



NHLBI Gene Therapy Resource Program



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Gene Transfer and Rare Disease Workshop
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Program Origins

- Major Research Challenges Identified by NHLBI Gene Therapy Working Group at June 2005 Meeting:
 - Producing large scale, well-characterized viral vectors under current Good Manufacturing Practices for use in clinical trials
 - Conducting pharmacology and toxicology studies in small and large animal models
 - Meeting the regulatory requirements of the FDA, IBCs, IRBs, NIH RAC, and DSMB
- The NHLBI responded to the recommendations of the Working Group by establishing the Gene Therapy Resource Program in March 2007

Woo SL, Skarlatos SI, Joyce MM, Croxton TL, Qasba P. Critical resources for gene therapy in heart, lung, and blood disease working group. Molecular Therapy. 13, 641-643 (2006)

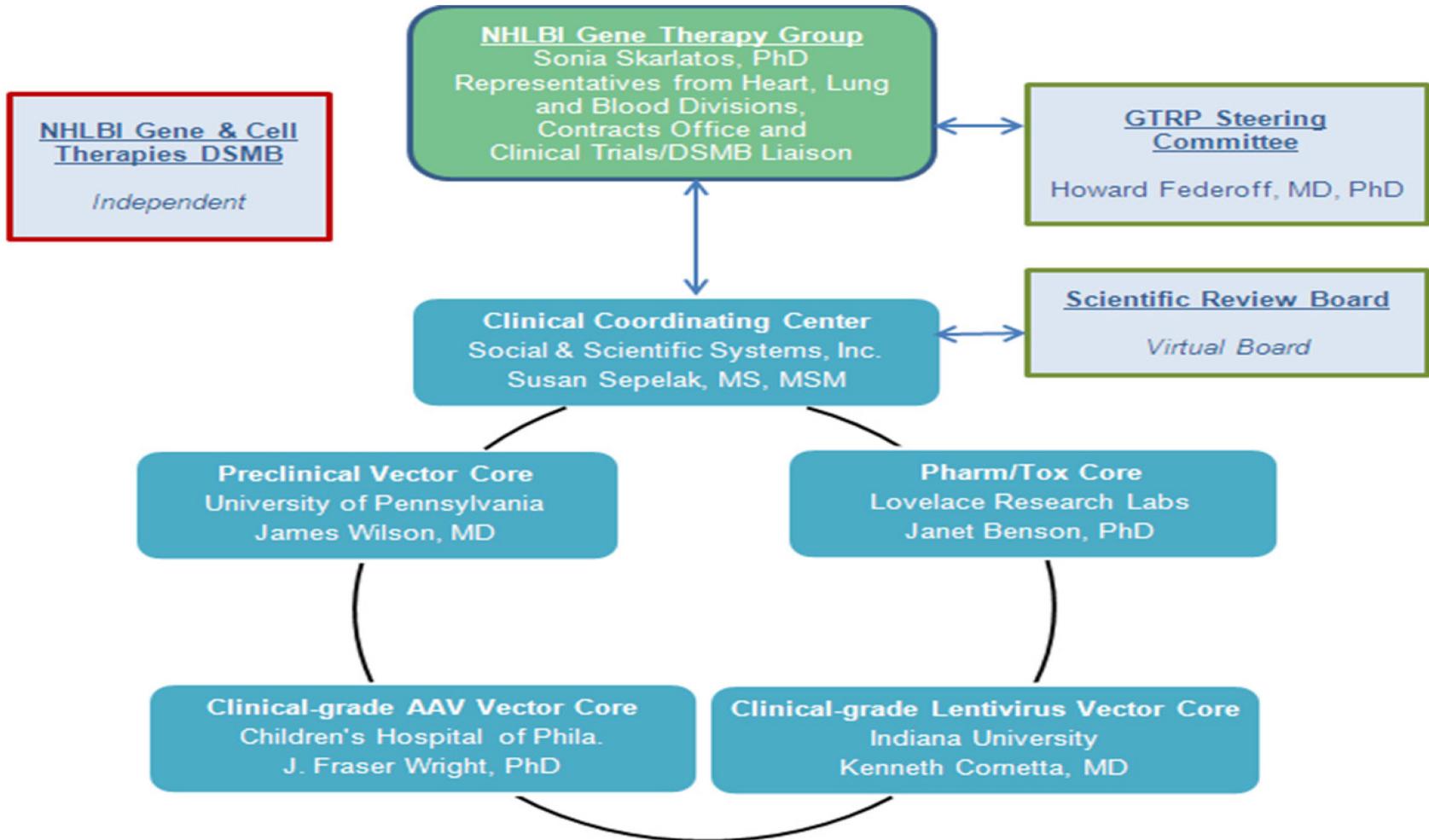
Current Challenges in Gene Therapy Field

