Introduction to Recombinant DNA (Genetic Engineering) and Institutional Biosafety Committees (IBC)

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Biological Safety Officer
Schulman IRB
About Schulman IRB

- Established in 1983
- Superior audit history with FDA—six consecutive audits with no findings
- 21 CFR Part 11 compliant electronic systems
- Compliant with FDA, OHRP and Health Canada requirements
- Full Board meetings **five days a week**
- Dedicated **daily expedited review** of qualifying minimal risk protocols
About Schulman IRB

- Review outcome provided within **one business day** of new study review
- **One business day** turnaround for complete new site submissions
- Dedicated streamlined processes tailored to **Phase I timelines**
- **Expert oncology IRB members** experienced in all phases of oncology research
  - National IRB for **Cancer Breakthroughs 2020** initiative
- Customized services for **institutions**
- **Experienced primary points of contact** for sponsors, CROs, institutions and sites
About Schulman IRB

Clinical Quality Assurance (CQA) and Human Research Protection (HRP) consulting services provided by:

www.provisionrcs.com  www.falconnest.com
About Schulman IRB

- Coming this Spring!
About Today’s Presenter

Daniel Eisenman, PhD, RBP, SM(NRCM), CBSP
Biosafety Officer, Schulman IRB

- PhD in molecular biology and immunology
- Certified Biological Safety Professional, American Biological Safety Association
- Specialist Microbiologist in Biological Safety, National Registry of Certified Microbiologists, American Society for Microbiology
- A decade of experience in biosafety program management
- Experienced educator and presenter in the fields of biological safety, genetic engineering, immunology and infectious diseases
- Previously ran the Institutional Biosafety Committee program at UNC Chapel Hill
  - Also served as Alternate Responsible Official for select agents and Institutional Contact for Dual Use Research
I. What is an IBC? Why do we need an IBC?

II. Introduction to Recombinant DNA

III. Recombinant DNA in Clinical Trials

IV. Oversight of Recombinant DNA Research

V. Guidance for Submitting Applications for IBC Review
I. What Is an IBC? Why Do We Need an IBC?
What Are Recombinant DNA and IBCs?

Recombinant DNA: Engineered genetic material. The product of genetic engineering.

The National Institutes of Health (NIH) provides oversight of federally funded research involving recombinant DNA under NIH Guidelines.

Research involving recombinant DNA that is performed with federal funds or at sites that receive NIH funding must be reviewed by an Institutional Biosafety Committee (IBC).
Abbreviated as “NIH Guidelines”

Framework created at a 1976 Asilomar academic conference by researchers in response to public fears over:
- gene therapy
- creation of “super bugs”

The guidelines were later adopted and implemented by the NIH.

Most recently revised in April 2016.

The guidelines require institutions receiving NIH funds to self-police through IBCs that report to the NIH.
Both committees focus on risk.

IBC focuses on risks posed by recombinant DNA (genetically modified material) to study personnel, the community and the environment.

- At least 5 members
- Collectively possess the expertise to assess the risks for the proposed research
- Local component: Two community members for each site who are not associated with the institution / site
NIH Guidelines: Mandating Risk Assessment

- Ensure adequate risk assessment for the proposed research

- Containment levels per NIH Guidelines, elaborated on in BMBL

- Adequacy of facilities, equipment, PPE, SOPs, training and waste disposal practices

- Inspection

- Post approval monitoring
  - Safety reports
  - Incident reports
Risk Assessment for Human Gene Transfer

Predictable Adverse Events
- Mutagenicity
- Carcinogenicity
- Teratogenicity
- Toxicity

Risk to Public Health / Environment

Exposure to Health Care Workers

Risk Assessment
Predictable Adverse Events
Mutagenicity  Carcinogenicity
Teratogenicity  Toxicity

Risk to Public Health / Environment

Exposure to Health Care Workers

Horizontal Transmission
Transmission from person to person
Biodistribution
Route of transmission (entry / exit)
Participant training / safety precautions

Risk Assessment for Human Gene Transfer
Risk Assessment for Human Gene Transfer

Predictable Adverse Events
Mutagenicity  Carcinogenicity
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Risk to Public Health / Environment

