

# **From the Bench to the Bedside: Ethics and Policy in Translational Biotechnology Research**

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# Presentation Objectives

- To discuss some of the most important ethical and policy issues arising in translational laboratory, animal, pharmaceutical, and first-in-humans clinical research using gene- and cell-based interventions.
- To examine the ethical roles and perspectives of researchers who work with novel biotechnologies at all research stages, and of policymakers, members of research oversight committees, and health care providers.
- To explore examples that help to illustrate these important considerations and help to guide practice when translational biotechnologies yield products and treatments.

# Key Research Ethics Stakeholders

- **Laboratory Researchers**
  - whose work is purely in vitro (creating iPS cells, propagating cell lines, seeking genetic associations, testing drugs on organoids)
  - whose work is intended to lead to animal and human trials (such as tissue engineering using bioprinting and bioreactors)
- **Animal Researchers**
  - who create animal models (such as humanized chimeras)
  - who gather data for human trials
- **Clinical Researchers**
  - FIH and other human trials
  - gene- and cell-based interventions, regeneration technologies
- **Biobankers**
  - who collect and store stem cells and cell lines & make them available for research & treatment
- **Oversight Bodies & Funding Agencies**
  - who must apply regulations fully and fairly
  - who must review the value and validity of research
- **Health Care Providers & Public**
  - who advise patients & research subjects
  - who need to understand the relationship between research & treatment
  - who should help set research priorities

# Translational Technologies with Ethical Implications

- **Gene-based interventions**
  - gene transfer, gene editing
- **Cell-based interventions**
  - iPSC creation, regenerative medicine
  - determined stem cells, MSCs, highly multipotent stem cells, hESCs
- **“Body on a chip” organoid arrays for pharmacological and pharmacogenomic testing**
- **“Humanized” chimeric animal models**
- **Regenerative medicine combination products: wafers, organs, etc.**
- **Innovation and stem cell tourism**
- **Stem cell banks**

# Why Is Ethics Important in Research?

- Ethics is part of being human
- All people have moral relationships and obligations – that is, we are all **moral agents**
- People have many moral roles
- Researchers and members of research ethics boards
  - have moral roles in research
  - should use their own moral experience
- Research ethics rules should make sense as a matter of **personal & professional moral agency**

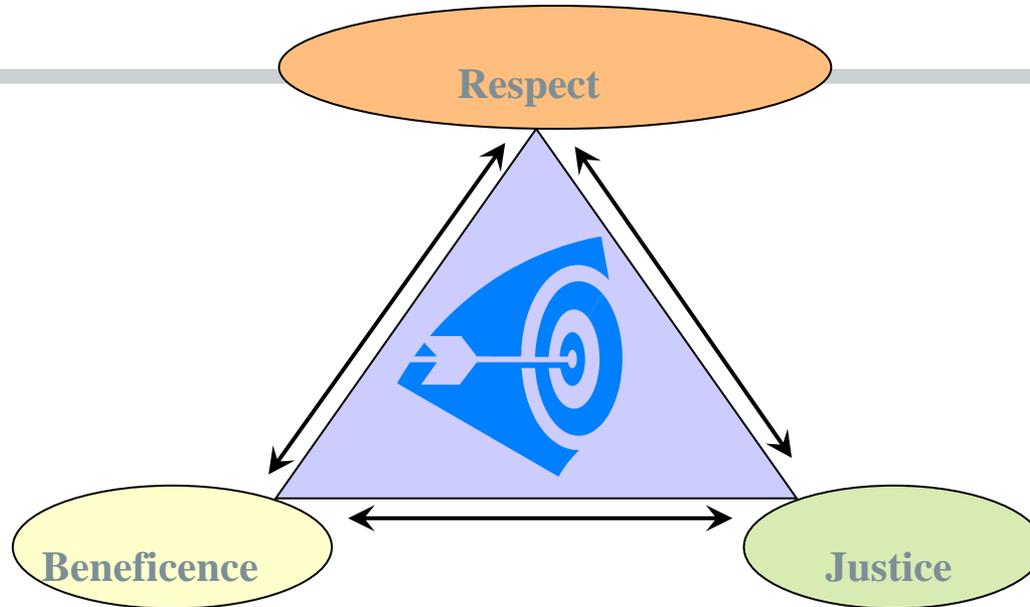
# Translating Ethical Principles Into Regulations



Always remember:

Regulatory requirements stem directly from ethical principles.

