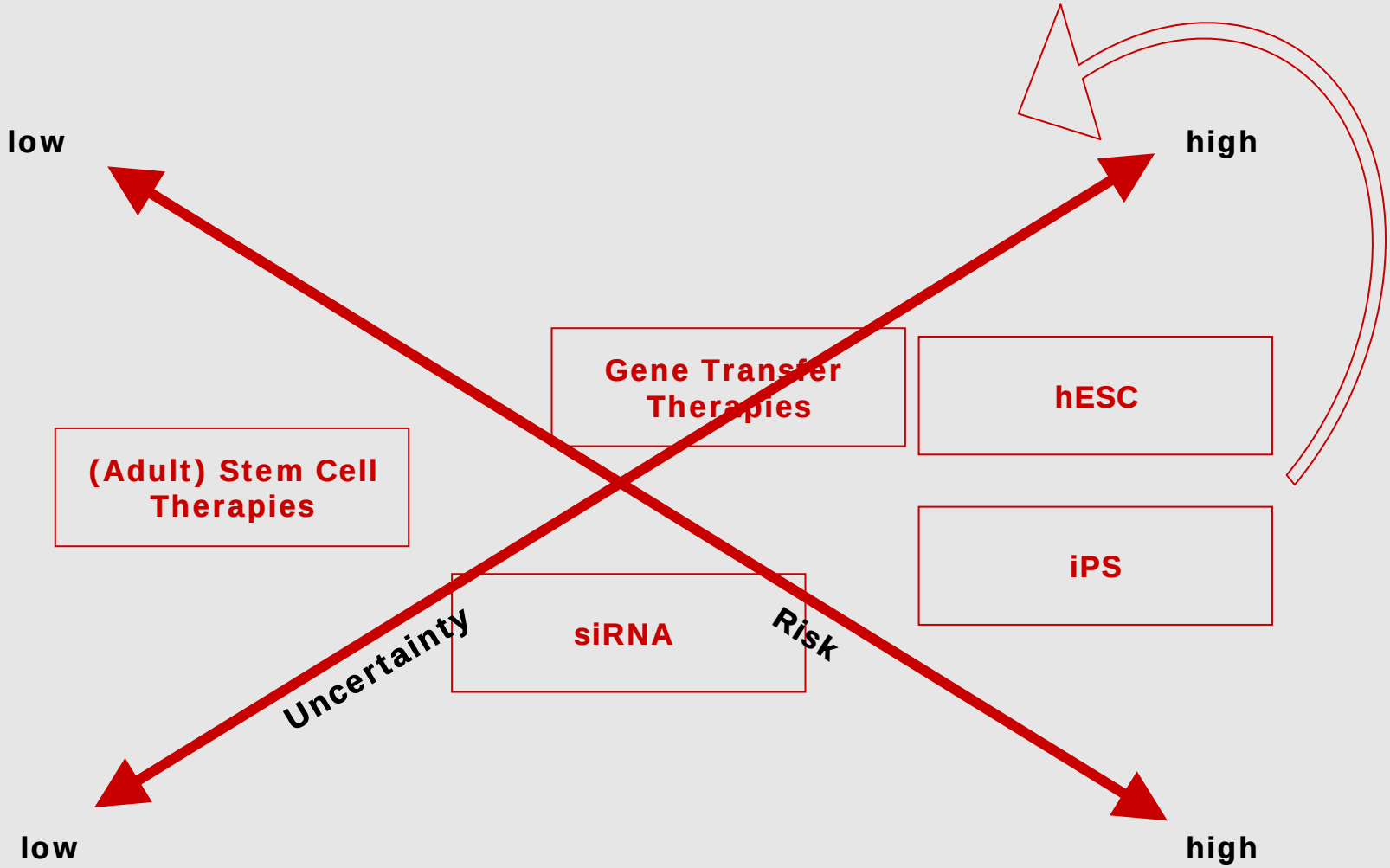
Presentation at the Conference “Beyond Pattison: Challenges to Stem Cell Translation and Policy”, Welcome Trust Centre, May 7-8, 2009