- Identifying and targeting cells/tissues to treat a specific disease/disorder
- Obtaining appropriate animal model(s) for a specific disease/disorder
- Determining potential immune responses
- Identifying optimal gene delivery method(s)
- Understanding how to proceed through the preclinical to clinical regulatory process
- Obtaining funding for pharm/tox and Phase I clinical studies
- Producing GMP-grade vectors for clinical trials
- Demonstrating safety (and efficacy) of product prior to initiating a Phase I clinical trial

Program Goals

- Facilitate the translation of gene therapy research into clinical interventions
- Provide resources for gene therapy research in heart, lung, and blood diseases and sleep disorders
- Provide resources to investigators at other NIH institutes through transfer of funds

Program Infrastructure



Step 1: Investigator Registration and Approval

Step 2: Submit RSA

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Gene Therapy Resource Program

National Heart, Lung, and Blood Institute



**Investigator
Registration**

**Request for Service
Application (RSA)**

Core Laboratories

**Scientific
Review Board**

Steering Committee

**NHLBI Gene
Therapy Group**

HIGHLIGHTS

> [Instructions for Submitting an RSA](#)

> [RSA Review Process](#)

INFORMATION CENTER

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> [Regulatory Resources](#)

» [Regulatory Guidelines](#)

» [Fundamental Elements in Gene Vector Development](#)

WHAT IS THE NHLBI GENE THERAPY RESOURCE PROGRAM?

The NHLBI Gene Therapy Resource Program (GTRP) facilitates the translation of gene therapy research into clinical interventions. The GTRP provides resources for gene therapy research primarily in heart, lung, and blood diseases as reflected in the NHLBI Mission (<http://www.nhlbi.nih.gov/about/org/mission.htm>). Requests for resources for gene therapy research that are consistent with the missions of other NIH Institutes may also be considered by the Program.

Resources are provided in the form of preclinical and clinical-grade vector production, pharmacology/toxicology testing, immunology testing, clinical trials funding assistance, and [regulatory support](#) at no cost to the investigator. Investigators must first receive approval of their Registration with the Program in order to request resources.

The GTRP, directed by the NHLBI Gene Therapy Group, consists of three vector production cores, a pharmacology/toxicology testing core, and a clinical coordinating center. A Scientific Review Board and Steering Committee review Request for Service Applications and make recommendations to the NHLBI Gene Therapy Group regarding the applications' scientific merit, feasibility, and compatibility with the Program's mission.



National Heart
Lung and Blood Institute

Services Provided by Cores

- Preclinical Vector Core
 - Produces research-grade AAV, lentivirus, and recombinant adenovirus vectors
 - Provides immunology testing services on preclinical specimens
- Pharmacology/Toxicology Core
 - Performs toxicology and biodistribution studies in rodents, dogs, pigs, and non-human primates as a prerequisite for use of vector in clinical studies
 - Prepares final study reports for IND submission