# Balancing Research Ethics Principles



- Moral tension is expected and inevitable
- Principles carry equal moral weight
- Requires good-faith contextual judgment calls
- Reasonable people may disagree

# Research Goals in Translation I: What All Experiments Must Do

- Promote development of generalizable knowledge
- Pursue lines of research that have social value
- Ensure integrity, transparency, & reproducibility
  - of methods
  - of data
- Ensure validity of research results
- Justify next research steps
- Listen to independent review that is
  - autonomous
  - well-informed

# **Research Goals in Translation II: Especially for Animals & Humans**

- **Balance & justify risks of harm & potential benefits**
- **Choose the best research subjects for safety & knowledge production**
- **Reduce risks of harm**
  - for animals
  - for human subjects
  - for future patients
- **Make only fair offers of research participation to potential subjects**
- **Support free & informed decision-making for all stakeholders**
- **Inform practice to improve health**

# Moving from Bench to Bedside I

- When choosing disorders as research targets, consider:
  - need (severity, prevalence, lack of effective standard treatment or symptom control)
  - science (easy to study, biomaterials available, generalizability of new knowledge)
  - society (advocacy group interest, available funding)
  - research goals & products
  - harm-benefit balance & probable affordability
- Envision the translational research trajectory
- Justify study goals & design at every stage
- Identify preclinical data needed:
  - to detect rare events
  - to demonstrate safety & validity
  - to demonstrate value (safety, fairness, payoff)
- Move to first-in-human trials when it is possible to:
  - Learn about both effects & mechanisms
  - Conduct adequate monitoring & long-term follow-up
  - Manage informed consent & ensure reasonable expectations

# Research Ethics

## Questions for Biotechnologies

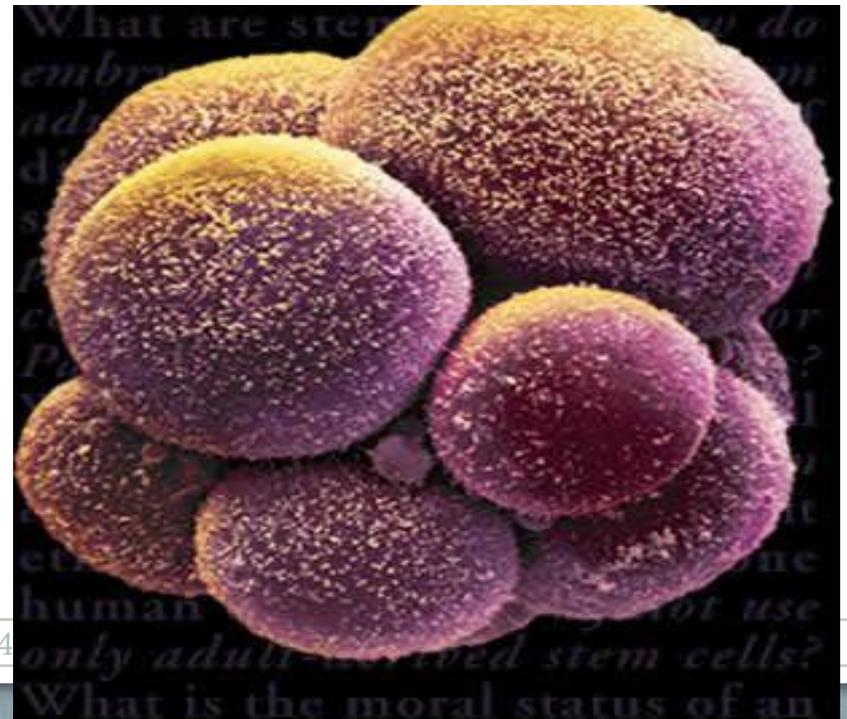
- **Is this research worth doing?**
  - who gets to decide?
  - timed for knowledge production, projected translational payoff
  - much is basic research, rapid moves from bench to bedside, rapidly changing understanding
  - “worth” has strong justice valence: cost, access
- **Will this research produce good data?**
  - good design, monitoring of conduct, data integrity
  - manage conflict of interest
  - industry competition and data-sharing
  - good data analysis and dissemination of results
- **Is this research fair to subjects?**
  - avoid premature move to animals and humans
  - safety, uncertainty minimization, relational duty of care
  - long-term effects? reversibility?
  - comparison with available alternatives essential