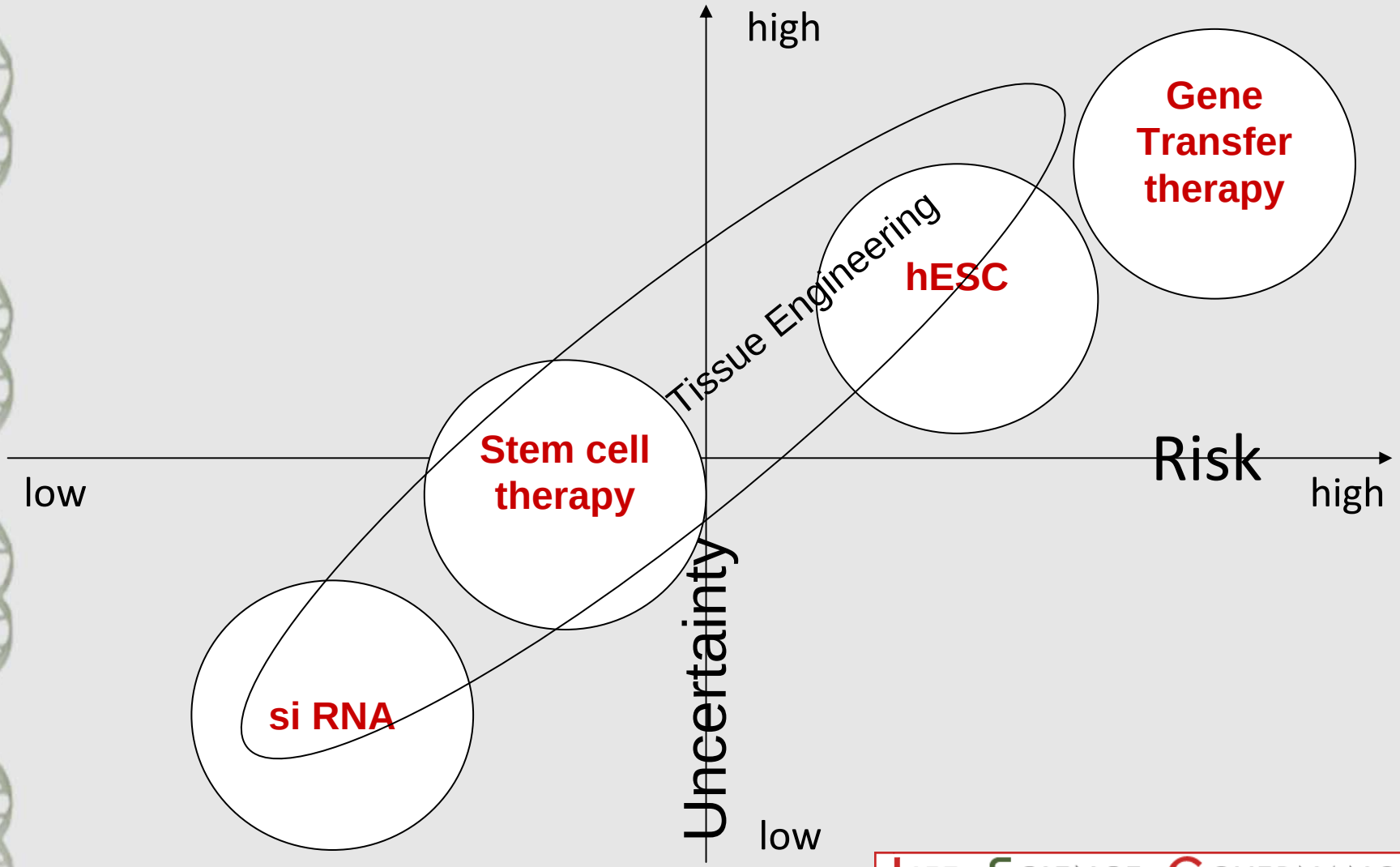
Outline of the presentation

1. Human Embryonic Stem Cell (hESC) Challenges for Ethics and Policy
2. Adult Stem Cells (aSC): Ethics and Policy Challenges Ahead
3. From (basic) Stem Cell Research Towards “Advanced Therapies”
4. Finding New Cures: The Role of Clinical Research
5. Towards Advanced Therapies Governance: from uncertainty to risk?



