

**Challenges to Clinical Trials:**  
**Observations from the National**  
**Gene Vector Laboratory**

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# Questions

- **What is the NGVL?**
- **What can we say about vectors that make it to trial and those that don't?**
- **From my perspective, what are some of the current and future challenges?**
- **Why am I in the FDA section of this meeting?**

# **National Gene Vector Laboratories**

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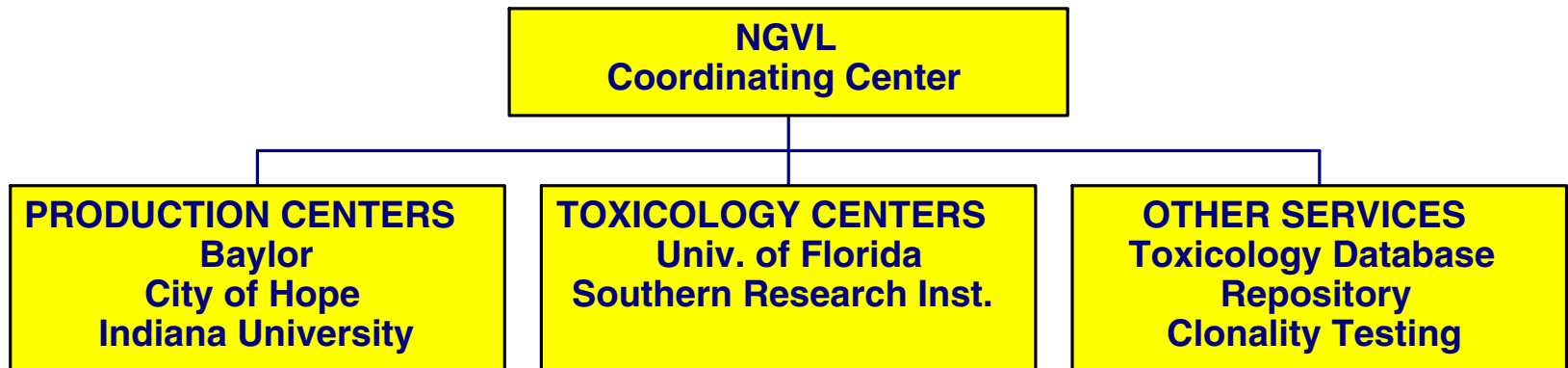
**The NGVL is an NIH sponsored interactive group whose goal is to supply investigators with clinical grade vectors and toxicology support for gene therapy applications.**

# Origins of the NGVL

- **The NIH has invested in gene therapy basic research**
- **Many projects are approaching clinical trials**
- **Advancement of these projects require access to clinical grade vector**
- **Vector production is costly and not covered within most grants**
- **NCRR sought to provide vector resources to NIH funded investigators**

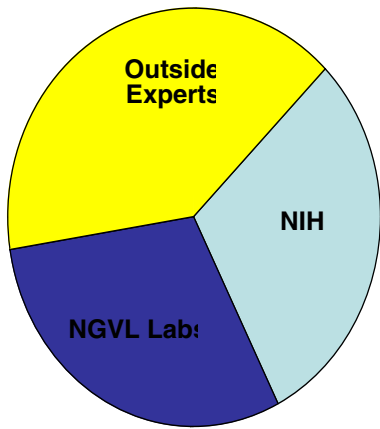


[www.NGVL.org](http://www.NGVL.org)



# Two Levels of Review

- Scientific Review Board - Composed of approximately 30 individuals with expertise in gene therapy, clinical medicine and ethics. Three individual are assigned per application.
- Steering Committee - All applications are reviewed by the full Steering Committee, taking into consideration the comments of the Scientific Review Board and the expertise of the Steering Committee members.