# Human Research Ethics in a Nutshell

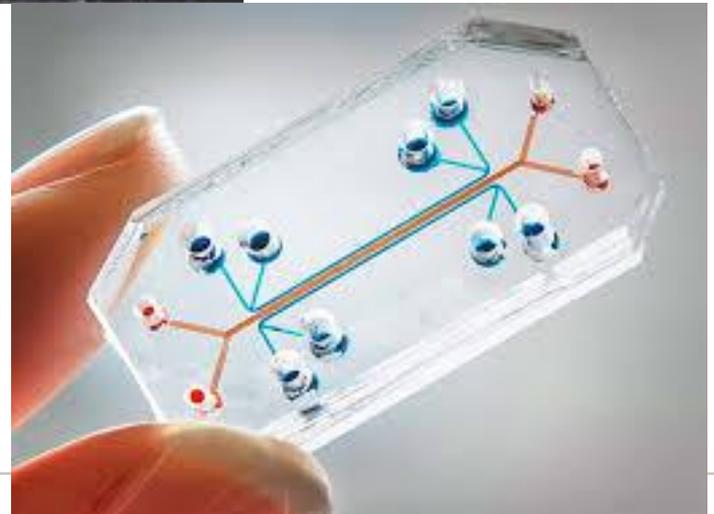
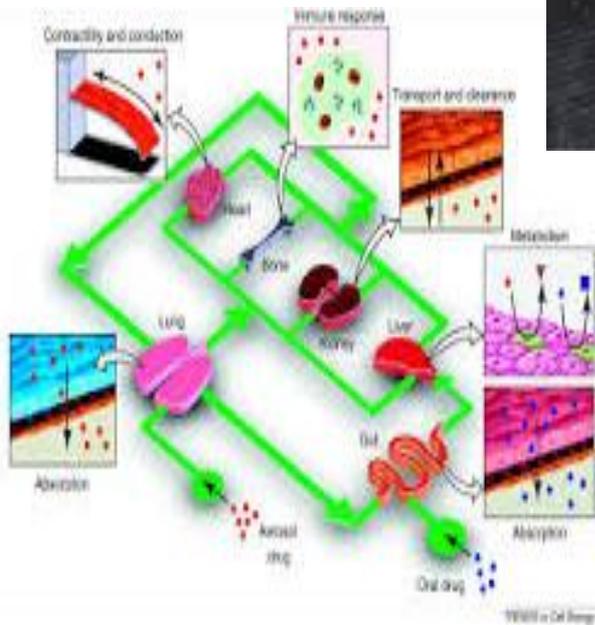
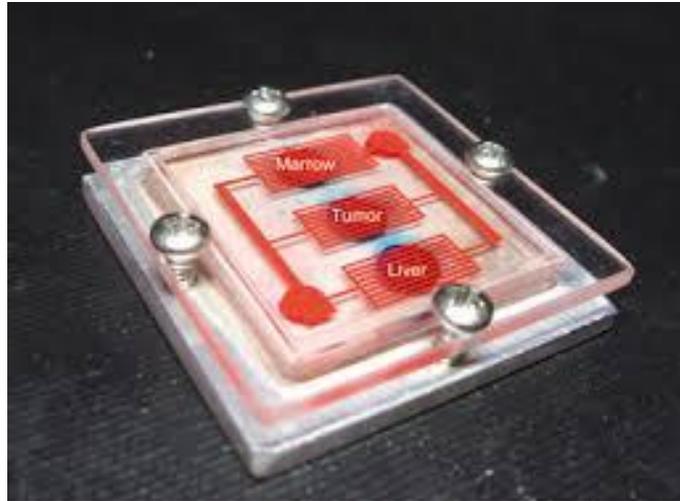
- **Respect for persons**
  - Supporting autonomy of subjects
  - Informed consent
  - Privacy & confidentiality
- **Beneficence/Nonmaleficence**
  - Minimizing risks of harm through study design and conduct
  - Monitoring and long-term follow-up
  - Maximizing benefit to society
  - Balancing risks of harm and potential for benefit
- **Justice**
  - Subject selection
  - Use of results

# Example: Stem Cell Research

- Cell line creation using animal cells
  - employed to test safety, simplicity, & stability of methods
  - may involve recombinant DNA
  - may involve engraftment leading to chimera animal creation
- Cell line creation using human cells
  - sourcing requirements include informed consent
  - may involve recombinant DNA
  - may require proof-of-concept comparison with hES cell lines
  - may involve engraftment leading to humanized animal creation
- Intervention research with hES cells & iPS cells
  - unknown likelihood of tumorigenesis
  - uncertain capacity/stability of hES & iPS cell lines
  - subject selection, “therapeutic window” and FIH design
- Other stem cell interventions need clear descriptions
  - determined stem cells: autologous and allogeneic
  - mesenchymal stromal/stem cells
  - stem cells encapsulated in wafers