Governing Stem Cell Science




high
Gene Transfer therapy
Tissue Engineering
hESC
Stem cell therapy
Risk
low
high
si RNA
Uncertainty
low

[1] Human Embryonic Stem Cell (hESC) research Challenges for Ethics and Policy-The Politics of Uncertainty

- Fundamental scientific, legal, social and ethical uncertainties put pressure on policy making
- Constellations of uncertainty refer to situations of undecidability where there is a lack of criteria to arrive at decisions
- hESC research today constitutes a highly regulated and politicized field of biomedical research
- Characterized by highly globalized policy and research networks
- Nevertheless, the “nation state” remains a significant actor in the stem cell sector
  - Actively shapes stem cell and cloning research by drafting regulations and state key in allocates of funds
  - Private sector has only reluctantly invested so far in hESC research

- Striking differences how nation states govern and regulate hESC and cloning research

There are

- permissive
- flexible, or
- restrictive regulations

- Policy options range from:

  [1] Prohibition of procurement of hESCs from human embryos *(Austria, Germany, and Italy)*

  [2] Prohibition of procurement but allowing importation *(Germany, Italy)*

  [3] Allowing procurement of hESCs from supernumerary human embryos *(Australia, Brazil, India, Iran, Israel, South Korea, and UK)*

  [4] Prohibition of creation of human embryos for research purposes including cloning *(Austria, Brazil, Germany, and Italy)*

  [5] Allowing creation of human embryos for research purposes including cloning *(Australia, India, Iran, Israel, South Korea, and UK)*

  [*cf Salter/Salter 2007,* International Consortium of Stem Cell Networks (ICSCN) 2008, Larijani&Zahedi 2008]

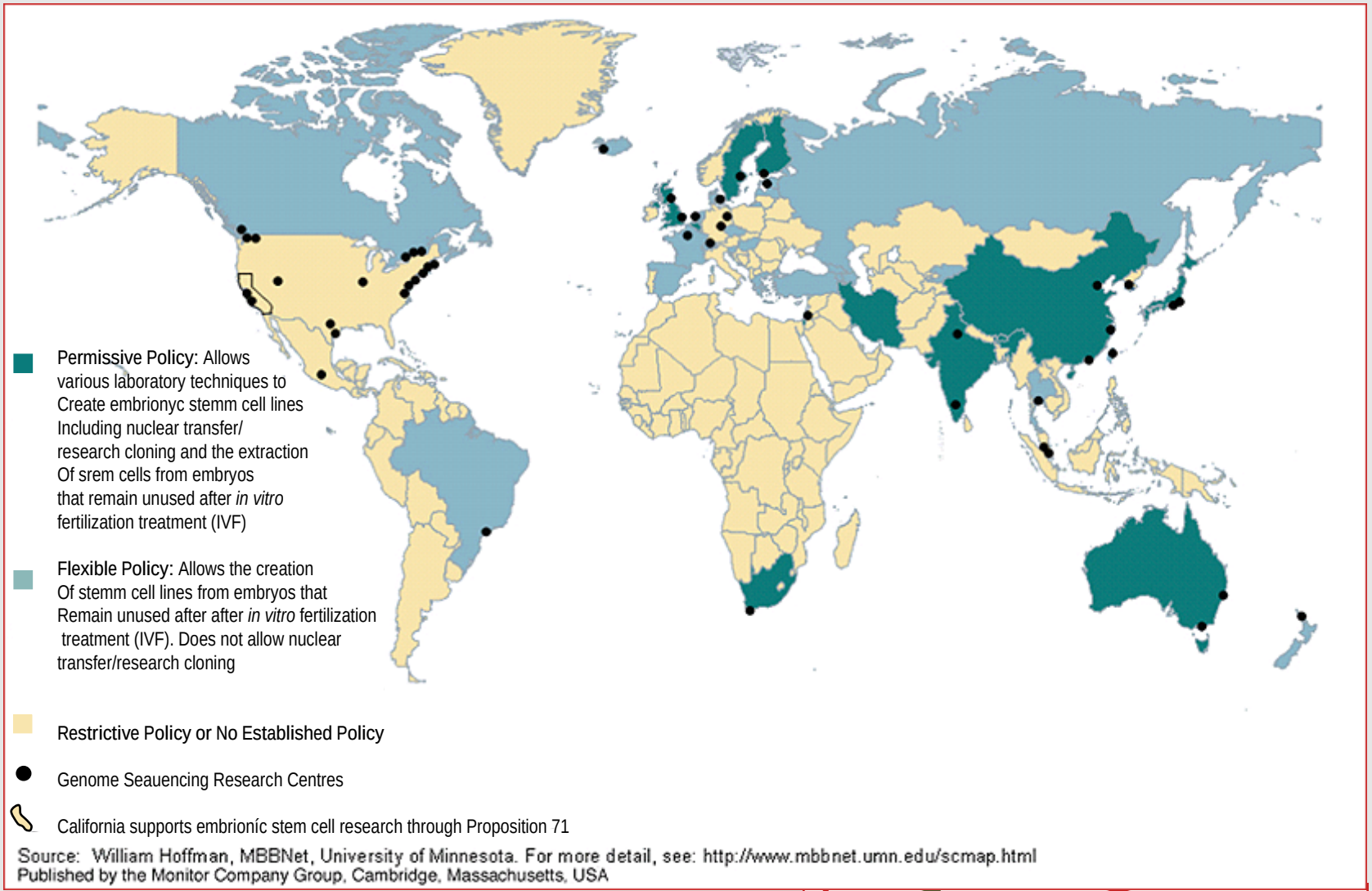
The Global Regulation of hESC Science (2008)

