

Gene Therapy Resource Program (GTRP) and the National Gene Vector Biorepository (NGVB)

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National Heart, Lung, and Blood Institute

Gene Therapy: Charting a Future Course

National Institutes of Health (NIH)

Office of Science Policy

Office of Biotechnology Activities

April 12, 2013



Overview of Presentation

- **GTRP-Gene Therapy Resource Program**
 - Program Goals
 - Organizational Structure
 - Cores and Services
 - Facilitating Translational Research
 - Participating in GTRP
- **NGVB-National Gene Vector Biorepository**
 - Policy and Procedure overview
 - Program Goals
 - Resources Offered to facilitate gene therapy research

NHLBI Gene Therapy Resource Program

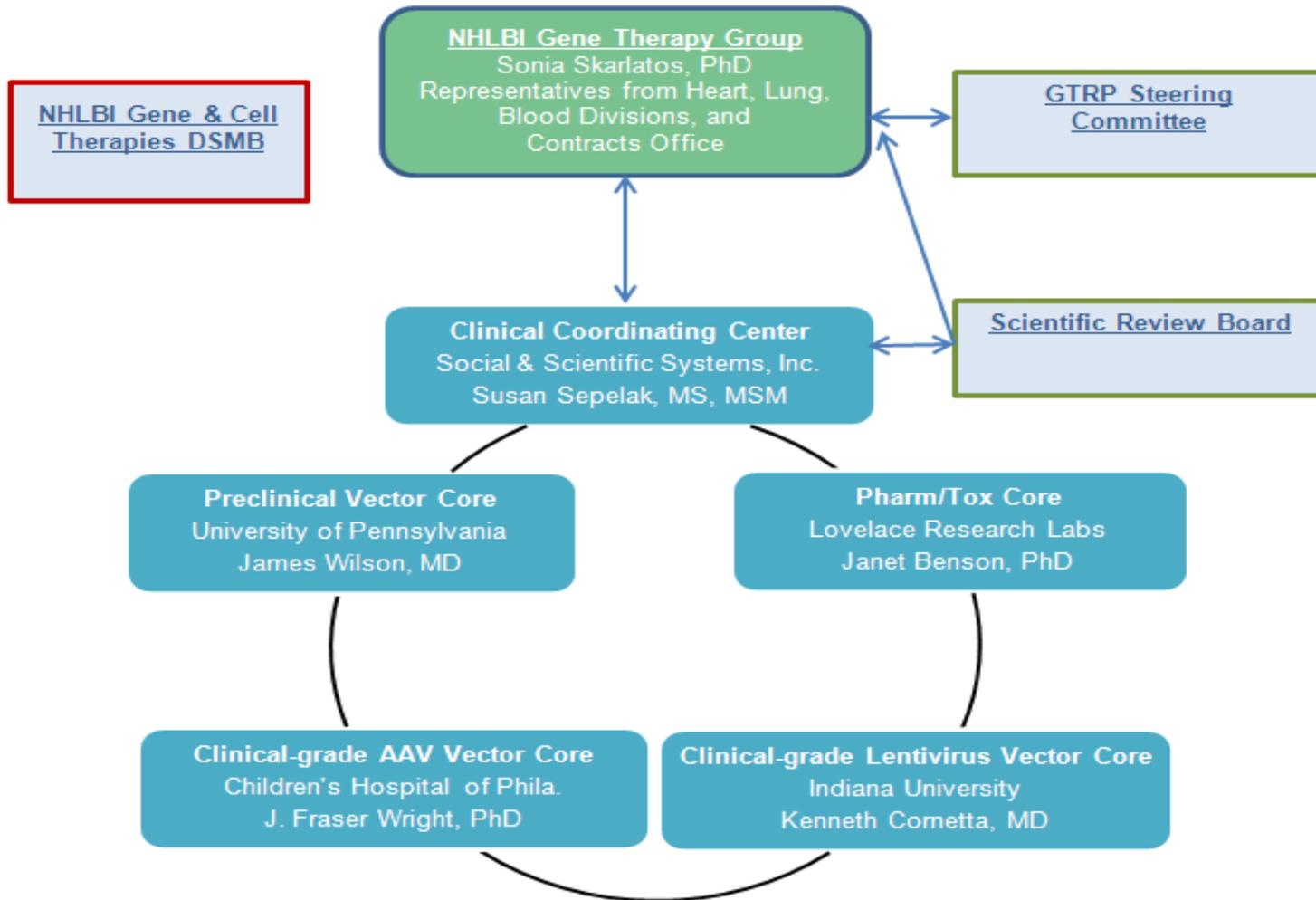
Overarching Goal of the NHLBI GTRP

To facilitate the translation of gene therapy research into clinical interventions in heart, lung, blood, and sleep disorders.