# Body on a Chip



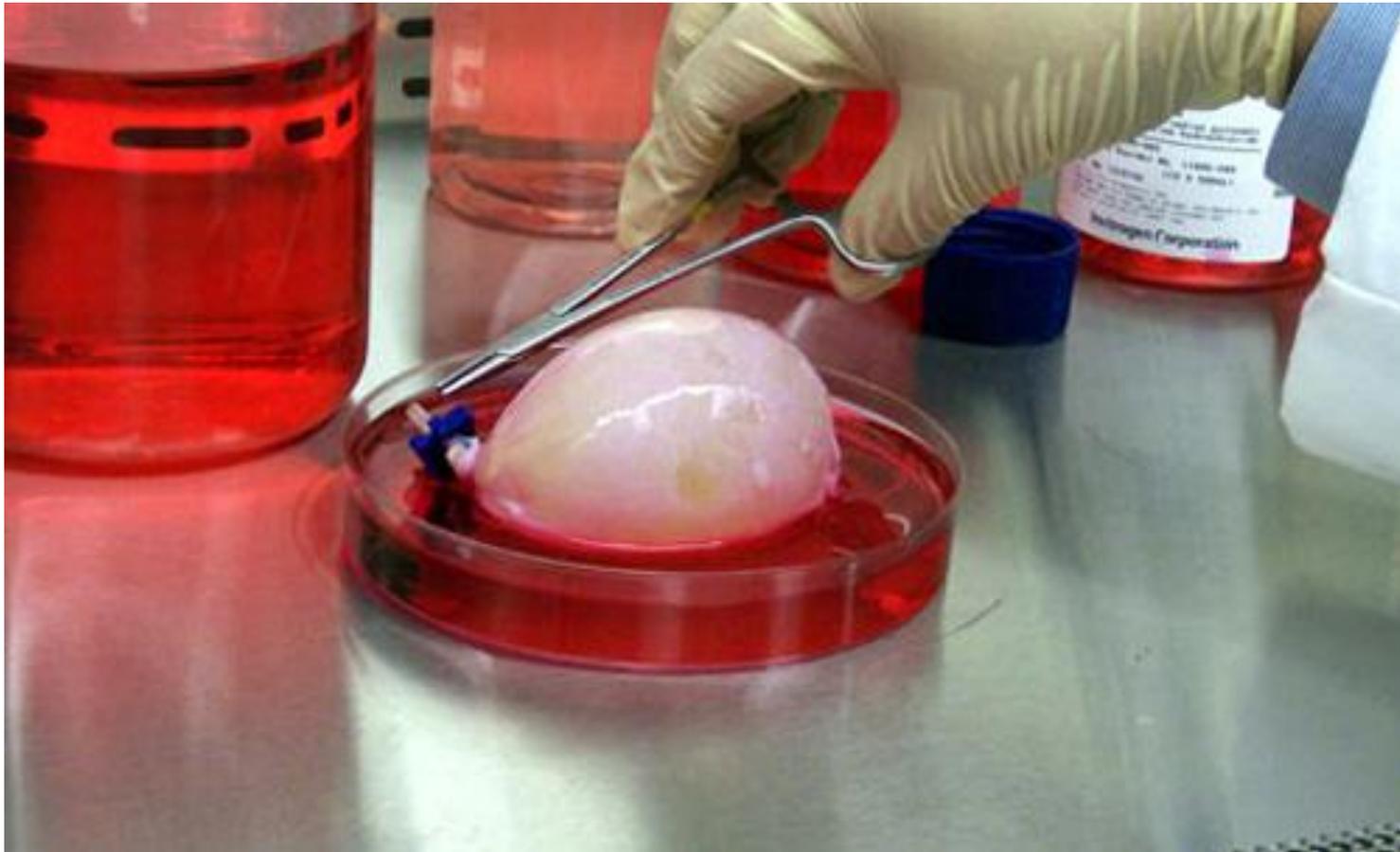
# Example: Gene Transfer Research

- Inserting multiple correct copies of mutated or missing genes for somatic cell gene correction
  - involves recombinant DNA by definition
  - Substantial oversight of animal and human studies
- Safety and risk reduction
  - uncertain and unknown harms to animal and human subjects
  - monitoring and long-term follow-up; late effects? reversibility?
  - risk of insertional mutagenesis
  - virus shedding in lab or clinic
  - risk of germline effects
- Standard first-in-human clinical trials issues
  - subject selection
  - harm-benefit balancing
  - informed consent, risk of therapeutic misconception

# Example: Organ & Tissue Regeneration

- Preclinical considerations:
  - bioprinting
  - bioreactors
  - scaffolding
  - regulatory complexities of combination products
- Standard first-in-human clinical trials issues
- Ethical complexities of surgical research
- Organ and tissue regeneration
  - endogenous
  - ex vivo
- Digit and limb regeneration
- Research/treatment/enhancement questions
- Uncertainty, monitoring, and long-term follow-up
- Questions about reversibility
- Production efficiencies: standardization, cost, access

