Biosafety Committees and Biological Materials Oversight: Past, Present and Future for Clinical Research

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Overview

- Setting the Stage
- Biosafety Past
- Biosafety Present
- Biosafety Future: Gene Therapy
Number of Human Gene Therapy Trials

<table>
<thead>
<tr>
<th>Year</th>
<th>Phase I</th>
<th>Phase II</th>
<th>Phase III</th>
<th>Total</th>
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<td>2011</td>
<td>44</td>
<td>35</td>
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<td>2012</td>
<td>49</td>
<td>51</td>
<td>6</td>
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<td>2013</td>
<td>50</td>
<td>26</td>
<td>5</td>
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<tr>
<td>2014</td>
<td>80</td>
<td>57</td>
<td>6</td>
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<tr>
<td>2015</td>
<td>~12</td>
<td>~200+</td>
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Indications Addressed by Gene Therapy

- Cancer diseases 64.3% (n=1223)
- Monogenic diseases 8.6% (n=167)
- Cardiovascular diseases 8.3% (n=158)
- Infectious diseases 8% (n=153)
- Neurological diseases 1.9% (n=36)
- Ocular diseases 1.5% (n=28)
- Inflammatory diseases 0.7% (n=13)
- Other diseases 1.4% (n=27)
- Gene marking 2.6% (n=50)
- Healthy volunteers 2.5% (n=43)
Recent Media - HBO’s “Killing Cancer”

60 Minutes: Killing Cancer (03-29-2015)
What are Biological Materials?

- **Biological Materials or Biohazards** are infectious agents or hazardous biological materials that present a risk or potential risk to the health of humans, animals or the environment.
  - CDC BMBL 5th ed.
- **Examples:**
  - Whole or "Wild-type" Microorganisms
  - Biological toxins
  - Blood or other potentially infectious materials
  - Recombinant or synthetic DNA resulting in organisms

Recombinant and Synthetic Nucleic Acids

- "Molecules that are constructed outside living cells by joining natural or synthetic DNA segments to DNA molecules that can replicate in a living cell, or molecules that result from the replication of those described above."
  - National Institutes of Health, 2013
- NIH funded research involving recombinant DNA (and in March, 2013, recombinant or synthetic nucleic acids, rsNA) requires a risk assessment by a local Institutional Biosafety Committee.
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History of Recombinant DNA Technology and Oversight

- Dr. Kornberg, 1968 U.S. Senate Subcommittee
  - Vettel, 2006

- Moratorium on rDNA experimentation after Paul Berg generated first genetically modified replication competent E. coli in 1973
  - Jackson, Symons, and Berg, 1972

- Gordon Conference Session request to National Academy of Sciences
  - Singer and Sol, 1973

- Assessment of recombinant DNA risks to be handled at Asilomar State Beach
  - Berg, Baltimore et al., 1974

Asilomar Conference

- The primary goal of the meeting was whether to lift the recombinant DNA moratorium and under what set of prescribed conditions.
  - Berg, Baltimore et al., 1975

- While little data beyond Berg’s experiment existed at the time, despite opposition, the Conference ended with the understanding rDNA research should proceed but under strict guidelines.
  - Berg and Singer, 1995

- 1976, NIH Guidelines for Research Involving Recombinant DNA Molecules
  - Frequent revisions through 2013
The Role of the IBC & Risk Assessment

- Institutional Biosafety Committee (IBC)
  - Capability to assess the safety of rDNA research
  - Be able to identify any potential risk to public health or the environment (NIH Guidelines, 2013)

- Risk Assessment
  - Identify hazardous characteristics
  - Evaluate exposure and consequences
  - Determination BSL, work practices, safety equipment, and facility design to prevent exposure (CDC BMBL 5th ed., 2010)

United States Regulatory Oversight of Biological Materials in Research

- NIH
  - rDNA
  - Dual Use Research of Concern
  - Gene Therapy

- CDC/USDA
  - Select Agent Program
  - Importation

- Federal OSHA
  - Bloodborne Pathogens
  - General Duty Clause

- Others Peripherally Associated
Figure 2. Biosafety & Biocontainment Oversight (USDA Federal Task Force, 2009)

Biosafety Levels 1 & 2

BSL-1

BSL-2
Feature Presentation

- Star-studded cast:
  - Morgan Freeman
  - Dustin Hoffman
  - Rene Russo
  - Kevin Spacey
  - Patrick Dempsey
  - Cuba Gooding Jr.
  - Donald Sutherland (underrated)
  - http://www.youtube.com/watch?v=1di7g4Hm1s

Biosafety Present

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2013 Survey of IBCs

- Survey:
  - Specific Aim #1: To investigate United States life sciences regulation for research involving biological materials to assess the adequacy of biosafety and biosecurity oversight.
  - Specific Aim #2: To evaluate IBCs charged to oversee research with biological materials to determine whether additional guidance and regulation is needed to protect staff, biological materials, and public health.
Survey Methodology

- Cross-Sectional Survey of NIH-OBA Registered IBCs
  - FOIA #40395 (August, 2012), 857
  - FOIA #41293 (May, 2013), 866
  - FOIA #42013 (December, 2013), 868
- Survey Design
  - 22 Questions
    - Institutional Type and Constituency of the IBC
    - Biological Materials Review
    - Protocol Review Determinations