Services Provided by Cores – Cont'd

- Clinical Lentivirus and AAV Vector Cores
 - Produce GMP process-comparable vectors for use in pharm/tox or other studies
 - Produce scalable clinical-grade vectors for use in clinical studies
 - Provide Chemistry, Manufacturing, and Controls (CMC) and Certificate of Analysis (CoA)
- Clinical Coordinating Center
 - Supports Program infrastructure
 - Provides regulatory assistance to investigators
 - Manages disbursement of clinical trial funds

Technologies Developed by GTRP Cores

Preclinical Vector Core:

- Development of a scalable, serotype-independent production method for AAV serotype vectors of interest for heart, lung, and blood applications (e.g. AAV1, 2, 5, 6, 7, 8, 9, and others)
- Development of a sensitive assay for the detection of pre-existing neutralizing antibodies
- Development of bicistronic vectors for coexpression of therapeutic and reporter genes
- Generation of tissue-specific, inducible expression vectors for heart, liver, and muscle applications
- Generation of vectors for the tissue-specific expression of shRNA and miRNA for gene silencing studies

Technologies Developed by GTRP Cores Cont'd

Pharm/Tox Core:

- Development or qualification of qPCR, ELISA, and other study specific endpoint assays.
- Development/implementation of unique vector delivery methods

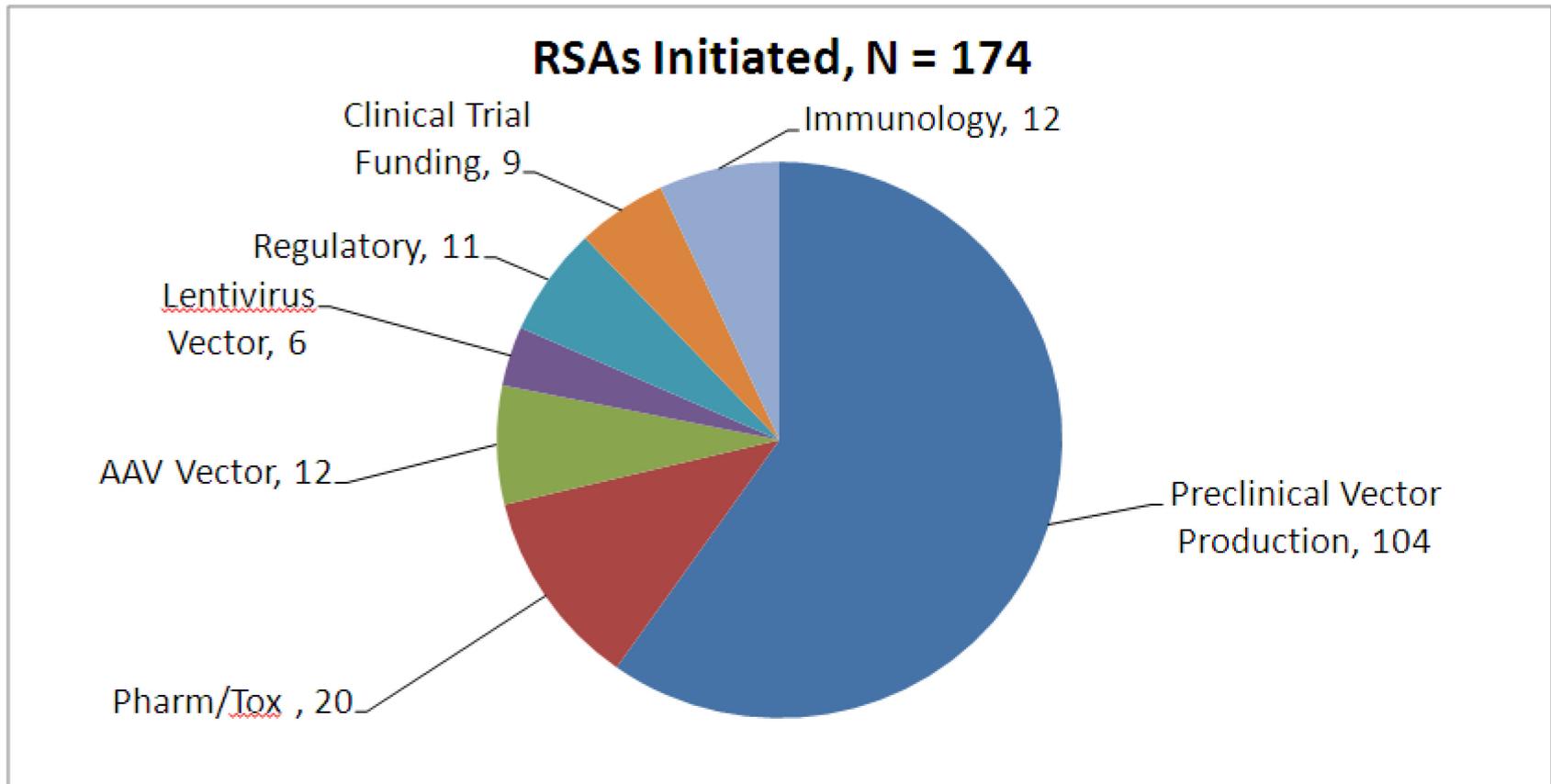
AAV Vector Core:

- Development and implementation of scalable vector generation and purification methods for serotypes AAV1, 2, 5, 6, 8, and 9
- Development of improved methods for vector characterization including identification of parameters that improve investigational product purity

Lentivirus Vector Core:

- Development of large scale production method for FIV pseudotyped with the GP64 envelope
- Development of RCL certification of lentiviral packaging cell line

Request for Service Applications (RSAs) Initiated



RSA Review by NHLBI Gene Therapy Group

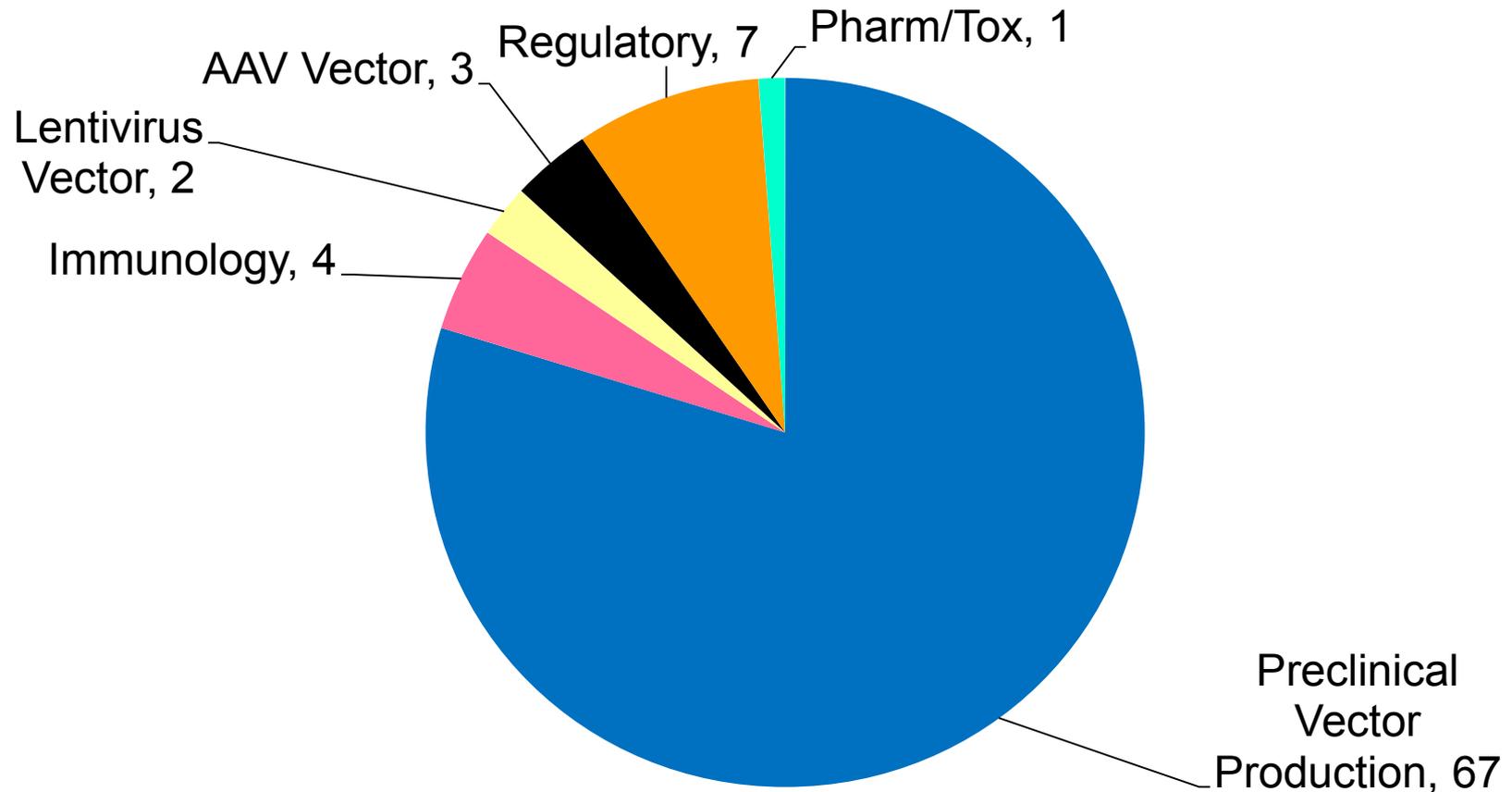
- Total RSAs reviewed: 127
 - Preclinical Vector Production (91)
 - Immunology Testing (7)
 - Pharmacology/Toxicology (8)
 - AAV Vector Production (5)
 - Lentivirus Vector Production (4)
 - Regulatory (9)
 - Clinical Trial Funding (3)
- Total RSAs approved: 113 (approximately 89%)