Specific Goals of the GTRP

- Provide a centrally coordinated program that offers NHLBI-funded investigators select resources at no cost, including:
 - Preclinical-grade vector production
 - Immunology testing on preclinical materials
 - Pharmacology/Toxicology testing
 - Clinical-grade AAV vector production
 - Clinical-grade Lentivirus vector production
- Provide regulatory affairs assistance to NHLBI-supported investigators
- Provide funding assistance for gene therapy clinical trials
- Offer GTRP Core Lab services to other NIH Institutes & Centers

Operational Structure of the GTRP



NHLBI Gene Therapy Group

Sonia I. Skarlatos, Ph.D.

Program Director

Division of Cardiovascular Sciences

Cheryl L. McDonald, M.D.

Deputy Program Director
and CCC Project Officer

Ray F. Ebert, Ph.D.

Division of Cardiovascular
Sciences

Susan Banks-Schlegel, Ph.D.

Division of Lung Diseases

Pankaj Qasba, Ph.D.

and

Rita Sarkar, Ph.D.

Division of Blood Diseases and
Resources

**Contracting Officers from the
NHLBI Office of Acquisitions**

Program Oversight Groups

■ GTRP Steering Committee

- Composition: Chair, Core PI and Lab Rep, Dr. Skarlatos, 3-4 outside experts, *ex officio* representatives from the FDA and NIH-OBA
- Function: Ensure compliance with Program procedures, conduct secondary review of applications, and monitor the progress toward achievement of Program goals

■ GTRP Scientific Review Board

- Composition: Scientific experts in heart, lung, and blood gene therapy; vectorology; biostatistics; ethics; and clinical trial design and conduct (virtual board)
- Function: Conduct initial peer review of RSAs for pharm/tox testing, GMP-grade vectors, and clinical trial funding assistance

■ NHLBI Gene and Cell Therapies DSMB

GTRP Core Facilities

Clinical Coordinating Center

Social & Scientific Systems, Inc.

PI: Susan B. Sepelak, MS, MSM

Preclinical Vector Core

University of Pennsylvania

PI: James Wilson, MD, PhD

Clinical AAV Vector Core

The Children's Hospital of Philadelphia

PI: Fraser Wright, PhD

Pharmacology and Toxicology Core

Lovelace Biomedical &
Environmental Institute

PI: Janet Benson, PhD

Clinical Lentivirus Vector Core

Indiana University

PI: Ken Cornetta, MD

Services offered by GTRP Cores

- Preclinical Vector Core

- Produces research-grade vectors based on AAV, adenovirus, lentivirus, and non-viral vectors
- AAV Serotypes: 1, 2, 5, 6, 6.2, 7, 8, 9, rh10
- Immunology testing services on preclinical specimens
- Consultation on vector construction and experimental design, and quality control services

- Pharmacology/Toxicology Core

- Performs preclinical 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 offered by GTRP Cores, continued

- Clinical AAV and Lentivirus Vector Cores

- Produce GMP process-comparable (pre-GMP) vectors for use in pharm/tox or other studies
- AAV serotypes 1, 2, 5, 6, 8, and 9
- Produce scalable GMP (clinical-grade) vectors for clinical trials
- Provide Chemistry, Manufacturing, and Controls (CMC) and Certificate of Analysis (CoA)