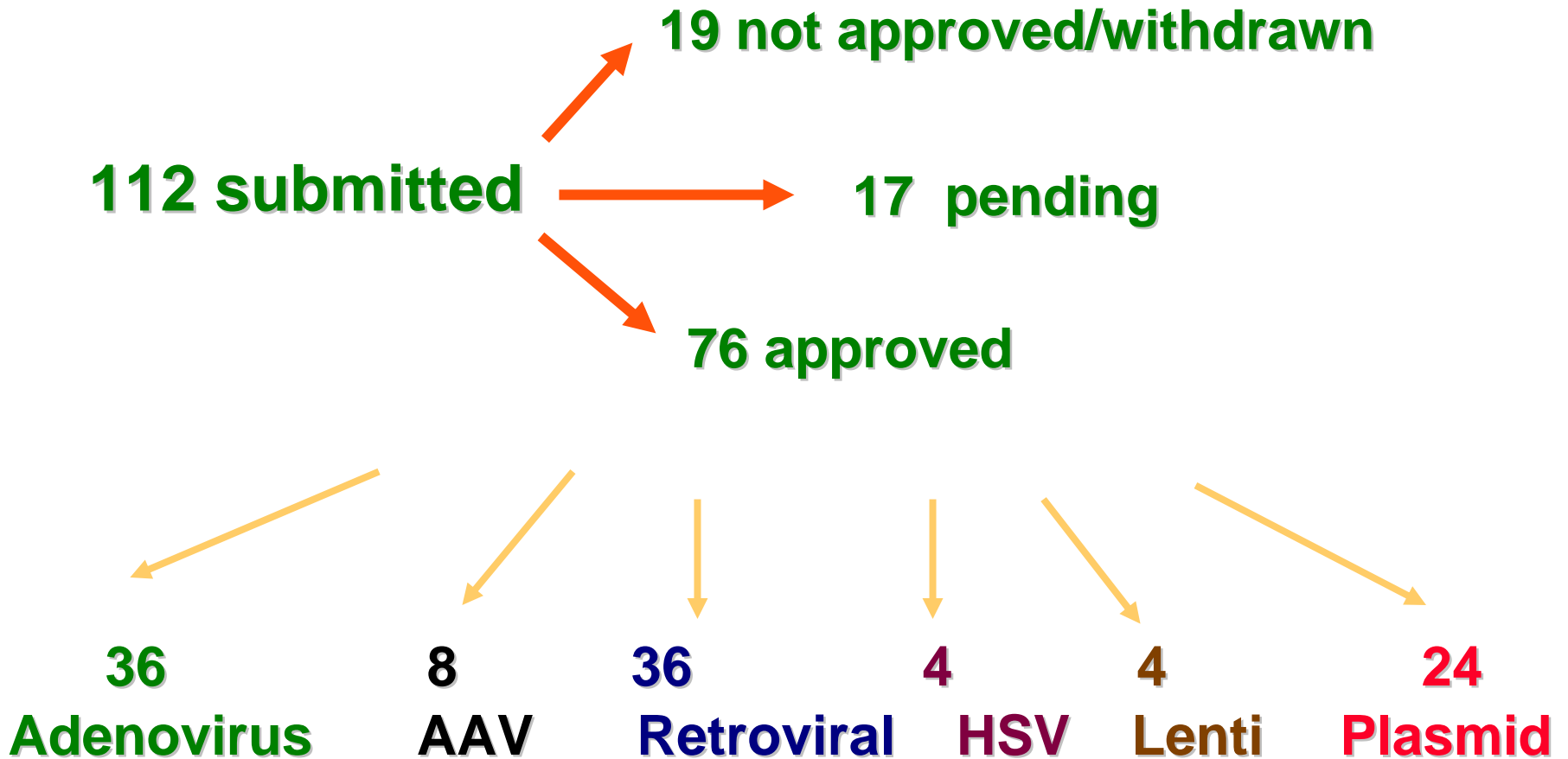


# NGVL Steering Committee

- **R. Michael Blaese**
- **Parris Burd**
- **Joy A. Cavagnaro**
- **Joseph C. Glorioso**
- **Michael J. Imperiale**
- **Doug Jolly**
- **Donald B. Kohn**
- **Jack A. Roth**
- **Nelson A. Wivel**
- **John Zaia**
- **NCRR**
- **NCI**
- **NHLBI**
- **NIDDK**
- **NIAID**
- **NICHD**
- **NIEHS**
- **NIAMS**
- **NINDS**
- **NIDCR**
- **ORD**
- **FDA \***
- **ORDA \***