RSAs Approved by NHLBI Gene Therapy Group

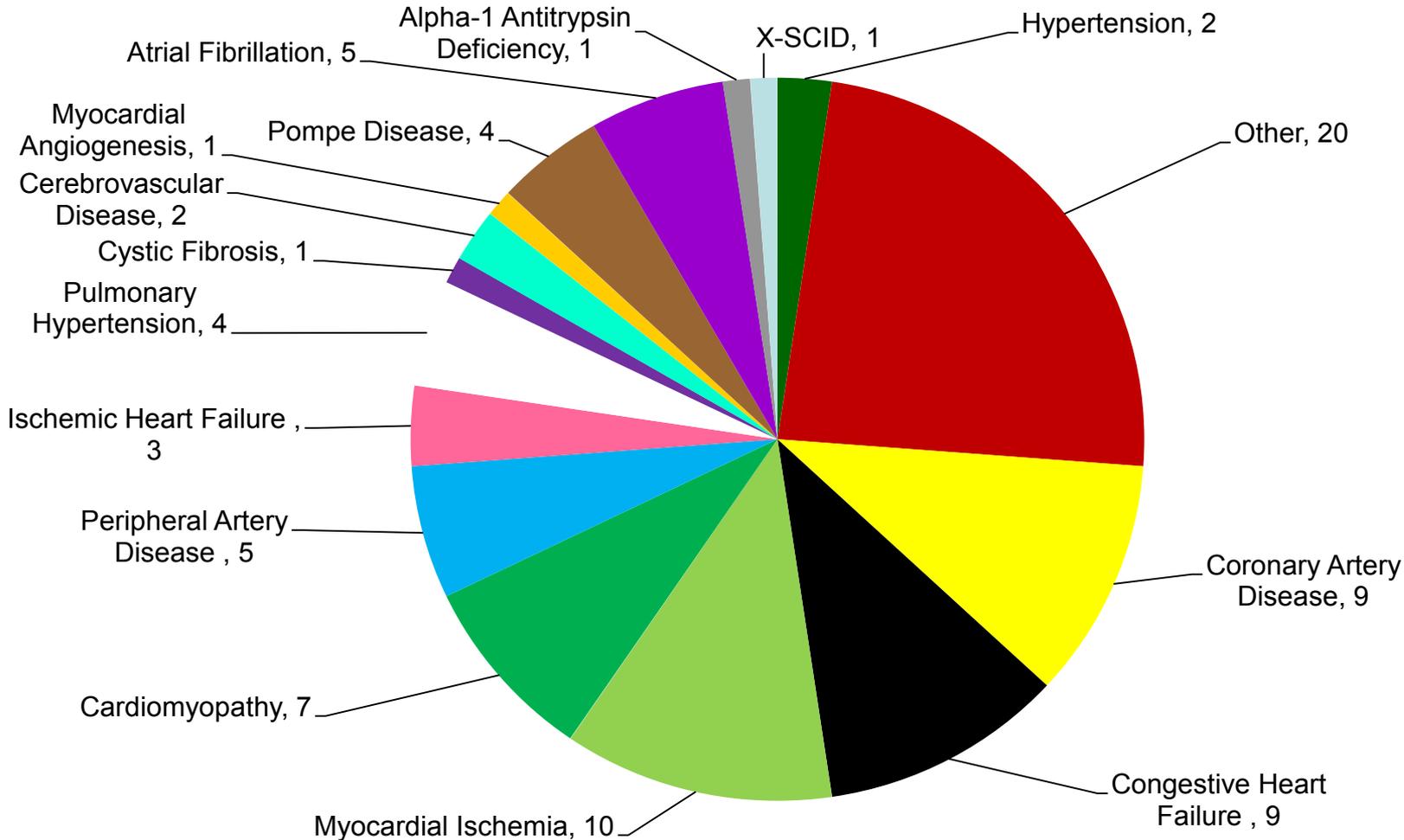
Total RSAs Approved: 113

- Preclinical Vector Production (81/91)
- Immunology Testing (7/7)
- Pharmacology/Toxicology (5/8)
- AAV Vector Production (4/4)
- Lentivirus Vector Production (4/4)
- Regulatory (9/9)
- Clinical Trial Funding (3/3)

RSAs Completed by Service Type N = 84



RSAs Completed by Targeted Disease N= 84



Completed GTRP Studies Targeting Rare Diseases

- **Fabry Disease** – preclinical study to assess multiple AAV vectors in mice
- **Pneumocystis Carinii Pneumonia** – preclinical study to assess AAV5 vector in mice
- **Duchenne Muscular Dystrophy** – preclinical study to assess multiple AAV vectors in dogs
- **Cystic Fibrosis** – preclinical study to assess AAV6.2 in ferrets
- **Alpha-1 Antitrypsin Deficiency** - toxicology testing in mice evaluating intramuscular injection of an AAV1 vector