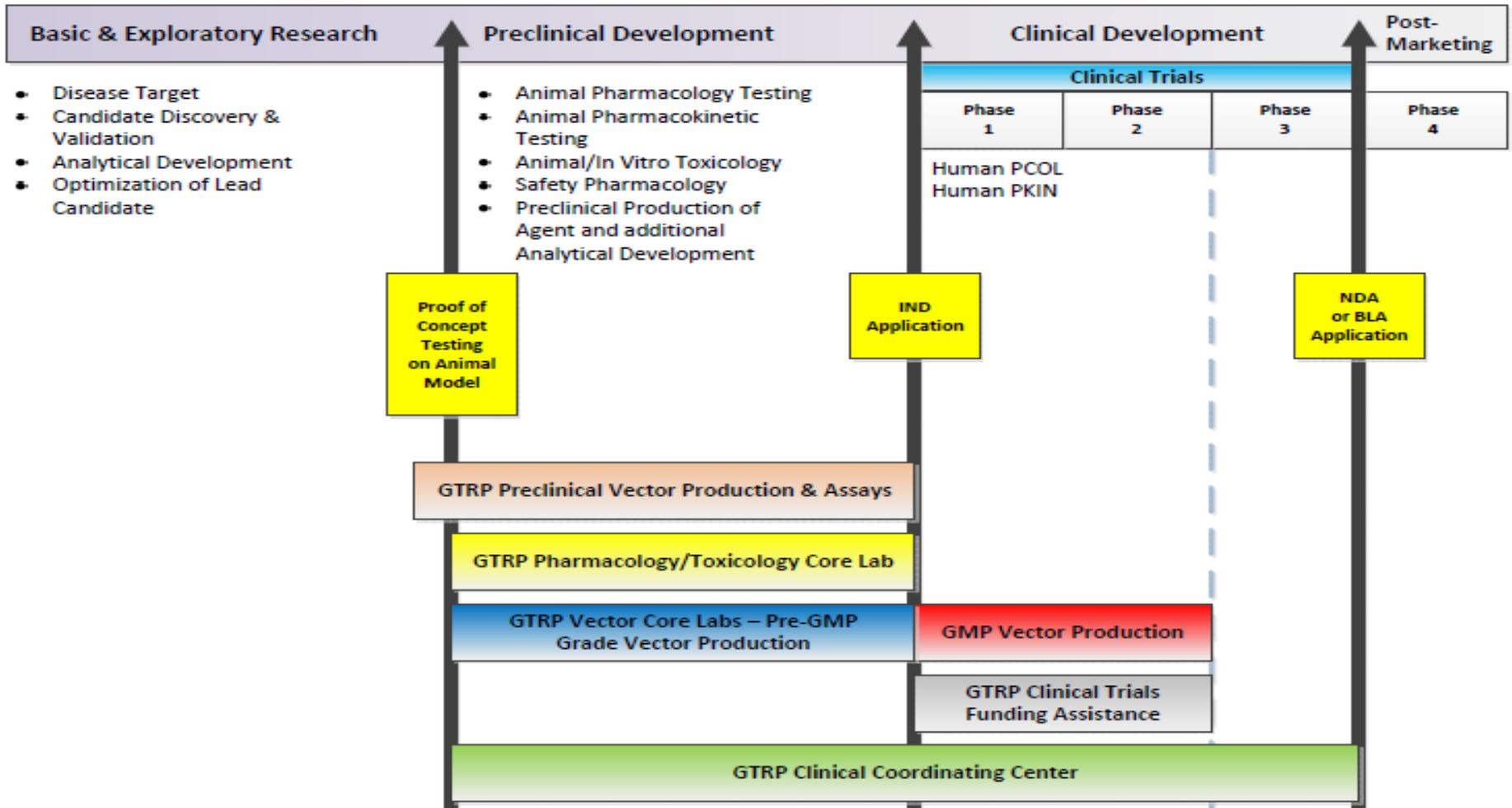
- Clinical Coordinating Center (CCC)

- Coordinates all program activities (e.g., Investigator registrations and RSAs; Interactions between Investigators and Core Lab; the SRB, SC, and assist with DSMB activities)
- Provides regulatory assistance to investigators
- Manages disbursement of clinical trial funds

Regulatory Support offered by the GTRP

- Assist in arranging and preparing for pre-pre-IND and for pre-IND meetings with FDA
- Provide scientific advice on preclinical and clinical study designs
- Assist in preparation and submission of materials to oversight bodies such as FDA, IBC, IRB, NIH-OBA, and the DSMB
- Assist in securing an IBC for oversight of a protocol at an institution without a standing IBC
- Assist in preparation and submission of IND to FDA
- Additional services available to those receiving GTRP clinical trial funding assistance

Translational Research Pathway and the GTRP



Who Qualifies for GTRP Services?