**\* Non-Voting Steering Committee Members**

# Funding of Submitted Applications



# **IU NGVL - First 5 years**

**7 of 14 Producer cell lines submitted to the NGVL failed to generate clinical grade material**

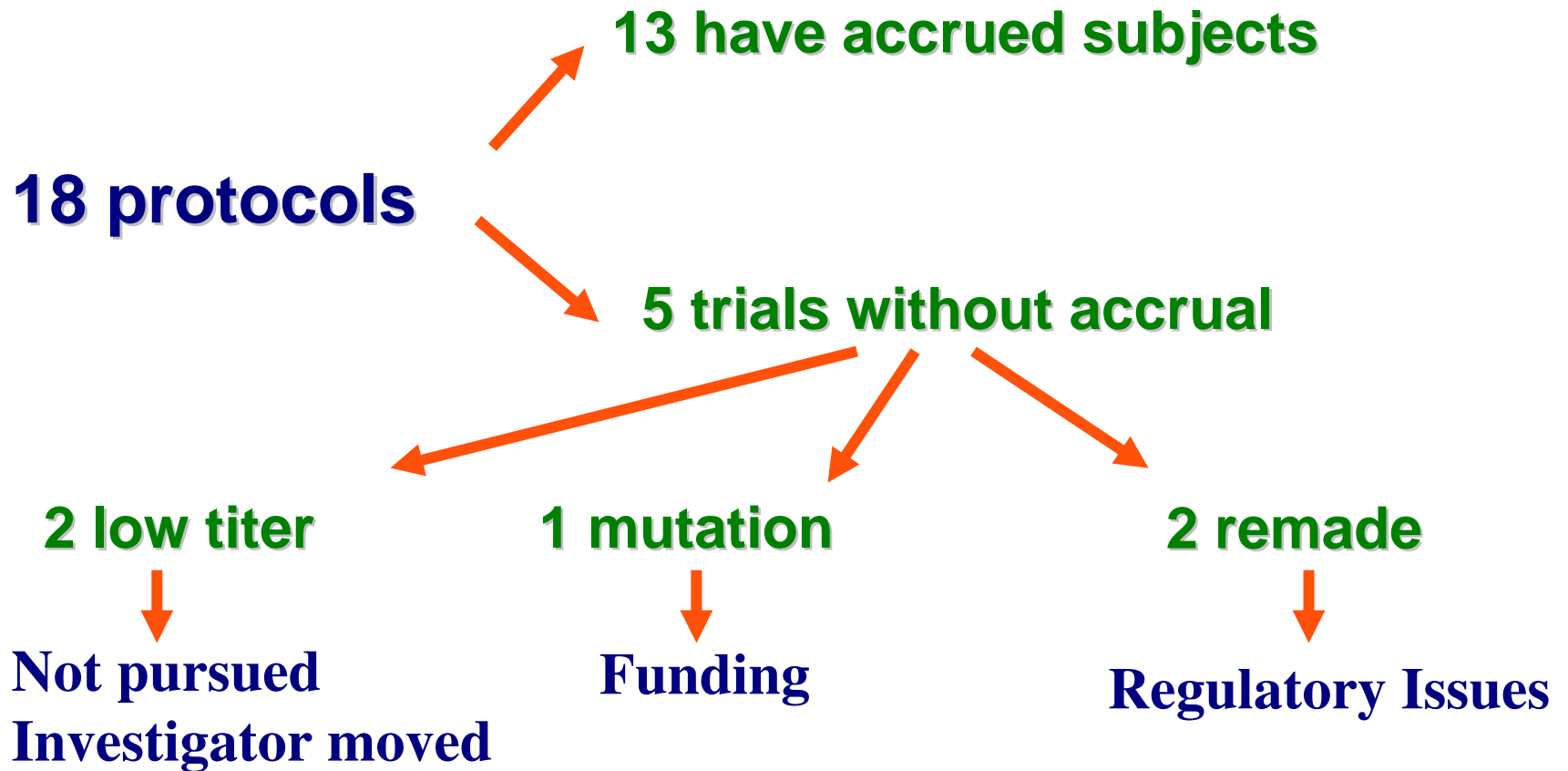
**1 Mycoplasma**

**1 Titer**

**5 RCR**

**Cell lines generated by investigators in their lab often do not meet standards.**

# IU NGVL First 5 years



# IU NGVL last 4 years

**14 protocols** → **1 accrued**

→ **4 cancelled / undecided**

→ **2 investigators moved/ unsure**

→ **1 institution withdrew support**

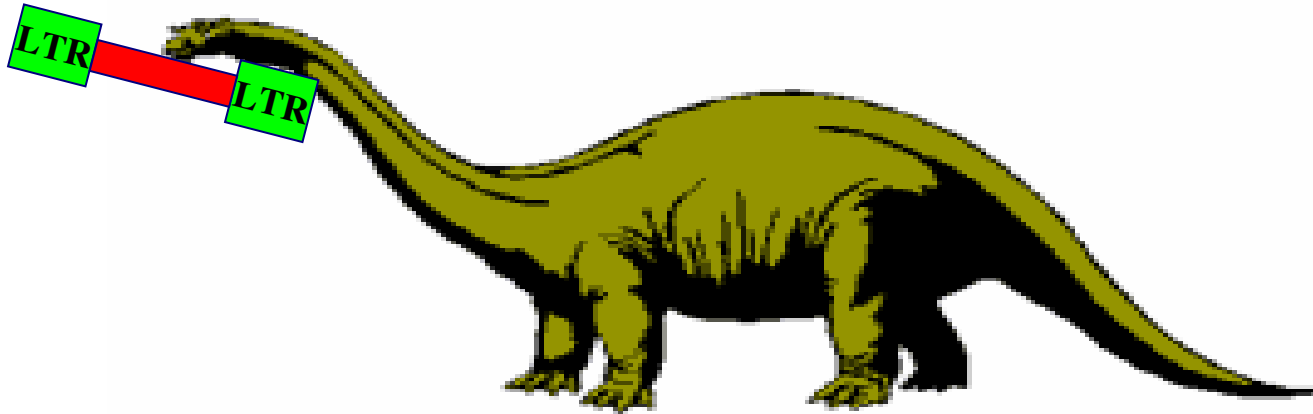
**Investigators are struggling with grant timelines and the regulatory issues related to adverse events.**

Current Challenges for the  
Physicians and Scientists trying  
to conduct Gene Therapy Clinical  
Trials

# Vectors are a rapidly moving target

- The first 22 vectors made in the IU NGVL similar murine packaging cells
- Of the last 4 vector requests three had unique challenges to production and certification (cell lines with RD114 env or VSV-G env under tet control, and a production using transient transfection).
- No Guidance for these productions or RCR testing of these variants.
- Time constraints are now the development and validation of production methods and certification testing for new vector systems.

