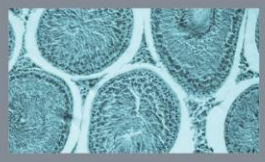
# Biosafety Committees and Biological Materials Oversight: Past, Present and Future for Clinical Research


**HealthCare Compliance Association** / 06-03-2014

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- Senior Vice President of Biosafety and Gene Therapy at WCG
- Adjunct Instructor
  - University of Missouri
  - Saint Louis University
- Former Biosafety Professional at:
  - University of Missouri
  - Saint Louis University
  - The Scripps Research Institute
- Doctorate in Public Health – Biosecurity and Disaster Preparedness

# Overview

- Setting the Stage
- Biosafety Past
- Biosafety Present
- Biosafety Future: Gene Therapy



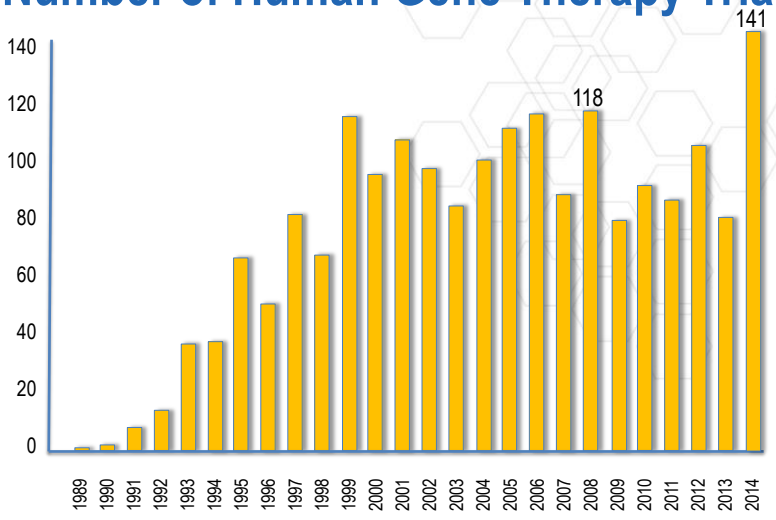
# Popular Culture

# What is Biosafety?



# What is Human Gene Therapy?

# Number of Human Gene Therapy Trials




data from www.wiley.co.uk/genmed/clinical

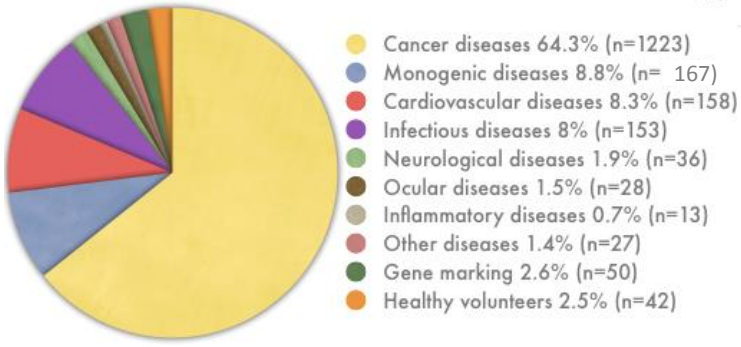


# Gene Therapy Research- Increasing

| Year | Phase I | Phase II | Phase III | Total |
|---|---|---|---|---|
| 2011 | 44 | 35 | 7 | 86 |
| 2012 | 49 | 51 | 6 | 106 |
| 2013 | 50 | 26 | 5 | 81 |
| 2014 | 80 | 57 | 6 | 143 |
| 2015 | | | ~12 | ~200+ |