Exposure to Health Care Workers

Risk Assessment

Horizontal Transmission
Transmission from person to person
Biodistribution
Route of transmission (entry / exit)
Participant training / safety precautions

Vertical Transmission
Infection of germline cells (sperm / ovaries)
Transmission to offspring
IBC VS. IRB: Different Focus, Similar Processes

Protocol Submission → Initial Review → Distribute to IBC

Approval Letters ← Minutes (Subject to FOIA) ← Meeting

Continuing Review
Overview of Oversight

- NIH Guidelines, Annual IBC Registration Site Inspection Program
- BMBL, Biosafety Guidelines for Infectious Agents
- Workplace Safety
- Infectious Waste Disposal
- Watchdog Groups
- Political Activists
- Freedom of Information Act (FOIA)
- IBC Meeting Minutes
II. Introduction to Recombinant DNA
Humans are made of cells. When cells malfunction, disease can result.
If a cell is a factory....

DNA
Blueprints to all proteins made by the cell

Proteins
Perform cellular functions or “work”
Gene: a piece of DNA that contains the information necessary to create a protein product with a particular function.
Manipulating DNA allows us to create useful drugs and potential therapies.

Before the development of modern recombinant DNA technology:
- Not human
- Not pure
- Potentially contaminated with animal pathogens

Source: Smithsonian Institute http://americanhistory.si.edu/collections/search/object/nmah_1000969
Paraphrasing NIH’s Definition of Recombinant DNA
Molecules that are constructed outside living cells by joining natural or synthetic genetic material that can replicate in a living cell.

**Vector**
Vehicle for delivering DNA to cells

**Insert:** Piece of DNA that codes for the desired protein product

**Recombinant DNA**
Recombinant DNA Replicates Once Inside Living Organisms

New copies of the Recombinant DNA from the Parent Cell are inherited by the Bacterial Clones’ “Daughter Cells”

Each cell containing rDNA can make the protein coded by the insert
Manipulating DNA Allows Us To Create Therapeutic Substances.

Recombinant DNA

Insulin Producing Bacteria
What Are Synthetic Nucleic Acids?

ATCGAATT

Chemically Synthesized

Bind to genetic material or reproduce

Common uses include genome editing technology in viral vectors

Disease Causing Mutation
III. Recombinant DNA in Clinical Trials
To date, over 2,400* clinical trials have been initiated involving human gene transfer (HGT). HGT studies typically require IRB and IBC approval as well as registration with the NIH (based on NIH funding to study, site or institution).

- Human gene transfer involves delivering genetic material to humans with the goal of compensating for genetic mutations, conferring the capability to produce potentially therapeutic substances, or eliciting immune responses to fight disease.

Recombinant DNA has been utilized in clinical trials for various diseases.

Approximately 2/3 of HGT studies involve oncology research*.


Source: www.clinicaltrials.gov
Commonly utilized strategies in oncology research require delivery of recombinant DNA to study subjects.

Reprogrammed immune cells

Cancer vaccines

Oncolytics: Reprogramming viruses to kill cancer

Sources: istock.com/somersault1824; istock.com/Rtimages; istock.com/Rost-9D; istock.com/ttsz
Blood has a mixed population of immune cells called T cells, with the ability to kill cells that may be infected, foreign transplants or cancer.

Each color represents a T cell with a different target to kill.

Genetic reprogramming allows the T cells to pursue the same target.

Returned to Donor

Sources: istock.com/somersault18:24; istock.com/Jull1491
Cancer Vaccines

Cell-Based Cancer Vaccine

1. Cancer cells are removed from patient
2. Irradiation of cancer cells
3. Genetic modification of cancer cells
4. Patient receives modified cancer cells
5. Enhanced immune response

Viral Cancer Vaccines

(Adénovirus)

Source: istock.com/ttsz
Oncolytics: Reprogrammed Viruses to Kill Cancer

Oncolytics: Reprogrammed Viruses to Kill Cancer

Herpes Virus → ! → Melanoma

Imlygic, Amgen

Sources: istock.com/ttsz; istock.com/somersault18:24
Looking to Nature for Better DNA Delivery Vehicles