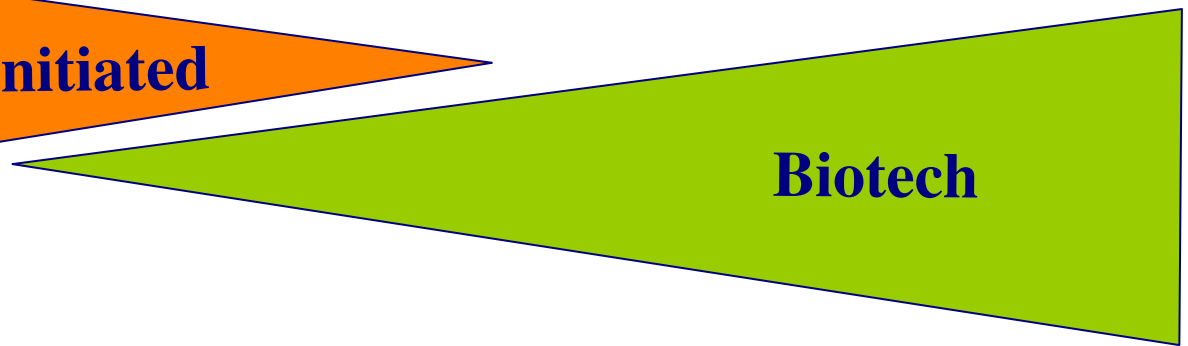
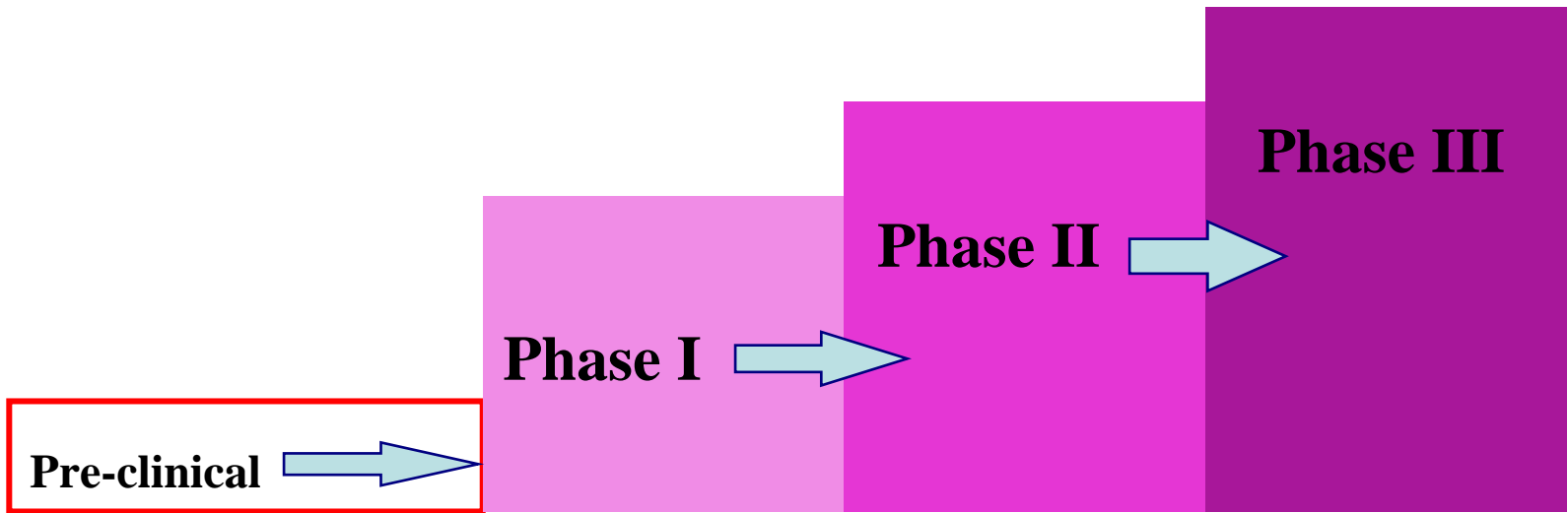
# TODAY'S HOT VECTOR IS TOMMOROW'S DINOSAUR



- **This limits availability of Guidance documents. Therefore, novel vectors mean developing a safety plan unique to your vector and your application.**
- **Developing new production and certification assays can add a year or more to vector production which further conflicts with grant timelines.**