data from www.wiley.co.uk/genmed/clinical

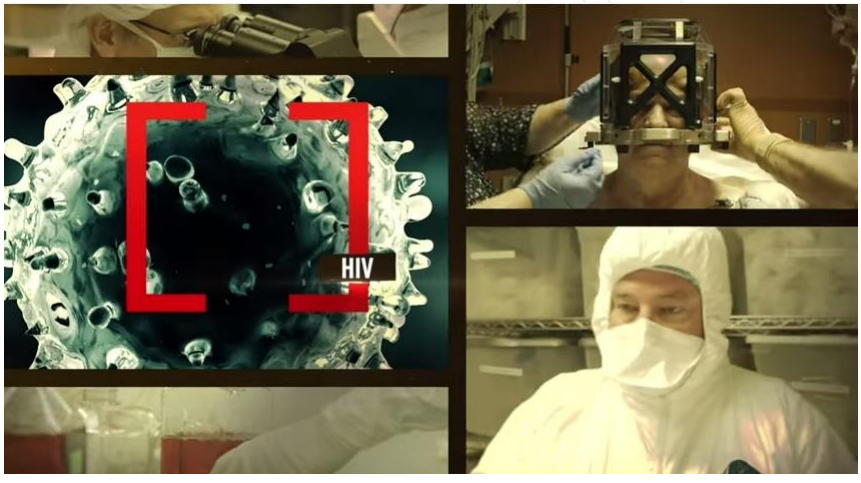
# Indications Addressed by Gene Therapy




The Journal of Gene Medicine, © 2013 John Wiley and Sons Ltd www.wiley.co.uk/genmed/clinical

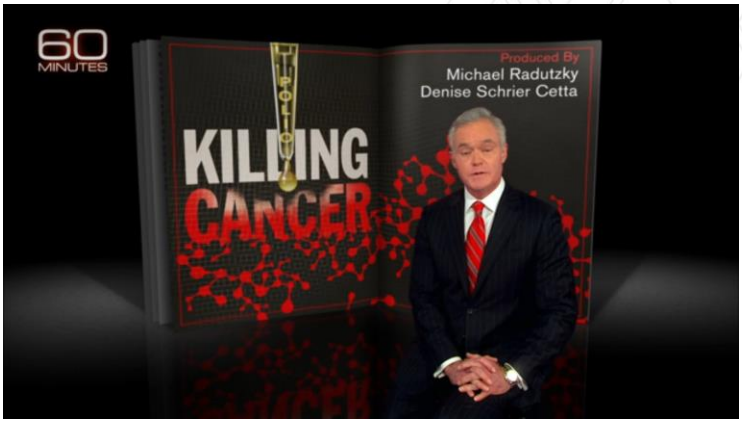


# Recent Media - HBO's "Killing Cancer"

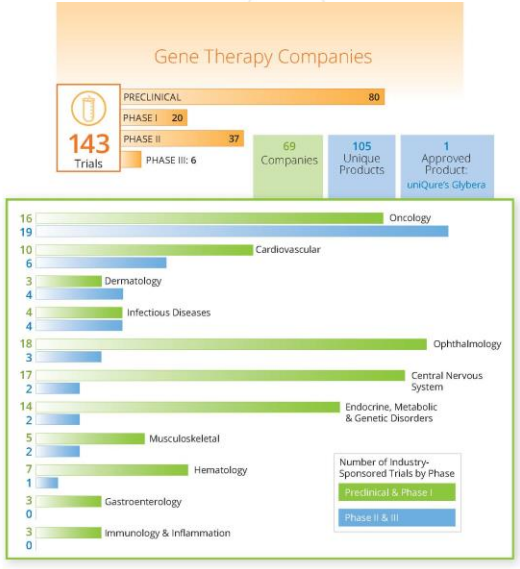


# 60 Minutes: Killing Cancer (03-29-2015)

- http://www.cbsnews.com/news/polio-cancer-treatment-duke-university-60-minutes-scott-pelley/



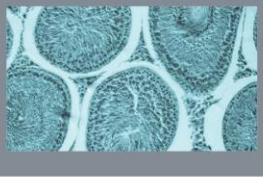



A Sampling of Trials with Expected 2014 Clinical Readouts

| Company | Product | Indication | Milestone | Estimated Date |
|---|---|---|---|---|
| uniQure NV | Glybera | Hyperlipoproteinemia | European Launch | 3Q14 |
| Taxus Cardium | Generx | Ischemic Heart Diseases | Phase III trial analysis | 3Q14 |
| Juventas Therapeutics | JVS-100 | Cardiovascular Failure | Phase II trial result | 4Q14 |
| Juventas Therapeutics | JVS-100 | Critical Limb Ischemia | Phase II trial result | 4Q14 |