NIH-OBA Registered IBCs

- 1976-2000: 12 IBCs added per year
- 2001-2013: 43 IBCs added per year

IBC Protocols By Year

- IBC Protocols by Year
  - from 22 Institutions
  - y = 51.736x - 369.59
  - R² = 0.7914
Institutional Case Study

Observed Trends in Biological Materials Oversight and IBCs

- Research involving biological materials has increased over time
- Protocol review data
- Expansion of IBC review beyond NIH Guidelines and Select Agent requirements
- Institutional support minimal beyond staffing

Biosafety Future: Gene Therapy
Gene Therapy

- Involves delivery of therapeutic genes into the human body to correct disease conditions created by faulty genes
- Two primary strategies
  - *Ex vivo* gene therapy
  - *In vivo* gene therapy

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**Ex vivo** Gene Therapy

- Cells from diseased person are removed
- Cells are modified in the lab
- Modified cells are reintroduced to the patient
- Generally, more effective than *in vivo*

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**In vivo** Gene Therapy

- Introduces genes directly into tissues or organs without removing body cells
- Challenge is delivering only to intended tissues
- Viruses, bacteria, and plasmids act as vectors for gene delivery
  - some vectors injected directly into tissue
Delivery of Therapeutic Genes

- Therapeutic genes often called “payload”
- May require long-term expression of corrective gene
- Others require rapid expression for short periods of times

Viral Vectors

- Viral vectors use viral genome to carry therapeutic gene(s) and to infect human body cells
  - Adenovirus (common cold)
  - Adeno-Associated Virus
  - Retrovirus (HIV)
  - Herpes Simplex Virus (cold sores)
  - Vaccinia Virus
- Viruses must be engineered so that they can neither produce disease nor spread beyond targeted organs and tissues

Vector Transfection

- Targeted gene therapy may result since some viruses infect certain body cells
  - Adenoviruses infect both dividing and non-dividing cells effectively
  - Adeno-Associated viruses do not cause illness in humans, can infect a wide variety of cells, & integrate 95% of time in same location
  - Retroviruses are of interest because they insert DNA into the genome of host where it remains permanently (integration), but often, randomly
  - Herpes simplex viruses (HSV-1) strain primarily affects central nervous system (CNS)
    - May help develop treatments for Alzheimer’s, Parkinson’s, etc.
  - Others include, vaccinia, measles, MMLV
- Although viral vectors may help, most human cells are not easily transfected
Unresolved Questions

- Can gene expression be controlled in the patient?
- What happens if a normal gene is overexpressed?
- How long will the therapy last?
- What is the best vector to use?
- What is the minimum number of cells needed to infect to achieve success?
- Regulatory oversight flux?

HGT Biosafety Considerations

- Consider the vector (replication competent, incompetent, attenuations)
- Consider the transgene (oncogene, proto-oncogene, immune stimulator)
- Consider mode of delivery (injection, cath lab)
- Comprehension of risk by populations traditionally not serviced by biosafety professionals
- Infection Control vs. Biosafety
  - Physicians/Clinicians
  - Pharmacists
  - Nursing Staff

Gene Therapy Regulatory Issues

- NIH
  - NIH Guidelines and IBC review apply only if Sponsor or entity receives NIH funding for rsNA
  - Take home message for clinical entities:
    - Ask the Sponsor if the product is a recombinant
    - Find out if you (the entity) or the Sponsor receives $1 of NIH funding which would then trigger IBC review.
Curing Genetic Disease

- More than 3,000 human genetic diseases are caused by single gene mutations.
- These are strong candidates for treatment by gene therapy:
  - Cystic Fibrosis
  - Huntington’s disease
  - Tay-Sachs
  - Hemophilia
  - Sickle cell disease
  - Phenylketonuria

First Human Gene Therapy

- Ashanti de Silva (4 years old) with severe combined immunodeficiency (SCID) treated in 1990 at NIH in Maryland.
- Lacked functioning immune system because of a defect in gene called adenosine deaminase (ADA), which is involved in metabolism of dATP (nucleotide precursor used for DNA synthesis).
- Accumulations of dATP are toxic to T cells.
- Normal gene cloned into vector introduced into nonpathogenic retrovirus.

First Human Gene Therapy Success

- *Ex vivo* approach used.
- T cells isolated from blood.
- Required multiple treatments.
- Within a few months, T cell numbers increased.
- After 2 years, ADA enzyme activity was high.
- She is currently enjoying a healthy life.
Success of Gene Therapy

- Success in Rhys Evans, a child born with X-linked Severe Combined Immunodeficiency Syndrome (SCIDS – aka bubble boy), in 2002.
- The team took stem cells that gave rise to immune cells from the boy’s bone marrow.
- They used a modified form of a retrovirus as a vector.
- The engineered stem cells were then returned to the boy’s body.
- Now, he has normal levels of T cells.

Risks of Gene Therapy

- Discussions of safety intensified when 18-year old Jesse Gelsinger died during a clinical trial at the University of Pennsylvania in 1999.
- Complications related to adenovirus that was used.
- Ornithine transcarbamylase deficiency (affects ability to break down dietary amino acids).
- 1st person to die of complications resulting from gene therapy.
Overview

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Thank You – Questions?