# Growing a Bladder Ex Vivo

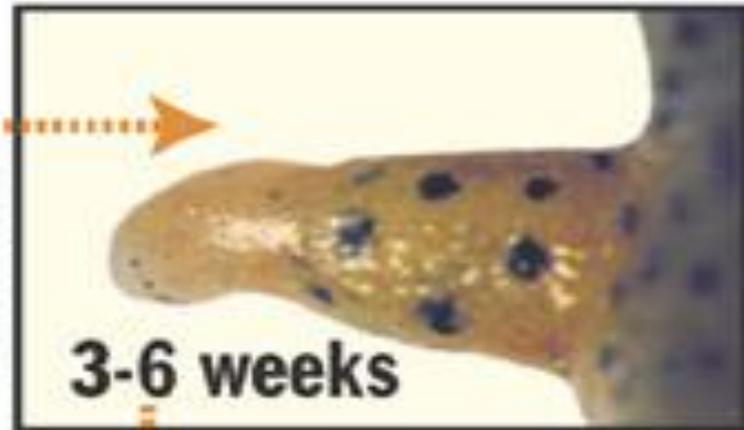


# Limb Regeneration

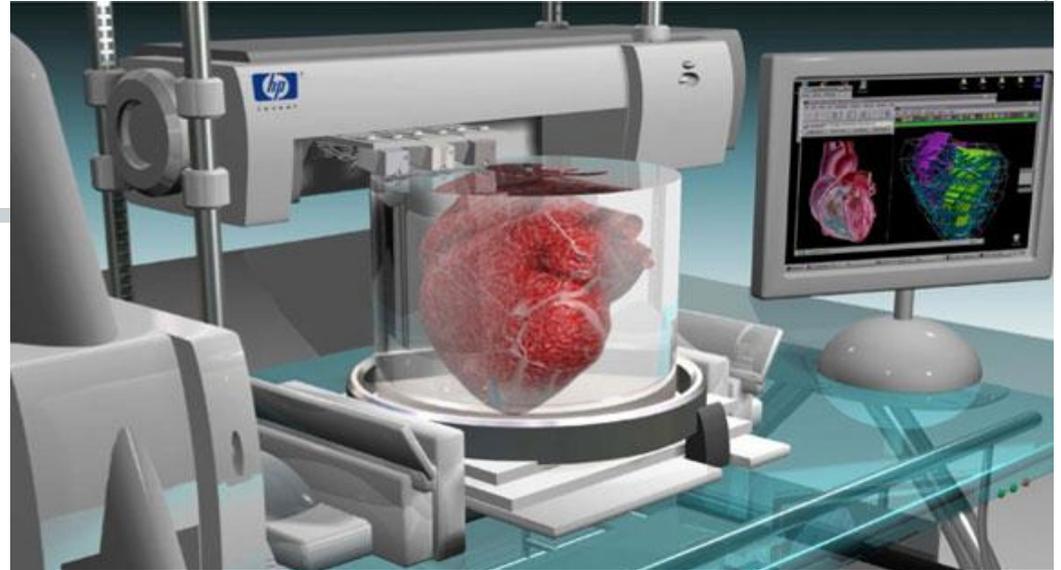
A newt can regenerate an entire limb within 7-10 weeks.



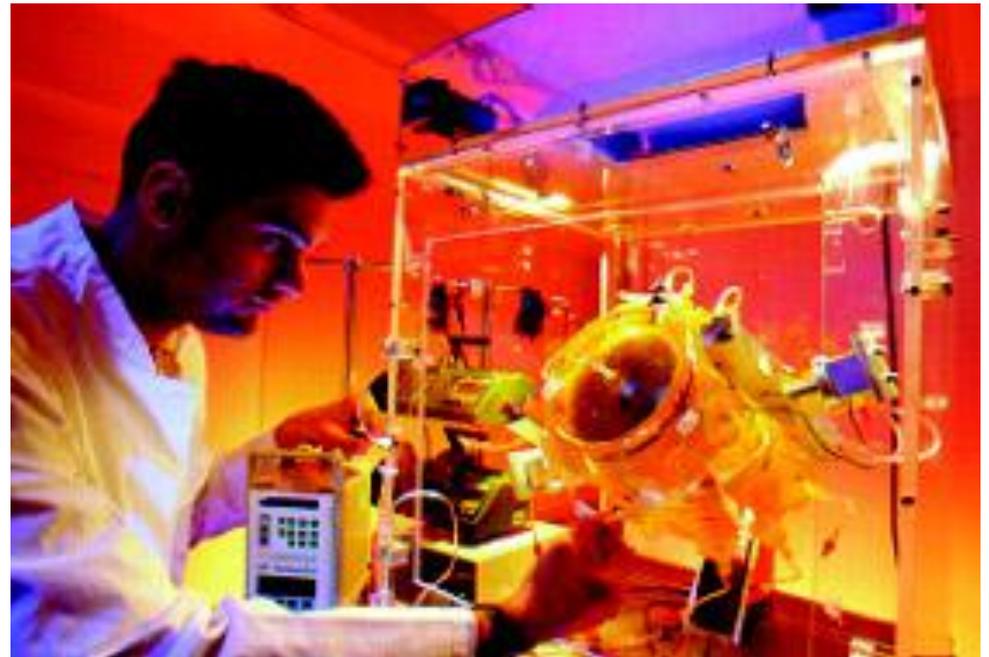
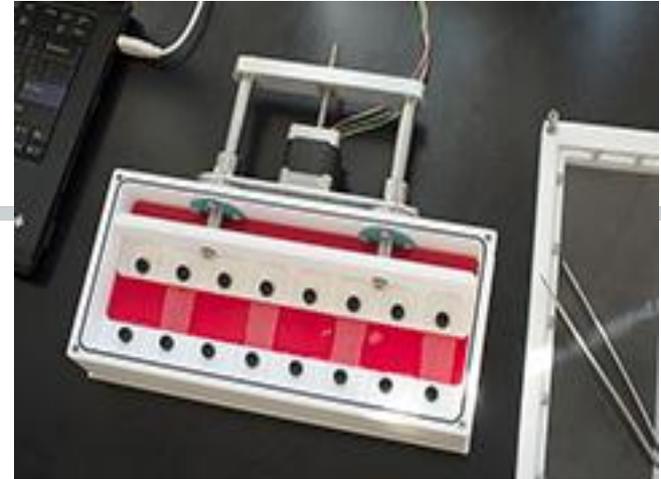
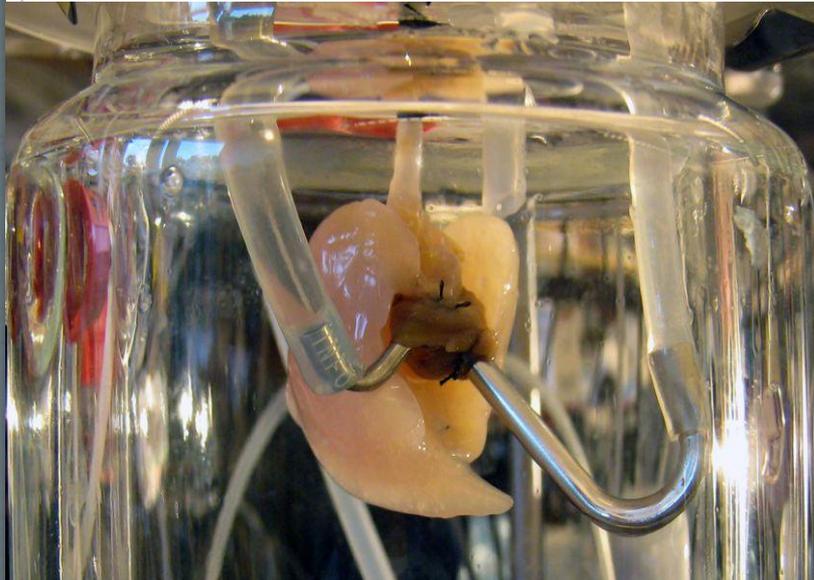
**Growth  
cycle**