Countries	Policies Option 1	Option 2	Option 3	Option 4	Option 5
Australia			X		X
Austria	X			X	
Belgium			X		X
Brazil			X	X	
Bulgaria	X				
Canada			X	X	
China			X		X
Cyprus				X	
Czech Rep			X		
Denmark			X	X	
Estonia			X	X	
Finland			X		
France			X	X	
Germany	X	X		X	
Georgia				X	
Greece			X	X	
Hungary			X	X	
Iceland				X	
India			X		X
Iran					
Ireland	X			X	
Israel			X		X
Italy	X	X		X	
Japan			X		
Latvia				X	
Lithuania	X			X	
Luxembourg					
Malta					
Mexico			X		X
Netherlands			X	X	
Norway				X	
Poland					
Portugal				X	
Russia			X		X
Singapore			X		X
Slovenia			X	X	
Slovakia				X	
South Africa			X		X
South Korea			X		X
Spain			X		X
Sweden			X		X
Switzerland			X	X	
Taiwan			X	X	
Thailand					
UK			X		X
Total (45)	**6**	**2**	**27**	**23**	**13**

Option 1: Prohibition of procurement of hESCs from human embryos
Option 2: Prohibition of procurement but allowing importation
Option 3: Allowing procurement of hESCs from supernumerary human embryos
Option 4: Prohibition of creation of human embryos for research purposes including cloning
Option 5: Allowing creation of human embryos for research purposes including cloning

Sources: European Commission, DG Research (2004) *Survey on Opinions from National Ethics Committees or Similar Bodies, Public Debate and National Legislation in Relation to Human Embryonic Stem Cell Research and Use,* volume I, EU Member States; volume II, Countries associated to FP6 and third countries (Brussels: European Commission); Walters R (2004) 'Human Embryonic Stem Cell Research: An Intercultural Perspective', *Kennedy Institute of Ethics Journal,* 14(1), 3-38, International Consortium of Stem Cell Networks (ICSCN) *'Global Regulation of Human Embryonic Stem Cell Research and Oocyte Donation'*, available at: http://icscn.files.wordpress.com/2008/09/global-regulation-hesc-research-oocyte-donation-sep-08.pdf [Date of Access April 30, 2009]

World Stem Cell Policy (2008)



Source: William Hoffman, MBBNet, University of Minnesota. For more detail, see: http://www.mbbnet.umn.edu/scmap.html
Published by the Monitor Company Group, Cambridge, Massachusetts, USA

Regulation of hESC within the United States

Former president George W. Bush's speech restricts federal funds since 2001

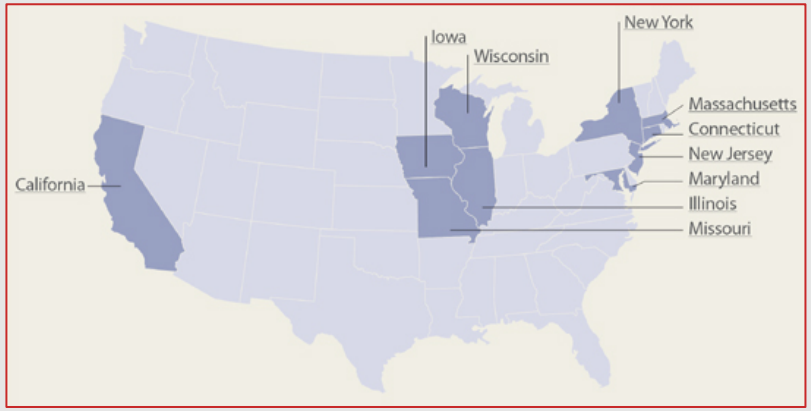
- This results in a regulatory patchwork on the state level
- The most prominent case is California where a public referendum floats $3 billion into stem cell research