Ongoing GTRP-Supported Studies Targeting Rare Diseases-1

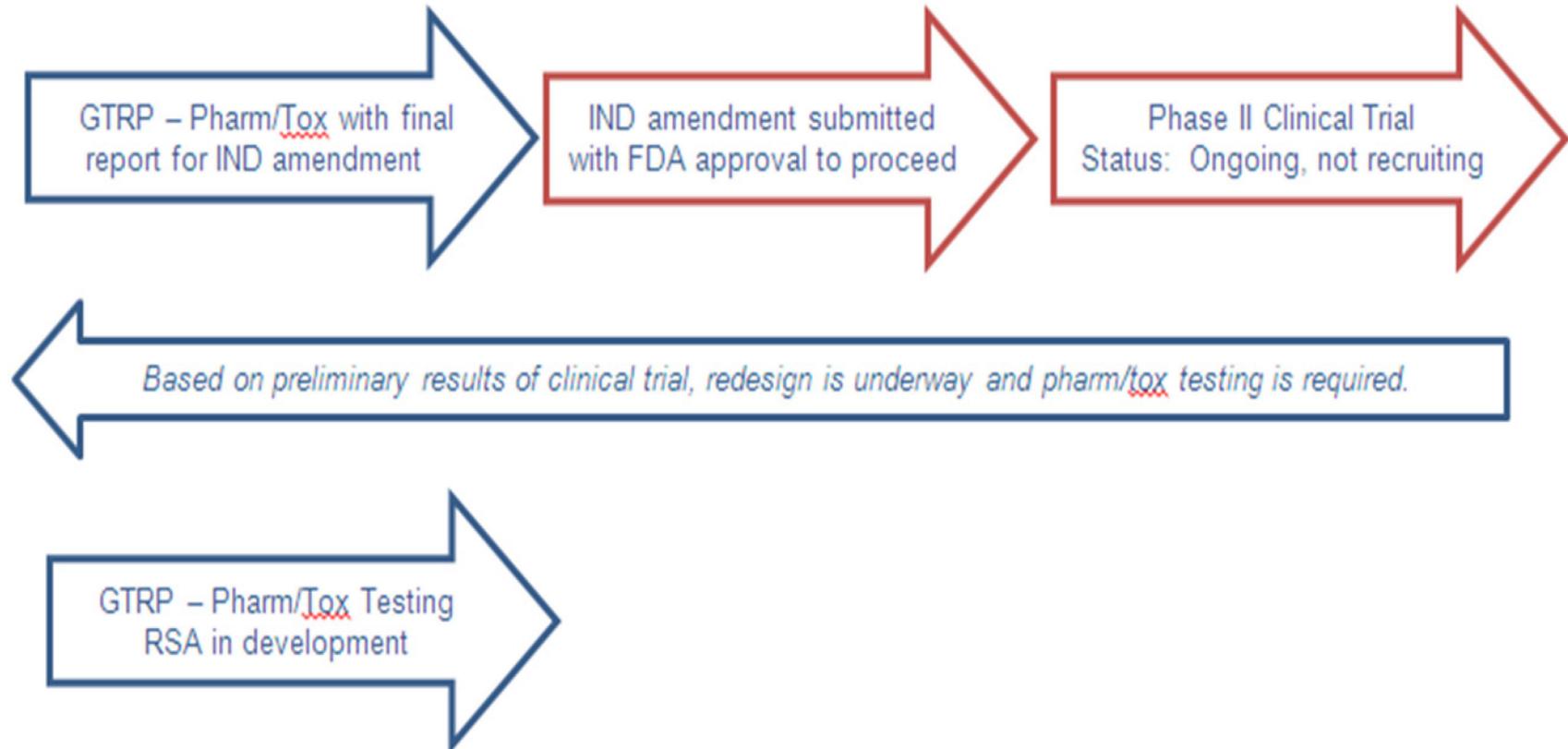
- **Cystic Fibrosis** – preclinical study to assess lentiviral gene transfer for the prevention or slowing of cystic fibrosis disease progression in pigs
- **Cystic Fibrosis** – pilot assessment of airway deposition of orally inhaled Technetium 99 or AAV1/AAV5 in rhesus macaques
- **ADA-SCID** – toxicology testing of EFS-ADA lentiviral vector in mice
- **Alpha-1 Antitrypsin Deficiency** – toxicology and biodistribution testing of AAV10 in mice and NHPs

Ongoing GTRP-Supported Studies Targeting Rare Diseases-2

- **X-linked retinoschisis** - toxicology and biodistribution study to assess AAV8 vector in pigs
- **Pompe disease** – toxicology and biodistribution testing of AAV2/8 LSPhGAApA immunomodulatory gene therapy in mice
- **Wiskott Aldrich Syndrome** – pilot and feasibility clinical study of hematopoietic stem cell gene transfer with w1.6_hWASP_WPRE lentiviral vector
- **Pompe disease** - Phase I/II clinical trial to assess the safety of diaphragm administration of rAAV1-CMV-GAA in children with Pompe disease and ventilator dependence