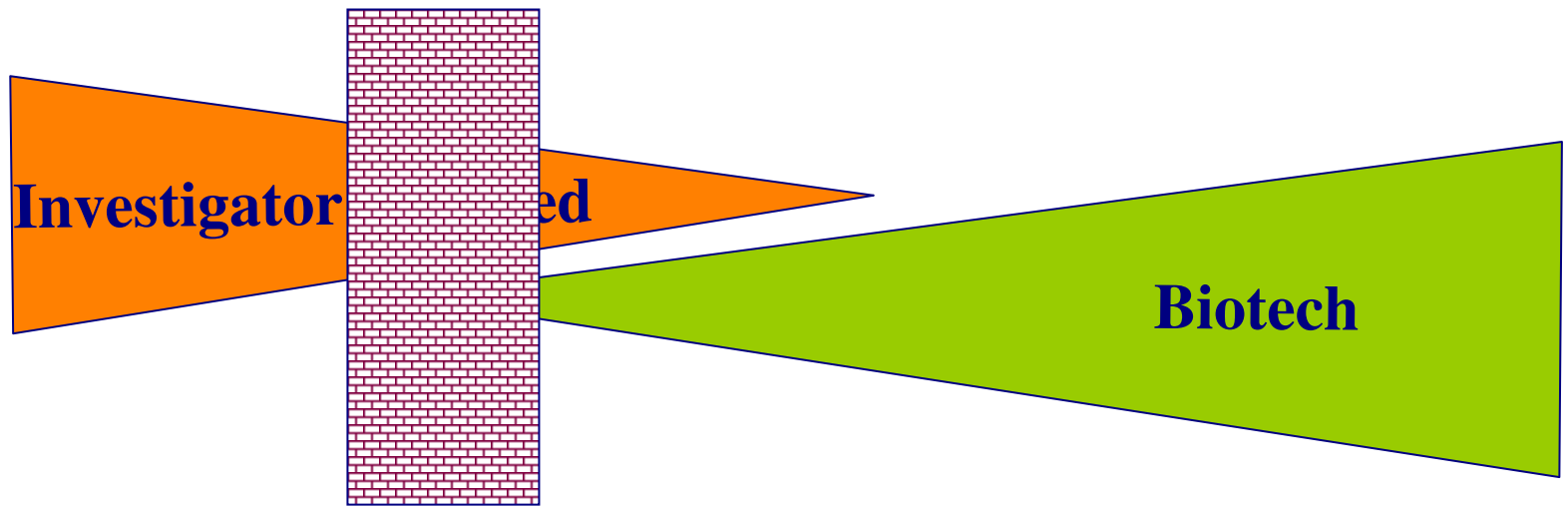
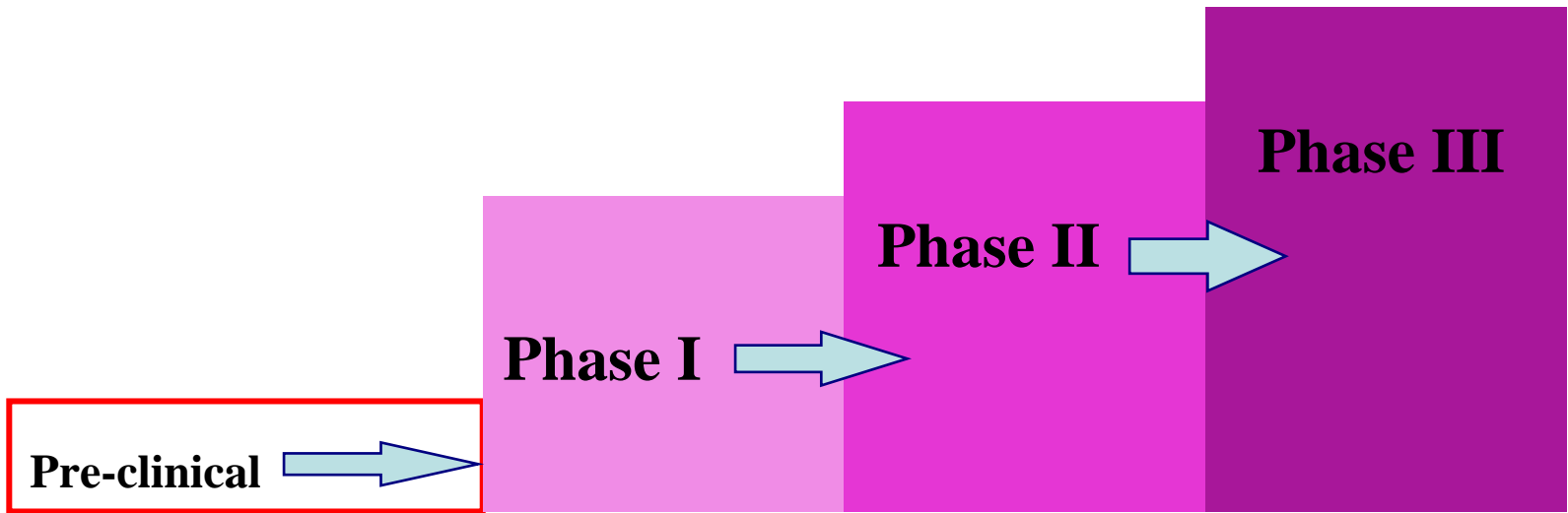
# Limitations of Current NIH Support