- A 'vital' clash between pro-life groups and patients' organizations
- Absence of successful trust-building
- No undisputed regulatory authority emerged

- On March 9, 2009 President Barak Obama signs an executive order lifting restrictions on Federally funded hESC research

“A patchwork of patchworks” (Winickoff et al. 2009)

- Due to the little central regulation various scientific organizations developed guidelines which served as the basis for the oversight and good practice of hESC research
  - The NAS (National Research Council and Institute of Medicine of the National Academies) in April 2005
  - The ISSCR (International Society for Stem Cell Research) guidelines in December 2006



States currently endorsing and providing support for hESC research

Source: Hynes, Richard O. (2008) ‘US policies on human embryonic stem cells’, *Nature Reviews Molecular Cell Biology*, 9, 993-997.

- After B. Obama’s executive order it is left to the NIH to issue final regulations by July 7, 2009 (draft guidelines currently under public consideration)

Regulation of hESC within Europe/EU

- Highly divergent topographies of hESC research regulation
- *UK or Sweden:* permissive regulations
- *Germany, Austria, Italy:* restrictive regulations

- Supranational level, EU follows "subsidarity principle"

Regulation of hESC within Asia and the Pacific Rim

- *Australia, China, India, Singapore*, and *South Korea belong* to most permissive regulatory regimes
- "Wild East?"
- Woo Suk Hwang scandal in South Korea to considerable extent result of bad governance
- China and India: (permissive) regulations in place, but serious implementation deficit

Regulation of hESC within the Middle East

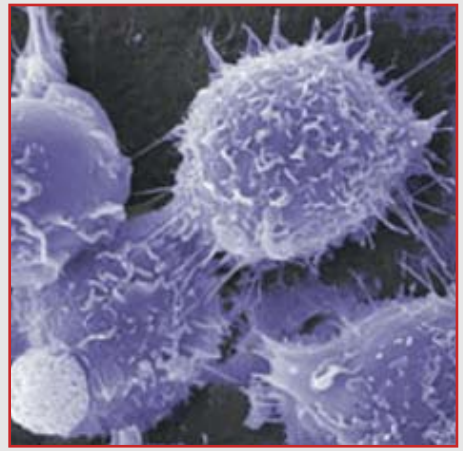
- *Israel* as leader in stem cell research: between Judaism and Zionism
- Within the Islamic world *Iran* is a pioneer of hESC research

2003 successful establishment of “Royan H1”, the first hESC line at the Fertility Research Centre Royan Institute
Supported by Iran’s Shiite religious authorities (the Grand Ayatollahs)
No comprehensive legal framework, regulated by positive fatwas
On the international level Iran played a decisive role by opposing the attempt by the United States and others to adopt a broad UN convention against cloning
hESC research an uncontroversial issue among Islamic scholars?

- The Gulf states embrace stem cell technologies

[2] Adult Stem Cells (aSC) – Challenges for Ethics and Policy

- Few laws or guidelines governing directly aSC research
- But aSC research is not an unregulated research field, rather, it is located in the broader context of biomedical governance
- Need to contextualize it within more general research ethics and medical research regulations
- With progress of clinical translation of stem cell research into effective therapies and the rise of SC clinical trials, stem cell approaches will become a increasingly an explicitly regulated field