- **In all cases:**
 - Investigator and the work must be U.S.-based
 - Proposed work must be geared towards translation, not purely exploratory or mechanistic in nature
- **Regulatory Support & Clinical Trial Funding:**
 - Proposed work must be in NHLBI Mission
 - Regulatory support: PI must be, or have been, an NHLBI grantee or be currently listed as personnel on an NHLBI grant
 - Trial Funding Assistance: Clinical Trial PI must be an approved GTRP investigator

Who Qualifies for GTRP Services? (continued)

- **Vector production (preclinical or GMP-grade), Immunology testing, Pharm/Tox testing:**
 - Proposed work must be translational and in heart, lung, blood, or sleep disorders unless:
 - 1.) other Institute or Center will transfer the funds to NHLBI
 - 2.) the investigator will use his/her research monies (savings on lab infrastructure support costs)
 - Non-NHLBI disease area researchers should indicate on their investigator registration and RSA how they will pay for GTRP services (e.g., vector production, immunology testing)
 - Non-NHLBI Pharm/Tox testing via BrIDGs program or case-by-case basis

GTRP Website
www.gtrp.org

Clinical Coordinating Center
(CCC)

E-mail Address:
gtrpccc@s-3.com

GTRP Website-Investigator Registration and Request for Service Application (RSA)

Investigator
Registration

Request for Service
Application (RSA)

Core Laboratories

Scientific
Review Board

Steering Committee

NHLBI Gene
Therapy Group

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.

Preclinical Vector Core	Clinical-Grade AAV Vector Core	Clinical-Grade Lentivirus Vector Core	Pharmacology/ Toxicology Core	Clinical Coordinating Center
University of Pennsylvania	The Children's Hospital of Philadelphia	Indiana University	Lovelace Biomedical and Environmental Research Institute	Social & Scientific Systems, Inc.

HIGHLIGHTS

- » [Instructions for Submitting an RSA](#)
- » [RSA Review Process](#)

INFORMATION CENTER

- » [Regulatory Guidelines](#)
- » [GTRP Presentations at the ASGT Meeting May 28, 2008](#)
- » [NHLBI Home](#)
- » [FAQs](#)

Registration and Service Request Steps

Become a Registered GTRP Investigator

Complete your
online
registration at
www.gtrp.org

The CCC will
contact you with
any questions.

The NHLBI GTG
will review
within one week.

RSA Initiation, Development and Submission

Initiate RSA &
save as prelim

Develop RSA w/
Core Lab & CCC

Submit RSA as
“Final”

RSA Success Rates

- **Total RSAs Reviewed: 139**
 - **Total RSAs Approved: 123/139 (88.5%)**
 - Preclinical Vector Production (88 of 100)
 - Immunology Testing (7 of 7)
 - Pharmacology/Toxicology (6 of 9)
 - AAV Vector Production (4 of 5)
 - Lentivirus Vector Production (4 of 4)
 - Regulatory (10 of 10)
 - Clinical Trial Funding (4 of 4)



NGVB

National Gene Vector Biorepository (NGVB)

Coordinating Center at
Indiana University
School of Medicine

www.ngvbcc.org

Principal Investigator:
Kenneth Cornetta, M.D.