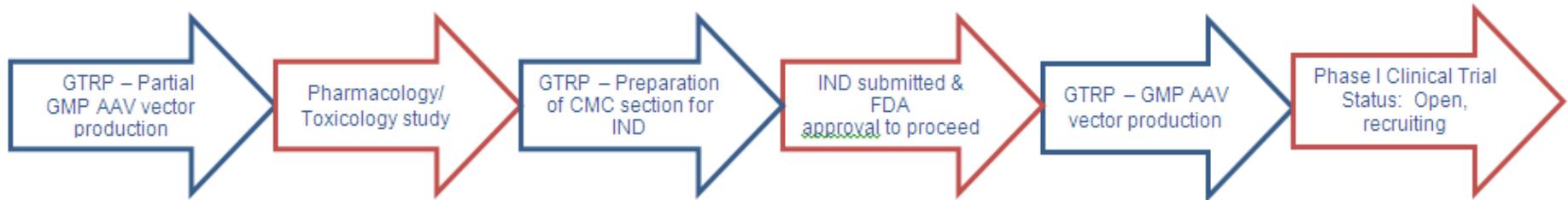
GTRP Support for Translational Science

Example 1:

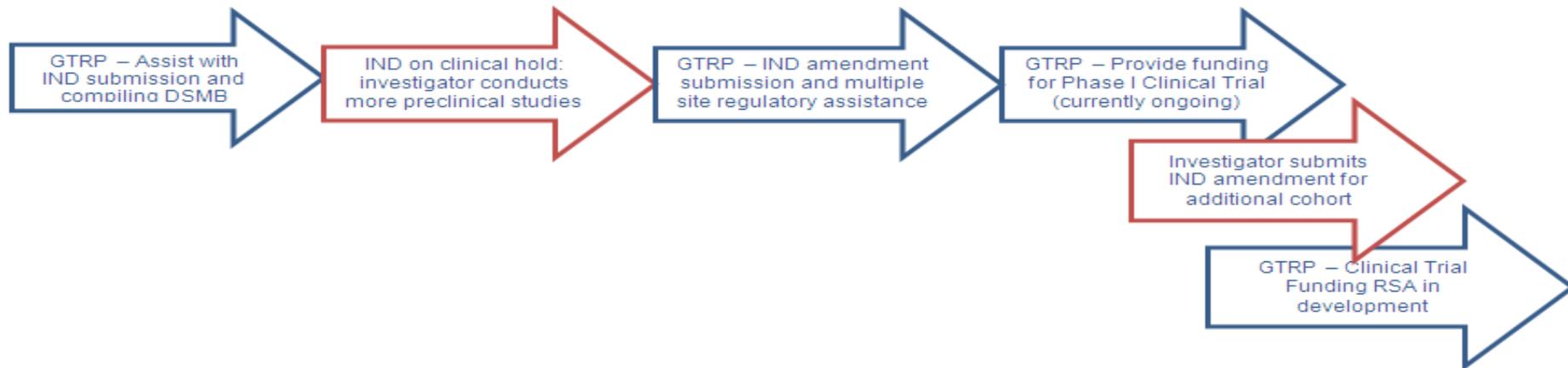


GTRP Support for Translational Science

Example 2:



Example 3:



Collaborations with Other NIH Institutes

- **National Eye Institute (NEI)**

To support an intramural investigator requesting GMP process-comparable AAV vector production for use in pharmacology/toxicology studies related to retinoschisis.

- **The NIH-RAID Program and the National Institute of Neurologic Disorders and Stroke (NINDS)**

To support an extramural investigator requesting GMP process-comparable AAV vector production for use in pharmacology/toxicology studies and clinical grade AAV vector production for use in a phase I clinical trial. Both studies are related to Parkinson's Disease.

- **The NIH-RAID Program**

To support an extramural investigator requesting pharmacology/toxicology testing in studies related to osteoarthritis.

For More Information

Visit our website: www.gtrp.org

E-mail the **Clinical Coordinating Center** at:
gtrpccc@s-3.com