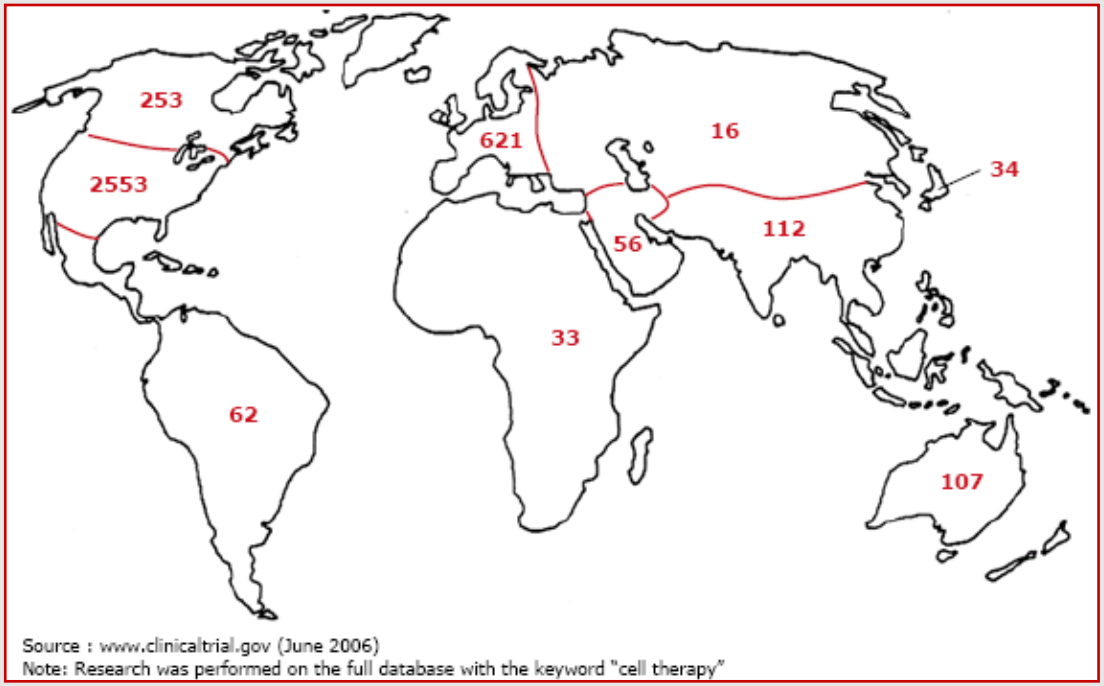
Current Topography of Stem Cell Trials

Adult stem cell trials currently operating [*Database Clinicalttrials.gov*]

Over 3500 registered clinical trials with "cell therapy" -products worldwide.

January 2009

first hESC trial run by Geron Inc. licensed by FDA (supposed to be a landmark study)

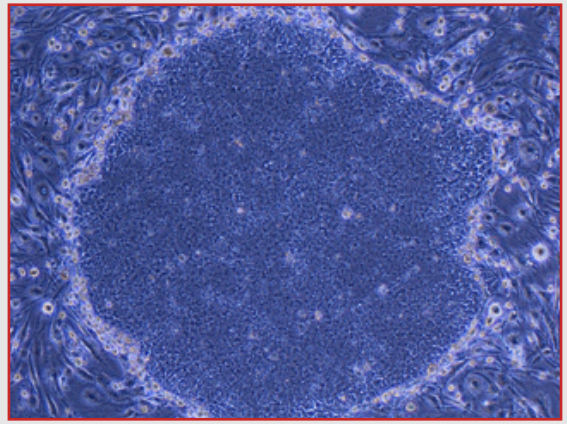


Source: BIONEST (2007): Cell therapies and tissue engineering Attractiveness and competitive position for France. Retrieved from *http://www.leem-recherche.org/wp-content/uploads/2008/02/cell-therapy-eng-v140207.pdf* on March 2, 2009.

[3] Beyond (basic) Stem Cell Research: Towards “Advanced Therapies”

Three strands of developments:

- new scientific developments: beyond basic SC science
- translation into products
- emerging societal/political demands/needs: pressure for cures



Transformation of Medicine

From making “great science” to establishing “a routine clinical practice” and to develop new innovative therapeutic products. (C Mason)

- Focus on translation: Translational Science: bringing basic science research findings to application.
- goes beyond established research fields, like e.g. "stem cell research“
  - "Regenerative Medicine" as an umbrella term to embrace these efforts to create products to replace and regenerate diseased or injured tissue and organs.
- many disciplines (biology, clinical medicine, tissue engineering, biochemistry, bioinformatics...)
- different material bio-bjects (genes, cells, tissues, devices)

[3] Beyond (basic) Stem Cell Research: Towards “Advanced Therapies”

iPS	
+	avoiding serious moral/ethical problems: egg donation, embryo research,...

But other issues might develop: creating oocytes/sperm?