Recombinant DNA
Viral Life Cycle

- Attachment
- Infection (transmission of genetic material)
- Assembly of Viral Particles
- Production of Viral Components
- Release of Viral Particles (Cell Death)

Sources: istock.com/Rtimages; istock.com/Rost-9D
Viral Life Cycle

- DNA loaded syringe
- Attachment
- Infection (transmission of genetic material)
Viral Vectors: A Genetic “Syringe”

Virus Vectors easily introduce genetic material into target cells during infection. Disease-causing genes are removed and replaced with genes of interest.

Gene therapy using an adenovirus vector

Sources: istock.com/Btimages; istock.com/Post-9D
Viruses Are Diverse!

Several animal virus families possessing varying properties, uses and risks.

Diverse risks lead to diverse possibilities for toxicities.
Retroviruses

Integration into host genome

Host DNA

Host Cell

Retrovirus

Retrovirus Genes
Severe Combined Immunodeficiency (SCID): The Boy in the Bubble

David Vetter required an isolator to prevent exposure to microorganisms until a bone marrow transplant could be performed.

Bone Marrow

White Blood (Immune) Cell

Mutated Gene

Immune Response Against Infection

Source: Baylor College of Medicine Archives
Rhys Evans became the first SCID patient to receive genetically modified bone marrow. SCID patient bone marrow was harvested and normal copies of the mutated gene were delivered via a retrovirus. Donors received autologous grafts. (9 of 11) Participants developed fully functional immune systems.

Unintended Consequences?
- 3 children developed leukemia
- Trial suspended
- Other trials found similar SAE

Corrective Action
- Vectors redesigned for safety
- Interventionary contingencies
- Informed consent modified
- Long term follow up for delayed adverse events

Serious Adverse Events and Lessons Learned

Strimvelis (GSK) approved for use in Europe to treat ADA-SCID. Only the second gene therapy approved in Europe.
Serious Adverse Events and Lessons Learned

“Gene Therapy Death Prompts Review of Adenovirus Vector”

Jesse Gelsinger (1981-1999)

- Was not fully informed of potential hazards
- Died as a direct result of an acute immune response to high dose adenovirus based viral vector injected into the liver
- Investigator did not disclose conflict of interest
- Halted clinical trials at the University of Pennsylvania
- Altered guidance for consent language and safety monitoring
Pox Viruses: The Higher End of Risk for Viral Vectors in Clinical Trials

- NOT related to chicken pox, which is a herpes virus
- Several species and strains with various degrees of risk
  - Vaccinia (smallpox vaccine)

- Potent stimulators of immune responses
  - Used in vaccination studies
- Usually replication competent (capable of spread)
  - Transmitted by needle sticks, contact with broken skin or mucus membranes

Source: By Dr Graham Beards at en.wikipedia, CC BY-SA 4.0, https://commons.wikimedia.org/w/index.php?curid=36392524
Pox Viruses: The Higher End of Risk for Viral Vectors in Clinical Trials

Shed from Inoculation Site
Protect with bandage
Dispose of properly
Avoid contact with others

At increased risk: Immune compromised individuals, children, elderly, pregnant women and people with conditions affecting the integrity of the skin.

Based on the type of pox virus and procedures, vaccination of study personnel may be recommended.

Vaccine Recommendations of the Advisory Committee on Immunization Practices (ACIP)

FIGURE 3. Vaccine site major reaction and progression after primary smallpox vaccination or revaccination after a prolonged period between vaccinations, using multiple-puncture technique

Source: CDC
Post Vaccination Transmission of Vaccinia


IV. Oversight of Recombinant DNA Research
Structure of Oversight for Recombinant DNA Research

NIH OSP
NIH Guidelines

RAC
National perspective

IBC
Local oversight
Recombinant DNA Advisory Committee (RAC)

Provides advice to the NIH Director on the conduct and oversight of research involving recombinant DNA

Comprised of up to 21 voting members with expertise in:
- Recombinant DNA and human gene transfer
- Public health
- Laboratory safety
- Occupational safety and health
- Protection of human subjects
- Environmental protection
- Etc.