# Bioprinting



# Bioreactors



# Moving from Bench to Bedside II

- Has enough preclinical information been collected so that the only reasonable way to learn more is to move to humans?
- Has enough been done to reduce the risks of harm to humans, and to maximize the likelihood that the intervention will ultimately show benefit in humans?
- Has the point of irreducible uncertainty been reached?
- Is the amount of irreducible uncertainty small enough that it is fair to subjects to ask them to become involved in the research?

# FIH Issues

- Goals of First-in-Human Trials:
  - Safety
  - Dosage information
  - Information needed to decide next research steps
  - Proof of concept
  - Preliminary data potentially signaling efficacy
- What does it mean to be a research subject?
  - Long-term Follow-Up
- What does “success” mean?
- Consequences of “failure”?

# Subject Selection I

- Which first subjects can be sufficiently protected from harm?
- Which first subjects can provide useful enough data to move forward?
- Very sick subjects may be at greater risk of harm, but may value chance of benefit highly
- Disease effects, intervention effects, and effects of prior treatment may be hard to disentangle in very sick subjects
- Healthier subjects may sometimes be too well to provide data needed to move to later-phase trials
- Which first subjects are most likely to benefit? (This is not a research question!)

# Subject Selection II

- **Who should be first**
  - when there is no effective treatment?
  - when standard treatment is imperfect?
  - when there is effective standard treatment?
  - when risks of harm are minor? moderate? great?
  - when uncertainty is great?
  - when the condition is life-threatening?
  - when the condition is less serious?
  - when in the disease course— late or early?
- **When should investigators return to preclinical studies**
  - to reduce risks of harm & uncertainty?
  - to increase likelihood of valuable data & ultimate benefit?

# Risks of Harm & Potential Benefits

- What risks of harm are *expected* or *conceivable*? Describe them:
  - *Nature, Magnitude* (severity, duration), *Likelihood*
  - Can they be minimized?
- Does available information & reasoning about potential benefit *from the line of research* (generalizable knowledge) support moving to humans?
- Does available information & reasoning support the expectation of *meaningful direct benefit* for patient-subjects *in this trial*?
- Describe potential direct benefit *if & when relevant*:
  - *Nature*
    - Clinical endpoint? Or surrogate endpoint?
  - *Magnitude*
    - Size (improvement? cure?), Duration( temporary? permanent?)
  - *Likelihood*