# Biosafety Past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## 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

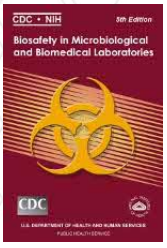


*Image courtesy of the CDC*

# 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.

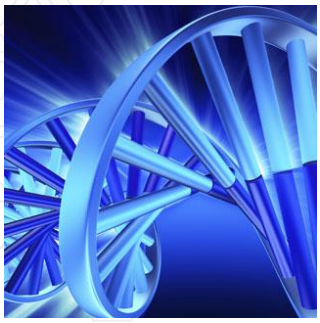

*Image courtesy of the Scientific American*



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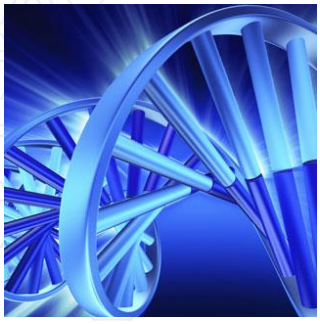


*Image courtesy of the Scientific American*

# History of Recombinant DNA Technology and Oversight

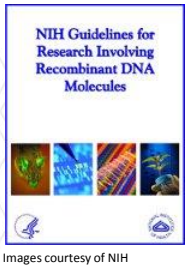
- Dr. Kornberg, 1968 U.S. Senate Subcommittee
  - Vettel, 2006
- Moratorium on rDNA experimentation after Paul Berg generated first genetically modified replication competent E. *coli* in 1973
  - Jackson, Symons, and Berg, 1972
- Gordon Conference Session request to National Academy of Sciences
  - Singer and Sol, 1973
- Assessment of recombinant DNA risks to be handled at Asilomar State Beach
  - Berg, Baltimore et al, 1974

Above, Dr. Frederickson, Director of the NIH, 1975-1981. Below, Dr. Paul Berg. Images courtesy of NIH and Nobel Institute

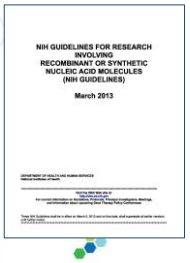


# Asilomar Conference

- 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* issued
  - Frequent revisions through 2013




Images courtesy of NIH



# 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)

Microsoft Office open-source images




# 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

National Institutes of Health Office of Biotechnology Activities

NATIONAL INSTITUTES OF HEALTH

CDC

USDA APHIS

OSHA

*Images courtesy of respective government entities*

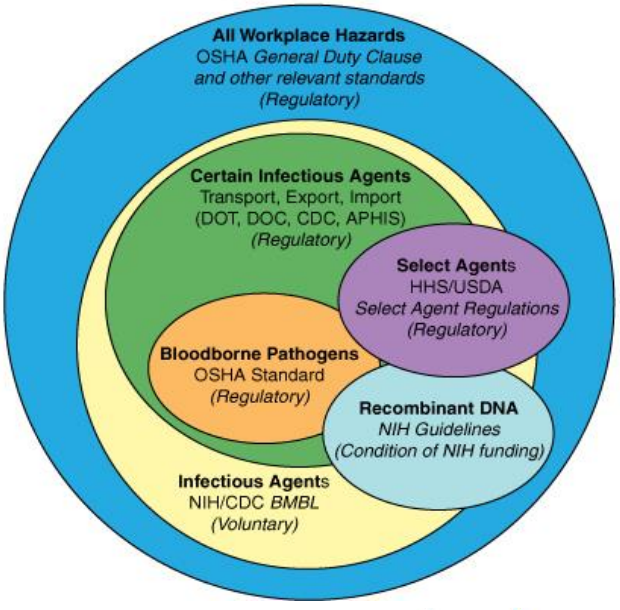



**Figure 1.** Biosafety & Biocontainment Regulations, Standards, and Guidelines Pertinent to High Containment and Maximum Containment Research (USDA Federal Task Force, 2009)