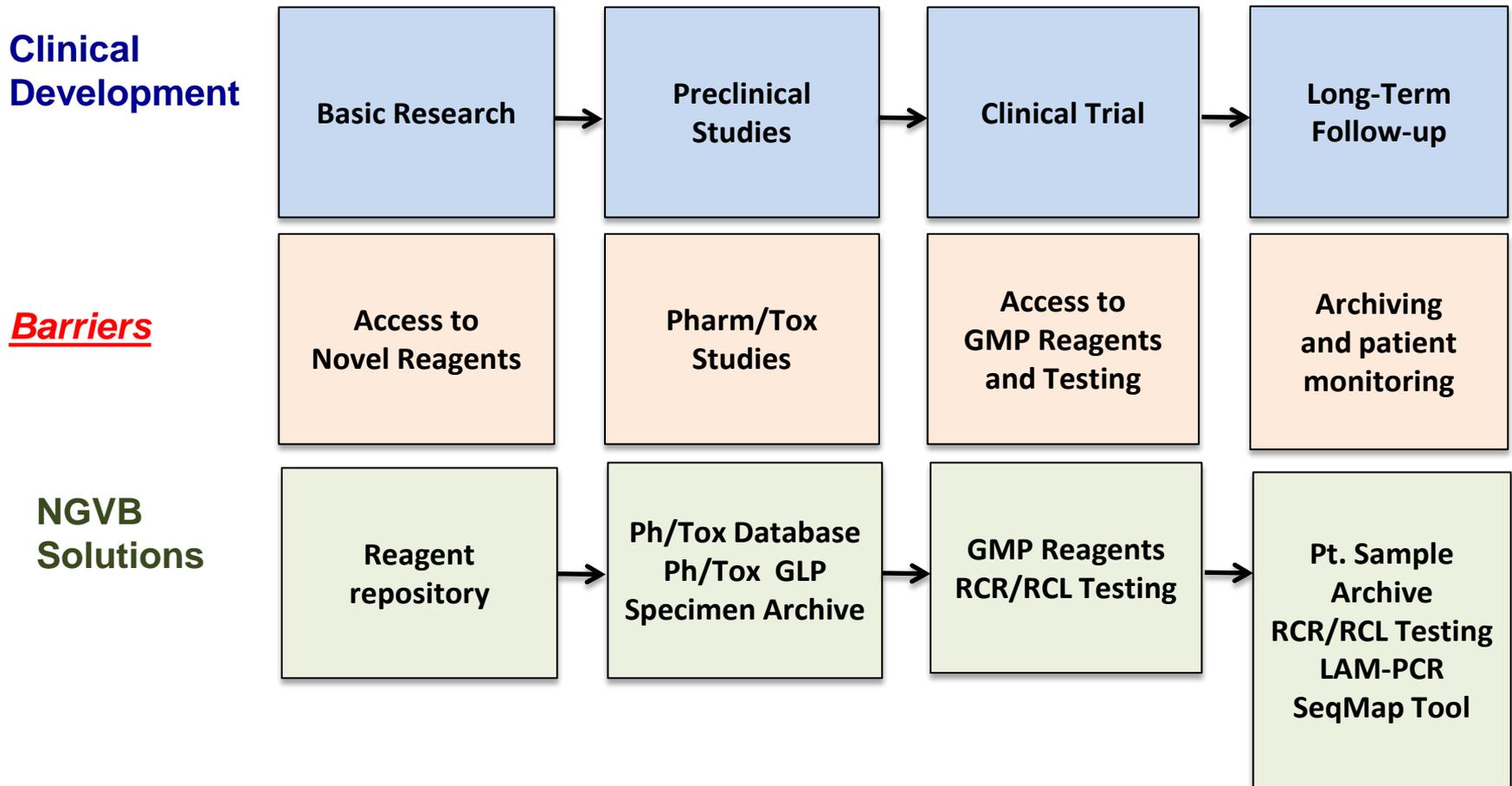
NGVB Governing Document

- NGVB Policy and Procedure Manual
 - Found under the “Info” menu tab on website at www.ngvbcc.org
 - Outlines eligibility to receive services and what is expected of the recipients
 - Not-for-profit organization or government agency
 - Follow regulatory guidelines
 - Acknowledge NGVB on all relevant publications
 - Agree to indemnification of the NGVB and NIH

National Gene Vector Biorepository (NGVB)

- NGVB Goal: *To provide gene therapy investigators with a variety of resources that can enhance their research*
- Efforts in the NGVB are focused in four areas:
 - 1.) Reagent Repository
 - 2.) Pharmacology and Toxicology Resources
 - 3.) Insertional Site Analysis
 - 4.) Archiving Services

NGVB Services across the Translational Pathway



NGVB Reagent Repository

- AAV vector plasmids (courtesy of Jude Samulski)
- Adenoviral vector stocks (Lowenstein/Castro)
- Retroviral vectors
- Lentiviral packaging line (J. Gray)
- Certified Cell Lines
 - HEK293
 - HEK293T
 - Phoenix cell lines
 - PG13
 - G7b-1

Reagents

Cart Checkout

Reagent Repository

Name
C8166 cells
GPRG
HEK293T
HEK293T/CD4 cells
K562/Lentiviral Integration Clone 6

All Reagent Type ▼ Vector Classification ▼

Antibody ▶	All
Cell Line ▶	AAV
Plasmid ▶	Adenovirus
Vector ▶	HSV
	Lentivirus
	Retrovirus

To order pull-down

Example

- Select **Reagent Type** cell lines
- Select **Reagent Type**

To continue to shop for reagents hit the reagents button at the top. To checkout hit the cart button to finalize your order.

ent to see from the cart.