# The Therapeutic Misconception in FIH Research

- Use of patients as research subjects
  - When nothing else has worked
  - When earlier intervention will yield better data
- Surgery's ambiguous research role
- Imperfect communication by researchers and providers
  - gene “therapy,” cell “therapy,” regenerative “medicine”
  - “You qualify for this research because you have failed all standard treatments”
- Over-optimism, hope, desperation, and wishful thinking
  - affects patient-subjects, families, and the press
  - affects researchers, providers, oversight bodies, and funders too

# Informed Consent Guidance: FIH Study Purpose

- You were asked to be in this study to help the investigators learn more about the type of disease you have. The investigators will try to keep the risks of harm to you from being in the study as low as possible. They believe that being in the study will not keep you from getting any treatments you may need for your disease.
- This study will enroll people with your disease [CHOOSE WHICHEVER APPLIES]
  - Whose disease has been treated unsuccessfully by all standard means
  - Who will continue to receive standard treatment
  - Who can probably put off standard treatment during the study
  - Who can probably stop or change standard treatment during the study

# Questions for FIH Trial Policy & Practice

- Are we changing the goals of first-in-human trials?
  - safety vs. efficacy
  - development of treatment or enhancement
- Are we changing what it means to be a research subject?
- Can partial success be measured?
  - consider: bladder regeneration, “seeding” of solid organs (pancreas, kidney, heart), paraplegia, limb regeneration
- Justice: Improving access, increasing risk?
  - personalization or standardization?
- Innovation and “off-label” use
  - ubiquitous; correctable?
  - ISSCR and stem cell tourism

# FIH Biotechnology Research: Conclusions

- Gene transfer interventions and cell-based interventions share many characteristics.
- Regulatory and research ethics considerations are similar for both types of research interventions.
- Gene transfer investigators have shown that well-designed research, collaboration, and knowledge-sharing produces results that may be slow but are sure and steady.
- Similarly, ISSCR has produced important guidance for reasonable and thoughtful research and innovation involving cell-based interventions.
- Translational progress is urgently desired for gene- and cell-based interventions. Careful and deliberate translational practice is good ethics policy, whether the practice is labeled research, innovation, or treatment.

# Why Bank Stem Cells?

- For research and cell-based interventions
- Numerous viable cell lines needed
- Multipotent and pluripotent stem cell lines may be created from stem cells found in amniotic fluid, umbilical cord blood, and other sources without embryo destruction
- Stem cell banks could collect, store, and share enough cell lines to make good (not perfect) HLA matches with the vast majority of the inhabitants of a country or region
- Potentially easier and less expensive to use widely than individually matched induced pluripotent stem cell lines

# Henrietta Lacks

- Henrietta Lacks (August 20, 1920 – October 4, 1951) was the involuntary donor of cells from her cancerous tumor, which were cultured by Dr. George Otto Gey to create an immortal cell line for medical research, now known as the HeLa cell line.
- HeLa cells have contributed to some of the most important advances in medicine, including:
  - Polio vaccine, chemotherapy, cloning, gene mapping, *in vitro* fertilization, cancer research, and treatments in leukemia, influenza, hemophilia, Parkinson's disease, STDs, etc.



# Stem Cell Banking Is Biobanking

- The collection, storage, and sharing of stem cells in and through “biobanks” raises well-known ethical and policy issues
- Stakeholders:
  - the individuals who provide their stem cells for banking
  - the biobanks that collect and store them
  - the investigators who use them for many types of research
  - the patient-subjects who receive them in research studies or innovative interventions

# What Is A Biobank?

- **Any collection of biospecimens or genetic material**
  - with or without associated data
  - with or without identifying information
- **Retained for sharing and/or future uses**
- **May be by design**
  - biorepository designed for storage and sharing
  - IRB-approved scope, consent forms, oversight
- **May be accidental**
  - materials kept in laboratory freezer = accidental bank
  - casual sharing = accidental bank
- **You are a biobanker if you have:**
  - kept any specimens beyond clinical need or after the end of the study
  - used any specimens for purposes unrelated to the initial collection
  - shared any specimens with anyone else

# Stem Cell Banking & Cell-Based Interventions: Ethical Issues

- **Privacy & Confidentiality**
  - Large data sets combine genetic data with phenotypic data, and continually link new data
  - Data-sharing plans spread information widely
  - Need to safeguard sensitive information while enabling continuing data collection
- **Return of results and incidental findings**
  - May compromise confidentiality
  - May increase therapeutic misconception & confusion between research and treatment
- **Scope and Control of Future Uses**
  - Large data sets merge and research questions change over time
  - Changes in scope may change risks & affect willingness to continue research contribution
- **Information, Consent, Both, or Neither?**
  - What choices should specimen providers have?
  - Improve data security? improve risk disclosure? other?
- **Group Harms & Justice**

# Informing without Consent?

- Individuals deserve to know they may be contributing to research
- Public deserves to know value of research using stem cells and associated data
- Provenance of cells and cell lines should be recorded and tracked
- How should research information and results be disseminated?
- A “citizenship model” of research participation

# Approaches to Informed Consent for Research on Stored Biospecimens

- **Specific consent:**

- Research participants are recontacted and asked to consent for each new use of their specimen or information that is outside the scope of the original consent.