HCCA / June 3, 2014 wcg

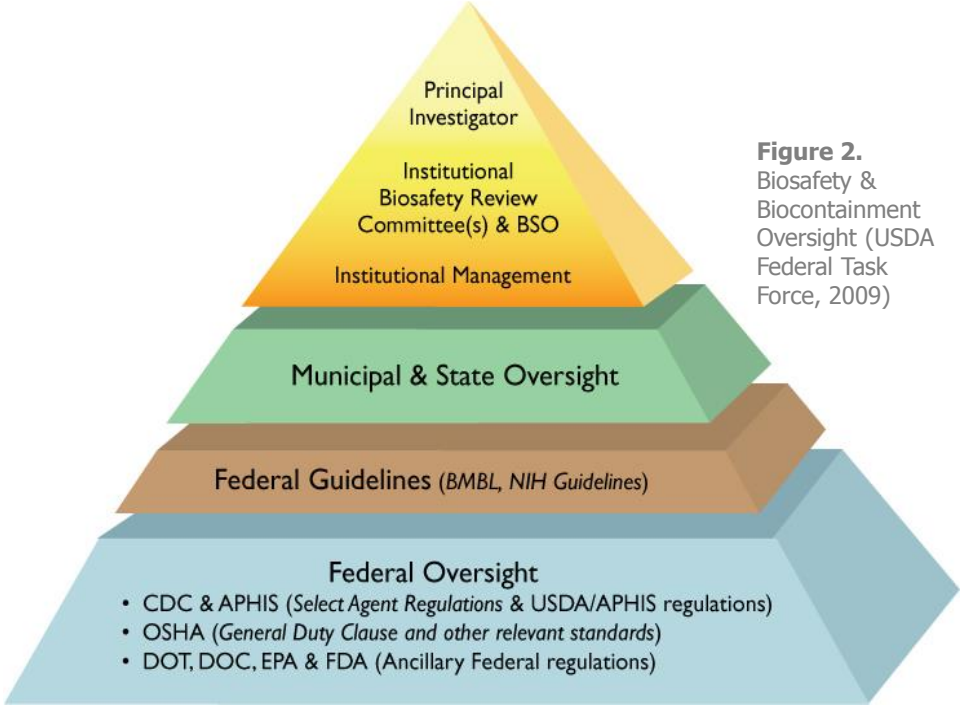



**Figure 2.** Biosafety & Biocontainment Oversight (USDA Federal Task Force, 2009)

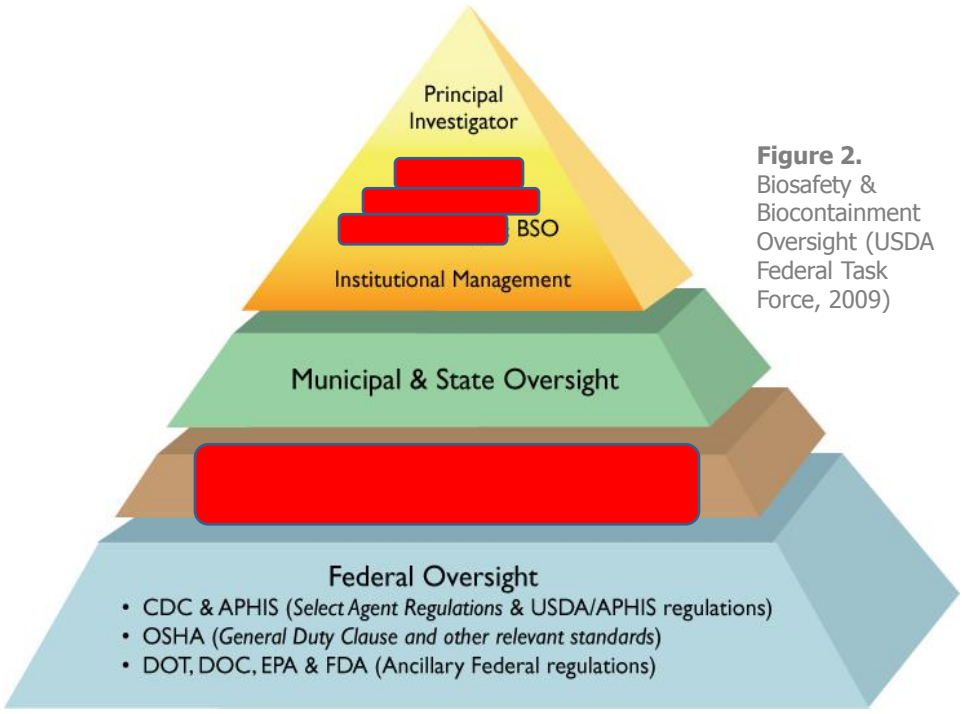
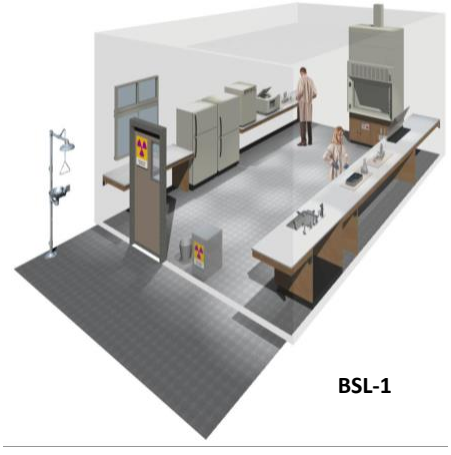