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all cell lines

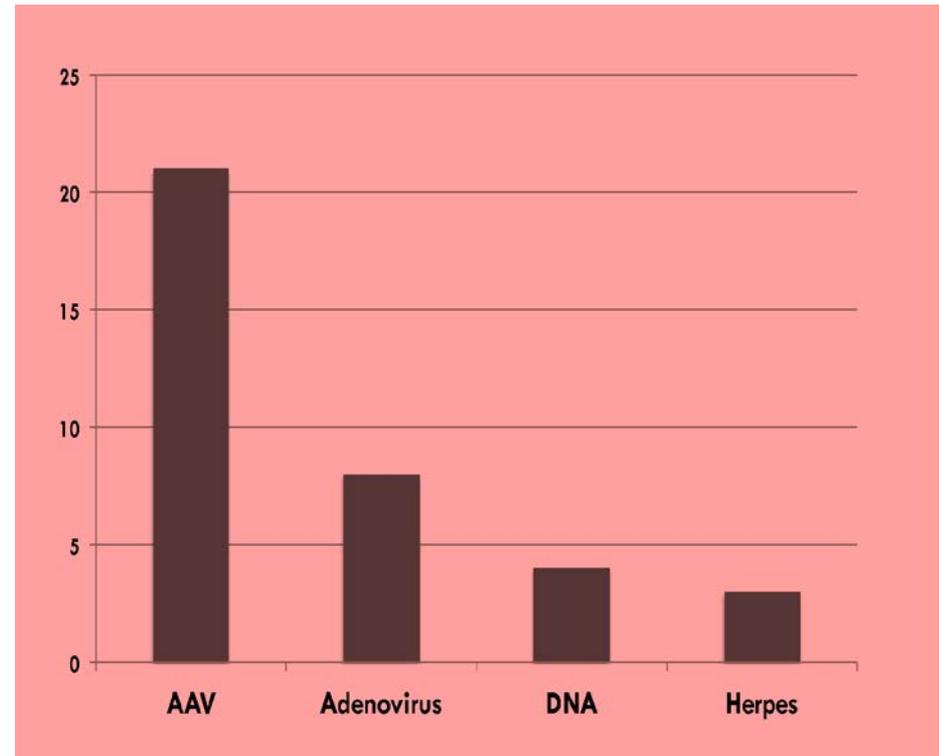
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Pharmacology and Toxicology Resources