- **Investigators need to secure at least 3 grants to cover basic research, vector/tox, and clinical trial.**
- **Average of six review boards before clinical trials approved.**
- **The 5 year NIH cycles are too short for clinical gene therapy initiatives, in part due:**
  - **the step-wise funding approach**
  - **preliminary data aimed at determining tox studies often not part of initial funding**
  - **vector and certification development usually not part of initial funding**



# Toxicology Challenges

- Traditional toxicology studies are not ideally suited to test biologicals.
- The wide variety of viral vectors makes standardization of testing difficult.
- Regulators think in term of GLP toxicology studies while many investigators focus on vector specific safety issues (ex. insertional mutagenesis).
- Establishing toxicology studies early in vector development is not easily incorporated into NIH funding efforts.



**The Brick Wall of Tox**

# Development of Gene Therapy Clinical Trials



**Preclinical Research**   **Protocol Development**   **Vector/Tox Production**   **Clinical Phase I**   **Phase II & beyond**



**R01**   **R01**   **NGVL**   **GCRC Insurance Industry**   **Biotech Pharma SBIR**



# Funding of Gene Therapy Clinical Trials

# Bench to Bedside

## Grants Support

- **Basic R01**
- **Toxicology Funding**
- **Vector Production Funding**
- **Clinical Trial Grant**
- **Long-term Follow-up**

***You may need 3 or more sources of funding for a single trial***

***3+ grants***

***3+ grant reviews***

# Bench to Bedside

## Committees

- **Animal Care**
- **IBC**
- **SRC**
- **IRB**
- **GCRC**
- **RAC**
- **FDA**
- **DSMB**

***6+ committees x # of reviewers = ? vigorous circle***

# The Positives

- **The science gets better and better**
- **The vectors get better and better.**
- **The NIH has had outstanding advocates for research and patient safety.**
- **FDA has been extremely dedicated and interactive.**
- **Dedication of the scientists from academia and industry.**
- **Academic institutions have made major investments in fostering clinical gene therapy.**

# The Struggle

- **Novel usually means sailing uncharted waters, you become the test case for development of guidance documents.**
- **While NIH institutes have been key supporters of gene therapy, from a macro view the NIH has not recognized the unique requirements of translational research involving product development. Territorial thinking has led to:**
  - **Redundancy in reporting requirements and funding efforts**
  - **Redundant production sites**
  - **Funding mechanisms and timeframes that are not consistent with the needs of gene therapy clinical work.**
- **Regulations are complex and while the need is recognized, the benefit is not apparent to investigators and patients.**