**Figure 2.** Biosafety & Biocontainment Oversight (USDA Federal Task Force, 2009)

# Biosafety Levels 1 & 2

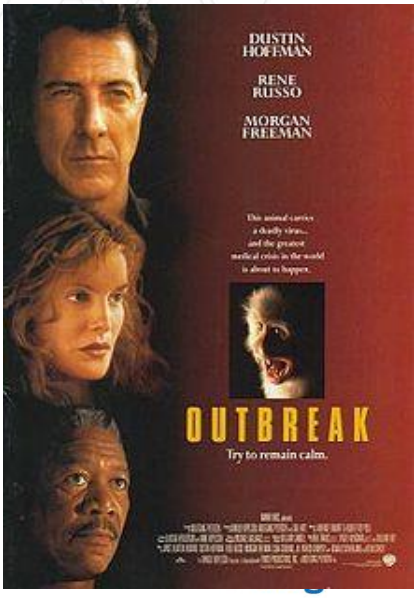


**BSL-1**

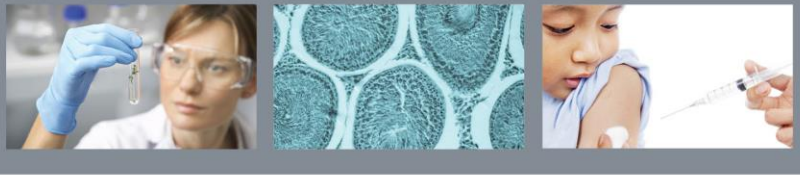
**BSL-2**

# Feature Presentation

- 2:35 of Outbreak (1995)
- 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.