- **Tiered consent:**

- At the time samples are collected, research participants are presented with a menu of options from which to choose, e.g., general permission for future use, consent only for future uses related to the original study topic, consent for future uses unrelated to the original study topic, and requiring investigators to obtain specific consent for any future use that differs from the original study.

- **General permission:**

- At the time samples are collected, research participants are asked to permit all future uses that a qualified ethical review board determines to be scientifically meritorious and ethically defensible.

- **Presumed consent:**

- At the time samples are collected, research participants are informed that their specimens will be used in future research unless they expressly deny permission.

--Mello MM & Wolf LE: The Havasupai Indian Tribe Case --

# A Citizenship Model for Biobanking & Research

- **Protection model**

- analogy to patients
- focus on rights & limiting power
- limited consent

- **Utility model**

- analogy to consumers
- focus on data security & public health
- blanket consent

- **Citizenship model**

- agency, awareness, democratic engagement
- focus on increasing science literacy, database transparency
- broad consent with opt-out mechanism

- *--Vilhjalmur Arnason, University of Iceland*

# Returning Results & Incidental Findings

- **Can confidentiality be preserved when re-identification is increasingly possible?**
- **Can confidentiality be preserved when re-identification is increasingly wanted?**
- **Recontact if medically significant information is found?**
  - what is significant – and who decides?
  - privacy tradeoffs
  - whose duty is this?
    - who has the knowledge to determine medical significance?
    - contact information and knowledge may be widely separated
  - information and oversight infrastructure could be extensive (and expensive)

# Interpretation & Dissemination of Results

- Group interests and group harms
- Dissemination & description of research results:
  - Race/ethnicity categories are inadequate or pernicious
  - Reporting and dissemination can stigmatize and foster discrimination against groups, even when individuals are not identified
    - individuals with family histories of stigmatized conditions
    - racial or ethnic minorities
  - Duties of investigators, sponsors, institutions to communicate with public about meaning (and limits) of stem cell science

# The Therapeutic Misconception in Stem Cell Banking & Biospecimen Research

- **Causes:**
  - Return of results & incidental findings controversy
  - Confusion about stem cell types
  - Stem cell tourism
  - Marketing of umbilical cord & AFS cell banking
- **Cures:**
  - Information & education
  - Researcher responsibility
  - Limits of knowledge & meaning of research
  - “Science citizenship”

# What is the Role of Oversight Bodies?

- Interpret and apply regulations, policies, and guidelines reasonably
- Examine both design and ethics
- Look for value, validity and fairness
- Assess and balance risks of harm and potential benefits carefully
- Consider vulnerability and its implications
- Ensure that publicity, recruitment, and advertising minimize science hype and the therapeutic misconception

# What is the Researcher's Role?

- **Education:**
  - Sponsors and oversight bodies
  - Media, advocates, and public
  - Patient-subjects
- **Study Design & Conduct:**
  - Minimize risks of harm
  - Make only fair offers of participation
  - Avoid science “hype”
  - Transparency, collaboration, and data-sharing promote scientific progress
- **Ethical Challenges are Shared Opportunities**

# More Justice for All?

- **Stem Cell Banking**
  - To be scientifically useful, stem cell banks must collect and share cells from many sources
  - To be clinically useful, stem cell banks must have good matches for most people
  - Public, coordinated, and well-managed stem cell banks require infrastructure, upkeep, and good policies, procedures, and practices
- **Pharmaceutical Biotechnology & Organoid Testing**
  - Faster, less costly drug development?
  - Better use of animal subjects?
  - Better use of human subjects?
- **Regenerative Interventions with Genes, Stem Cells, & Organs**
  - Can standardized production lower costs and increase access?
  - Will less invasive interventions change prevention and treatment?

# Conclusions & Recommendations

- **Potential utility of research using genes, stem cells, & regenerative technologies is great**
- **Translational basic & clinical biotechnology research can benefit both public health & the public interest**
- **Science changes rapidly; ethics must stay close, to help keep policy responsive**
- **More than minimal oversight of biobanking, data sharing & new uses of biotechnology is needed**
- **Awareness of data sensitivity, for both individuals & groups, can increase both researcher understanding & public trust**
- **Informing & involving the public can increase science literacy without constraining researchers**

# Closing Thoughts to Open Discussion

- What is worth doing?
  - --a policy discussion to which researchers can make valuable contributions
- In the meantime: Whatever is worth doing is worth doing well.
- Doing research well means:
  - thoughtful compliance
  - active engagement with perennial questions
  - nimble identification of new issues
  - using your moral agency at all times in all your research