-	hESC remains gold standard
	iPS cell technology cannot replace hESC research [*Minger & Gottweis 2008*]

Beyond (basic) Stem Cell Research: Towards “Advanced Therapies”

- New Scientific findings

- other new research findings suggest that cells can be reprogrammed
- idea "that all cells, not only stem cells, are a potential therapeutic opportunity"

- Tissue engineering and combined products: cells and biomaterials, cells and devices,...
  - many emerging boarder technologies that are hard to define and categorize: beyond classical SC research

- More and more overlap between cell biology and genetics (case of iPS), cells and materials and devices (tissue engineering)
- whole new fields of regenerative medicine and advanced therapies develop

Beyond (basic) Stem Cell Research: Towards “Advanced Therapies”

- Emerging societal needs

- During last years: focus in biomedical research on product development
- investors want return on their investment in basic research
- patients desperate for cures
- pressure on industry: high competition, high expectations
- Translational research "from laboratory bench to clinical application at the patient's bedside“

➲ pressure on clinic to produce deliver cures:
clinical research moves center stage

[4] Developing New Therapies – The Role of Clinical Research

- clinical research as a obligatory point of passage in medical products development
- to assess and ensure safety, efficacy and quality
- to obtain marketing authorization from competent authorities (European Union: EMEA, U.S.: FDA, ...)
- randomized controlled trials with human subjects as the "gold standard" in clinical research
- human subject's research: many ethical and practical challenges
- ethical governance of clinical trials:
  - World Medical Association's Declaration of Helsinki (latest revised version 2008)
  - very influential though legally not binding code of rules

Finding New Cures – The Role of Clinical Research

- U.S. Food and Drug Administration: powerful institution, also influential in standard-setting outside U.S.
- European Medicines Agency: an emerging "global" institution?
- Policy developments towards international harmonization and common ethical and legal standards
- International Conference of Harmonization (ICH): industry-led initiative, starting with U.S., Europe, Japan.
- today: ICH-guidelines have been implemented in various countries
- European Union
  - Clinical Trials Directive 2001/20/EC,
  - Good Clinical Practice Directive 2005/83/EC

SC Clinical Trials: Difficulties Ahead?

Stem cell based product clinical trials pose new difficulties compared to mainstream pharmaceutical trials:

- manufacturing: short shelf-life
- tailoring: experimental treatment must be patient-specific
- smaller number of experimental groups
- new safety issues: long term effects?
  mutation of genetic material?

Summarizing: lessons learned and challenges ahead

- Stem cell research to be located within the broader field of new biomedicine and “advanced therapies”
- Many (scientific, clinical, economic,…) uncertainties and few regulatory experience make it difficult to govern the field
- Various efforts to regulate and foster the field: policy and institutional innovation, network building and international collaboration, public engagement and new actors (patient’s organizations, media, religious communities,…)
- Pressure on the clinic: strong demand to develop innovative clinical products

Implications for Stem Cell Policy and Ethics?

Stem Cell Governance Between Uncertainty and Risk

- Sensitive issues of uncertainty:
  embryo research, clinical genetics, cloning, hybrids/cybids, ...
- Clinical research issues:
  GCP, informed consent, human experimentation
- New risk aspects:
  donor-site traceability, good tissue practice
- Product development between industry-academia, public-private
- Official/institutional review:
  need for expertise
- Law/economy:
  funding, reimbursement, IPR & patents, liability

[5] Advanced Therapies and Society: From Uncertainty to Risk?

- hybridisation of science --> hybrid regulations?
- difficult to classify (medicinal poduct, biological, medical device,...?)
- difficult to assess property: are autologous cell transplants drugs (owned by biotech company) or part of the patient's body?

  --> patent laws?
- Stem cell therapy: between hope and hype, between "clinical experiment" and "medical therapy“ – risk scenarios
- demanding collaboration: between academia and industry: different ends, different means --> different regulations needed?

Regulation in the US

- FDA: 2001 rule to register and licence Human Cells, Tissues, and Cell and Tissue-based Products (HCT/Ps)
- Scope: Cell and Tissue Products to be used in a clinical / commercial setting.
- "unified framework", but excluding gene therapy, as well as HCT/Ps combined with drugs or devices.
- 2-tiered, risk-based approach: Level of regulation proportional to degree of risk
  - Lower risk: Tissue regulation suffice (PHS Act, Section 361)
  - Higher Risk: HCT/Ps regulation (PHS Act, Section 351)

EU Model? - Towards Advanced Therapies Governance

Existing <- Medical Devices Directive ->		NEW <- Advanced Therapies Regulation ->			Existing <- Pharmaceutical Legislation ->	
Traditional Medical Devices	Medical devices made from human tissue engineering where the products only act as structure**	Tissue Engineered Products	Cell Therapy*	Gene Therapy*	Biotech Medicines	Chemical Medicines
	- E. g. Demineralised -bone	- Products that grow and interact with the patient´s Body -E.g., -Replacement cartilage and skin products	- Products that work by replacing diseased or dysfuctional cells with healthy, functioning ones	- Products that act by inserting genetic material to replace or correct genetic problems		

*Cell and gene therapies currently under the pharmaceutical legislation.
** Under discussion in current revision of the Medical Device Directive.