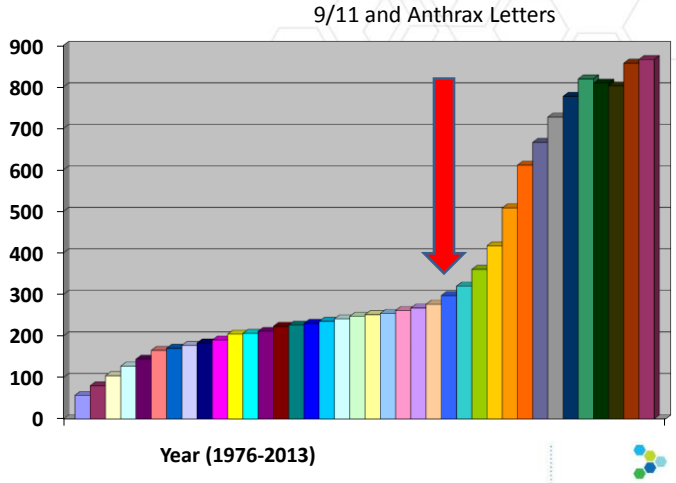


# Survey Methodology

- 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

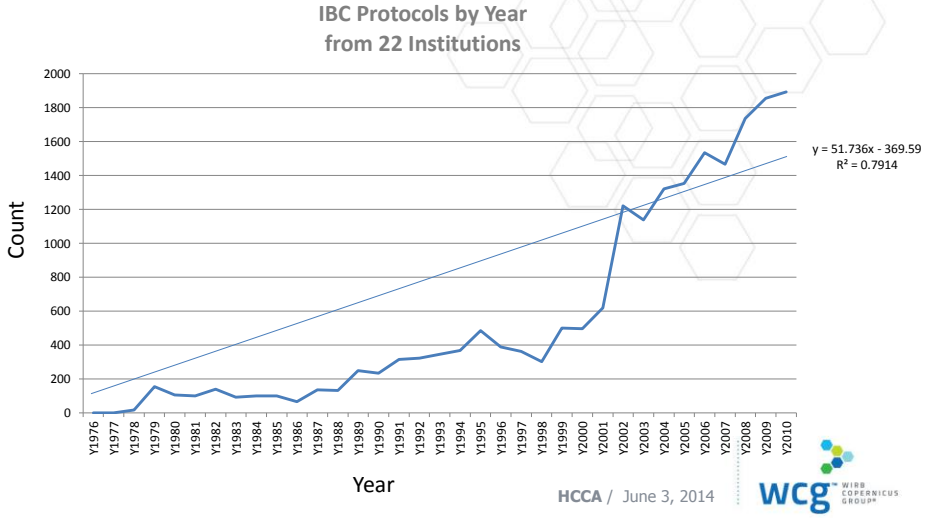
# NIH-OBA Registered IBCs

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

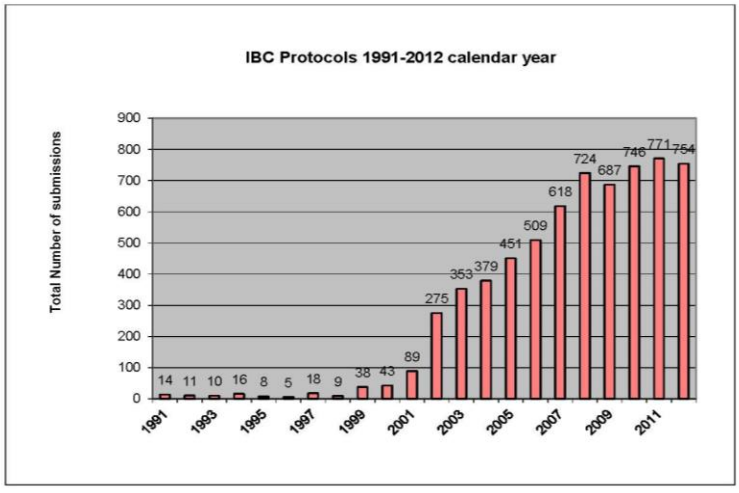





# IBC Protocols By Year



# Institutional Case Study

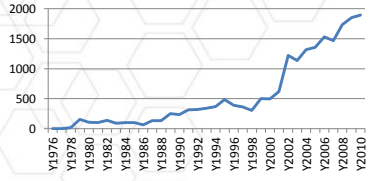




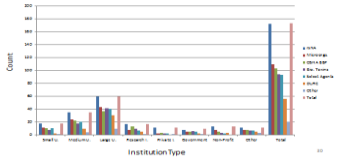

# Observed Trends in Biological Materials Oversight and IBCs

- 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

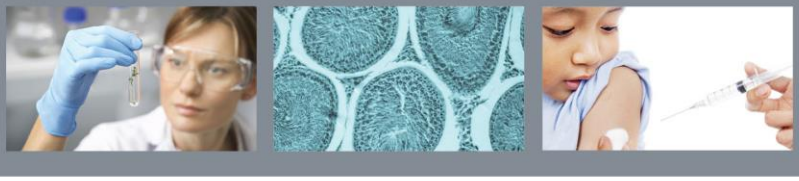
**Total IBC Protocols by Year from 22 Institutions**




