Regulatory Issues in Gene Therapy

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Gene Transfer Techniques

- Plasmid DNA with liposomes or electroporation *in vitro*.
- Naked DNA injection or gene gun *in vivo*.
- Recombinant viral vectors.
Life Cycle of Replicative Viruses

Integrate

Use the cellular machinery to produce progeny virions

Nucleus
Viral Vector

Genes that allow the virus to generate progeny virions

Genes that code for the viral envelope

Our favorite new gene
Life Cycle of Replication-Deficient Viral Vectors

Integrate

Nucleus

Use the cellular machinery to produce transgene products
Potential Applications

• Single gene diseases:
  – Hemophilia, Thalassemia
  – Immuno-deficiencies

• Cancer:
  – Suicide genes
  – Correction of gene mutations
  – Antisense
  – Genetic immunization

• Infectious diseases:
  – HIV
  – Malaria

• Cardiovascular diseases:
  – Anti-Angiogenesis

• Endocrinology:
  – Diabetes

• Neurology:
  – Altzheimer

• Psychiatry:
  – Maniac-depressive D
History of Regulatory Issues for Human Gene Therapy Trials

1974
RAC
Guidelines

1976
RAC

1980
1st Gene Therapy Trial (unapproved)

1988
1st Gene Therapy Trial (approved)

1999
1st Gene Therapy Death

2002
1st Gene Therapy Cancer
Major Problems with the U Penn OTC Deficiency Trial (Jesse Gelsinger case)

- Violation of protocol inclusion criteria.
- Lack of reporting of prior SAE and AE in study subjects.
- Lack of reporting of AE in preclinical primate studies.
- Lack of adequate viral banking techniques.
- Lack of full characterization of vector lot administered to human subjects.
- Lack of adequate monitoring and quality control measures.
Gene Therapy Oversight: Federal Regulatory Agencies

- FDA: Food and Drug Administration
  - CBER: Center for Biologics Evaluation and Research.
- NIH: National Institutes of Health
  - OBA: Office of Biotechnology Activities
  - RAC: Recombinant DNA Advisory Committee
Gene Therapy Oversight: Local Regulatory Agencies

- IRB: Institutional Review Board
- ISPRC: Institutional Scientific Peer Review Committee
- DSMB: Data Safety Monitoring Board
- MRSC: Medical Radiation Safety Committee
- IBC: Institutional Biosafety Committee
- CTRC: Clinical and Translational Research Center
Human Gene Therapy Clinical Trial Regulatory Review

Federal
- FDA
  - CBER

Local
- IRB
- ISPRC/DSMB

NIH
- OBA
  - RAC
- IBC
- CTRC
IBC, OBA and RAC Application

• Address the “Appendix M” or “Points to Consider”: “Points to Consider in the Design and Submission of Protocols for the Transfer of Recombinant DNA Molecules into One or More Human Research Participants.”

• Appendix M-I to V: Submission Requirements for Human Gene Transfer Experiments.

• Response: Letter stating if the protocol requires public RAC review vs. no need for open RAC review.

APPENDIX M or Points-to-Consider

• Description of the Proposal
  – Objectives and Rational
  – Why Gene Therapy?
  – Are there alternatives?
• Research Design
• Anticipated Risks and Benefits
RAC Application (2)
Appendix M or Points-to-Consider

• Structure and Characteristics of the Biological system:
  – Gene delivery system.
  – Manufacturing and lot release.

• Efficiency of the delivery system:
  – Is it integrated in target cells?
  – Transfection efficiency?
  – How many copies per cell?
  – Is the DNA chromosomal or extrachromosomal?
  – Is it stable in the target cells?
RAC Application (3)
Appendix M or Points-to-Consider

• Preclinical Studies, Risk-assessment Studies
  – Pharmacology and Toxicity in preclinical models.
  – Safety and Effectiveness in Humans

• Public Health Considerations
  – Possibility of DNA spread to the environment
  – Precautions for DNA spread
  – Birth control measures

• Qualifications of Investigators:
  – Curricula Vitae
  – Laboratory Facilities (JCCC GMP Suite)
  – Clinical Facilities (CTRC)
IND Application

1. Product Review
   – Characterization of Final Vector
2. Toxicology Review
3. Clinical Review

Need a final vector with complete testing before being able to submit an IND
IND Application
Final Vector Characterization

1. Identity: Does it have the composition that is expected to have?

2. Potency: Does it work the way it is intended to work?

3. Purity: Is it free from adventitious agents?
Logical Sequence of Applications for Gene Therapy Trial Approval

1. IRB Administrative Approval: Approval of the protocol and consent, pending IND.
2. ISPRC/DSMB
3. RAC
4. MRSC
5. IBC
6. CTRC
7. FDA Pre-IND meeting
8. Manufacture the Vector
9. FDA IND Application
10. IRB Approval Notice.

Concurrent with IRB review
Good Clinical Practice

Requirements for Gene Therapy Clinical Trials

• Ensure rights and safety of human research subjects (IRB, CTRC).
• Ensure that the data derived from the trials is accurate and credible (DSMB).
• Clinical research conducted for valid ethical (IRB) and scientific reasons (ISPRC).
• Performed according to written SOP (ISPRC).
• Performed by qualified investigators (IRB, ISPRC, HGMP).
• Human subject informed consent (IRB).
• Periodic monitoring/auditing of clinical trials (HGMP officer, JCCC QA/QC).
• Integrity of research materials (IBC, GMP Suite).
• Control of investigational medications (CTRC).
UCLA Human Gene Medicine Program
Clinical Trial Investigator Certification Required

• Human Subjects Research Certificate:
  – Web-based 2 hour test.
  – Requires renewal every 3 years.

• Human Gene Medicine Certificate:
  – 2-hour Gene Medicine Good Clinical Practice (GCP).
  – 2-hour current Good Manufacturing Practice (cGMP).
  – Requires renewal every 3 years.
Approved Gene Therapy Clinical Trial!!

- Subject Accrual
- Clinical Oversight
- Laboratory Procedures Monitoring
- Monitoring
- Abnormal Event Reporting
- Annual Reports
- Trial Ethics
- Trial Audits
Serious Adverse Event (SAE) Reporting

- Sponsor: 24 hours
- IRB
- ISPRC
- DSMB
- CTRC
- IBC: 2-5 days
- FDA
- RAC: 5-14 days

Send SAE reports as soon as information is available

- Unexpected Death: 24 hours to Sponsor, IRB, FDA and RAC
Annual Report

- IRB
- ISPRC
- DSMB
- IBC (every 3 years)
- FDA
- NIH/RAC
Factor - 14th Floor

Facilities Information for UCLA Gene Medicine Trials
TCR Engineering

Baseline 9/15/10

Before

MART-1 tetramer

F5 TCR retrovirus

CD3

RetroV F5

Cy+Flu

HD IL-2 + DC

Day +7 +15

Post + 35 11/9/10
Regulatory Binders

IRB/ISPRC/DSMB/IBC

RAC

FDA

QA/QC

DSMB

Correspondence

Save Everything!!!
Sources for Additional Information

- FDA/CBER web site:
  www.fda.gov/cber/ind/ind.htm
  www.fda.gov/cber/gene.htm

- OBA web site:
  www.od.nih.gov/oba/rdna.htm

- American Society of Gene and Cell Therapy web site: www.ASGCT.org

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