Source: EUROPABIO (2006):
EuropaBio Policy Brief. On the Proposed European „Advanced Therapies Regulation.
Retrieved from http://www.europabio.org/relatedinfo/Advancedtherapiesregulation.pdf
on March 2, 2009.

Regulation in China

- last years: vast regulatory uncertainty; how to classify SC based products; what guidelines to follow in clinical applications?
- March2, 2009: Ministry of Health Regulations on Clinical Applications of Medical Technology, came into force May 1, 2009
- Review and regulatory oversight of e.g. SC products by MoH.
- Medical technology: classification in 3 Types depending on
  - reliability of safety
  - Efficacy
  - ethical issues
  - the bio-objects use
- SC products (Type 3) regulated by MoH. Clinical safety studies now obligatory before application
- Implementation of third party review system

Conclusions: From Uncertainty to Risk – and Return?

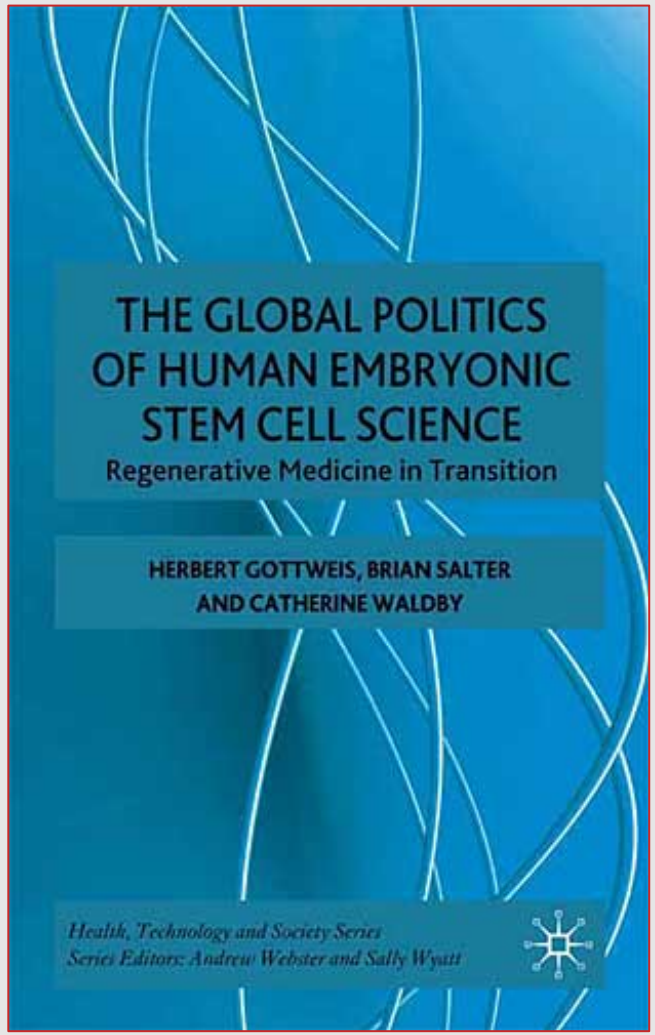
- Envisaging policy innovation:
  building trust within the realms of uncertainty
- Acknowledge these uncertainties and related public concerns as a fundamental feature of this bioscientific field
- Governing despite uncertainty:
  Finding ways to account for transformations of the field over time (EU Advanced Therapies Regulation!)
- Governing the risk of stem cell science as emerging challenge
- Emerging high risk/high uncertainty scenarios: Geron hESC trial as test case
- Acknowledge the global character of modern science: science, but also ethics knows no borders
- Early , proactive , and coherent efforts toward stem cell governance are more likely to yield success than half-hearted, delayed and contradictory approaches
- But uncertainties will continue to dominate the stem cell field

Recently published

Gottweis, Herbert/Salter, Brian/Waldby, Catherine (2009):

The Global Politics of Human Embryonic Stem Cell Science. Regenerative Medicine in Transition.

Palgrave Macmillan.



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