**Institution Type by Biological Materials Research**



# Biosafety Future: Gene Therapy



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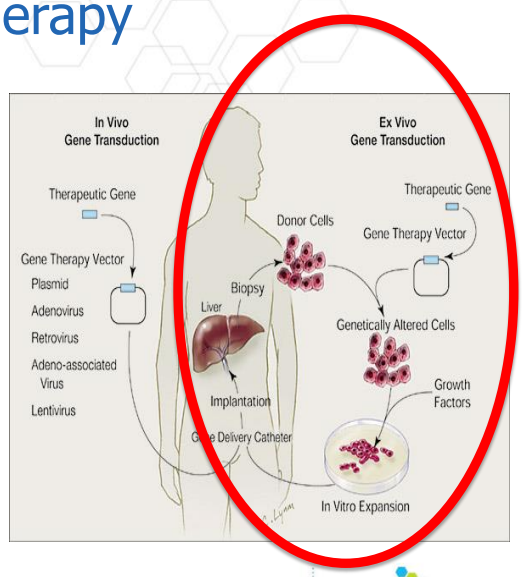
## Gene Therapy

- 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

# *Ex vivo* Gene Therapy

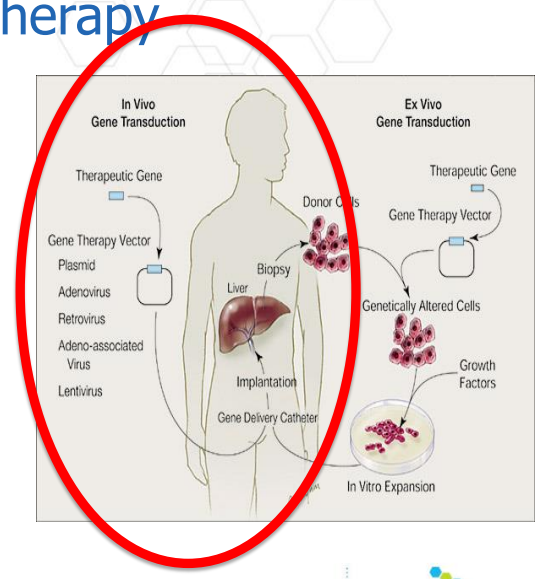
- Cells from diseased person are removed
- Cells are modified in the lab
- Modified cells are reintroduced to the patient
- Generally, more effective than *in vivo*





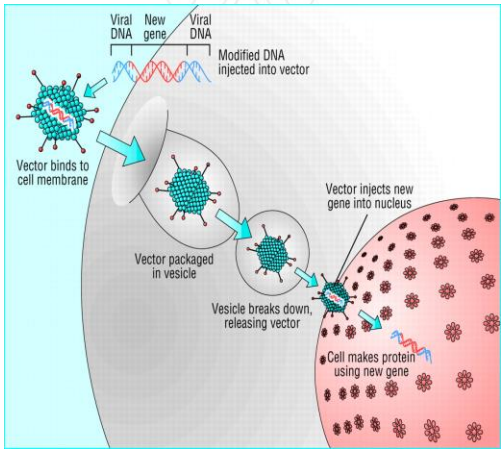

# *In vivo* Gene Therapy

- 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

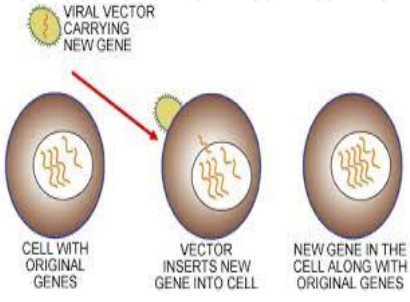
- Therapeutic genes often called "payload"
- May require long-term expression of corrective gene
- Others require rapid expression for short periods of times






# 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 in to 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 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.


Oversight and Review of Clinical Gene Transfer Protocols
Assessing the Role of the Recombinant DNA Advisory Committee

# 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 precurosor 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

**figure 13.33** The first person to receive gene therapy, Ashanti DeSilva (left), was treated for severe combined immunodeficiency (SCID) disease. R. Michael Blaese, M.D. (right) was the scientist at the National Institutes of Health that pioneered this gene therapy trial. A wild-type adenosine deaminase gene was introduced into Ashanti's T cells, which were then reinfused back into her circulatory system to partially restore her immune system.



# 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

- Biosafety Past
- Biosafety Present
- Biosafety Future: Gene Therapy



## Thank You – Questions?

# WIRB-Copernicus Group

A powerful, responsive and enthusiastic partner