Meets quarterly
Materials must be submitted 8 weeks in advance
PI must present study to the RAC
Original Registration Process for Clinical Trials Involving Human Gene Transfer

1. Investigator
   - NIH RAC

2. Local IBC
   - Approval

3. Local IRB
   - Approval

   - NIH OSP
Adding Sites After RAC Review

1. Local IBC
   - Approval

2. Local IRB
   - Approval

   NIH OSP

Investigator
Criteria for determining whether to recommend RAC review

i. The protocol uses a new vector, genetic material, or delivery methodology that represents a first-in-human experience, thus presenting an unknown risk;

ii. The protocol relies on preclinical safety data that were obtained using a new preclinical model system of unknown and unconfirmed value;

OR

iii. The proposed vector, gene construct, or method of delivery is associated with possible toxicities that are not widely known and that may render it difficult for oversight bodies involved in the review at an initial site(s) to evaluate the protocol rigorously.
New Registration Process for Phase I Clinical Trials at the Initial Study Site (April 2016)
Adding Sites After the Initial Site

1. Local IBC Approval
2. Local IRB Approval
   Investigator
   NIH OSP
New Registration Process for Phase I Clinical Trials at the Initial Study Site (April 2016)

Added burden on the IBC and IRB at the initial study site:

• Must make the initial determination of the level of risk and novelty of the science without input from the NIH RAC

• Pre-review before the NIH registration process

• Only the IBC and IRB at the initial study site can determine whether to recommend RAC review. Subsequent sites cannot make or change the determination.

If RAC Review is Required…

Meets quarterly
Materials must be submitted 8 weeks in advance
PI must present study to the RAC
V. Guidance for Submitting Applications for IBC Review
How Do I Know If I Might Need IBC Review?

NIH funded research

OR

Institutions / sites receiving NIH Funds

<table>
<thead>
<tr>
<th>Keywords Indicating IBC Review May Be Required</th>
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<tbody>
<tr>
<td>Genetically modified</td>
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<tr>
<td>Recombinant DNA (rDNA)</td>
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<tr>
<td>Gene editing</td>
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<tr>
<td>Viral vector</td>
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<tr>
<td>Plasmid</td>
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<td>Institutional biosafety committee (IBC)</td>
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Guidance for Submitting Applications for IBC Review

Be proactive in contacting the site’s IBC / Biosafety office.

Consider utilizing a central IRB with an associated IBC service if your site lacks an IBC or the requisite expertise.

Become familiar with the site’s existing policies / procedures for:

- IBC review
- Handling infectious agents
- Biohazardous waste disposal

The site’s PI will be ultimately responsible for all research activities.

- Can delegate tasks (NOT responsibility) to a study coordinator / Sub Investigator
Guidance for Preparing Site Personnel

Identify key study personnel at the site and prepare them for their duties.

Roles involving the recombinant DNA
- Shipping / receiving
- Storage
- Dispensing
- Transport
- Agent administration
- Waste disposal

Review / prepare training and SOPs

Review the Exposure Control Plan and infectious waste disposal procedures

Walk through the steps in using the agent to ensure potential safety issues are identified and addressed.
Guidance for Preparing Site Personnel

Potential Issues to Identify During Walk-Throughs

**Limiting access**: How many people have access to the areas where the recombinant DNA is stored or utilized?

*When the agent is manipulated, access should be restricted to minimize the number of people that could be exposed.*

**Transport**: Will the recombinant material need to be transported from the areas of storage, dispensing, use and disposal?

*Utilize sealed, leakproof and labeled secondary transport containers.*

**Spills and work surface decontamination**: Biologicals require disinfection with a specified contact time rather than a rinse with soap and water. Review spill response procedures.

**Limiting access #2**: How do you mitigate the risk of exposure from spills to other patients or family in shared infusion suites?

*When the agent is manipulated, access should be restricted to minimize the number of people that could be exposed.*
Contact Information

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Introduction to Recombinant DNA (Genetic Engineering) and Institutional Biosafety Committees (IBC)

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