Pharm/Tox Study Database and Pharm/Tox Specimen Archiving

NGVB Pharmacology/Toxicology Database

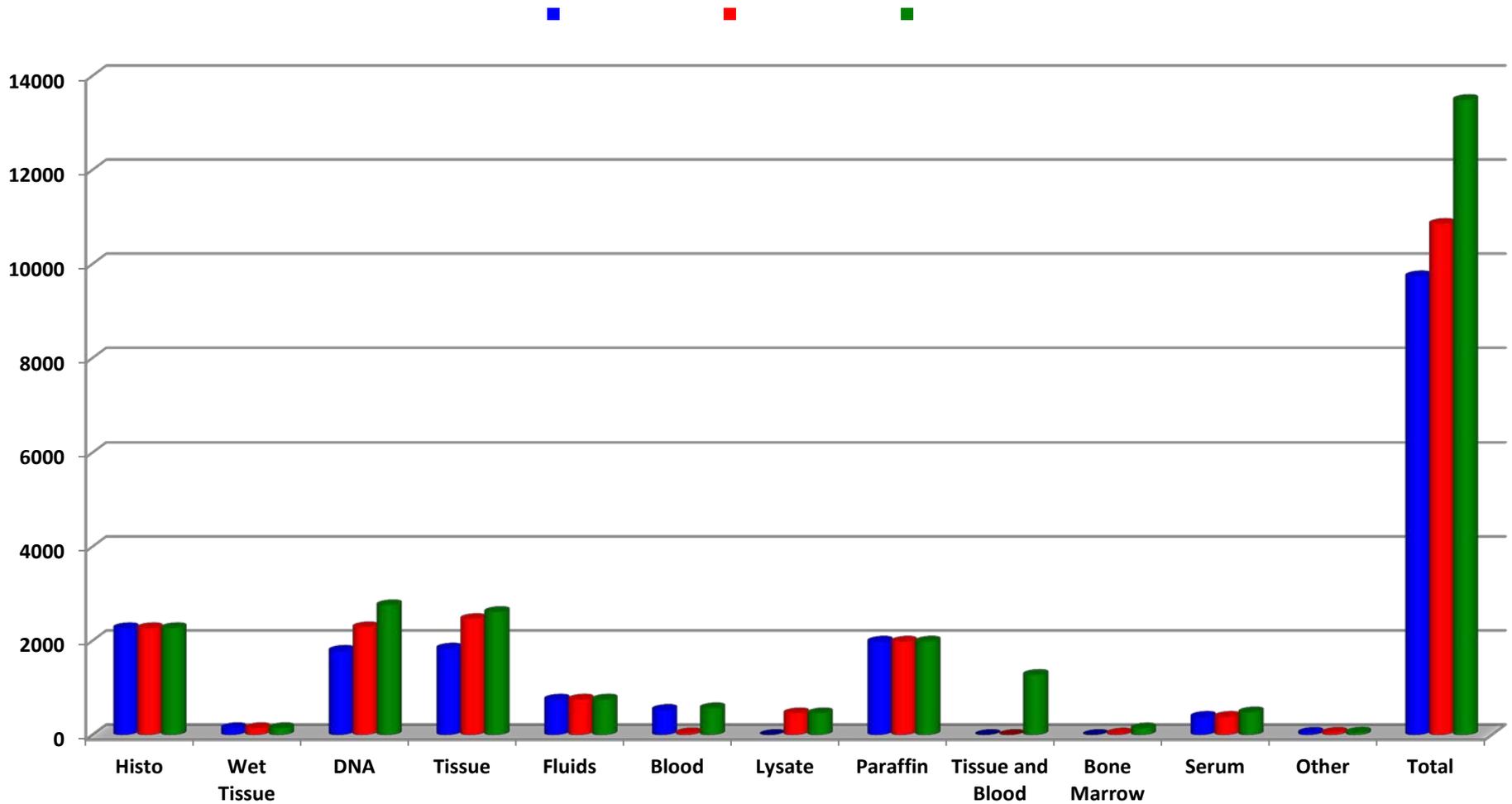
- Descriptions of pharm/tox studies submitted to FDA in support of gene therapy INDs
- If applicable info is in database, staff will assist with Letters of Cross Reference, which could limit new pharm/tox studies required
- Educational Tool



Types of Archiving Services

- **Pharmacology and Toxicology Samples**
 - NGVB will maintain samples (that require GLP storage conditions) from any gene therapy-related Pharmacology or Toxicology study submitted to the FDA by a U.S. academic investigator. (> 13,000 specimens)
- **Clinical-Grade Vector and Cell Lines**
 - Reserve or back-up GMP-grade vector and master cell lines ensures availability in case of catastrophic event at investigator's site
- **Clinical Trial Specimens**
 - Patient samples collected during post-trial monitoring phase to comply with FDA requirements

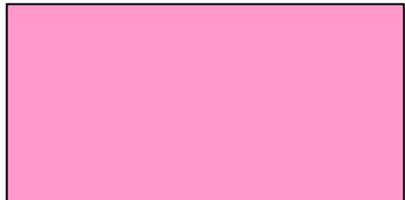
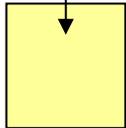
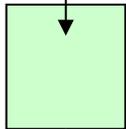
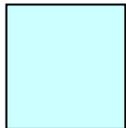
GLP Pharmacology & Toxicology Archive



Insertional Site Analysis and Post-Trial Monitoring

- RCR and RCL testing on clinical cell products
- RCR and RCL testing of patient samples
- LAM-PCR or other insertion site analysis
- SeqMap 2.0 – a bioinformatics tool to help analyze LAM-PCR and other integration analysis

SeqMap



original

vector

chr3

Proposed Insertion Site

TOP0_Start

LTR_AdaptorPrimer

LTR1

TOP0_End

Description (Edit Description)
 SEQ03-1.2
Sample (Edit Sample)
 SEQ03-1

Comment (Edit Comment)

BLAT Annotation (Full Summary)
 # Hits Found: 2
User Data
 Add User Data

Calculation of Top UCSC Hit

Gene Symbol:	Evi1
Gene Location:	upstream
Identity:	100.0
Strand:	-
Closest End (kbp):	109.4
Gene ID:	NM_007963
Human Ortholog:	EVI1

Calculation of Top Ensembl Hit

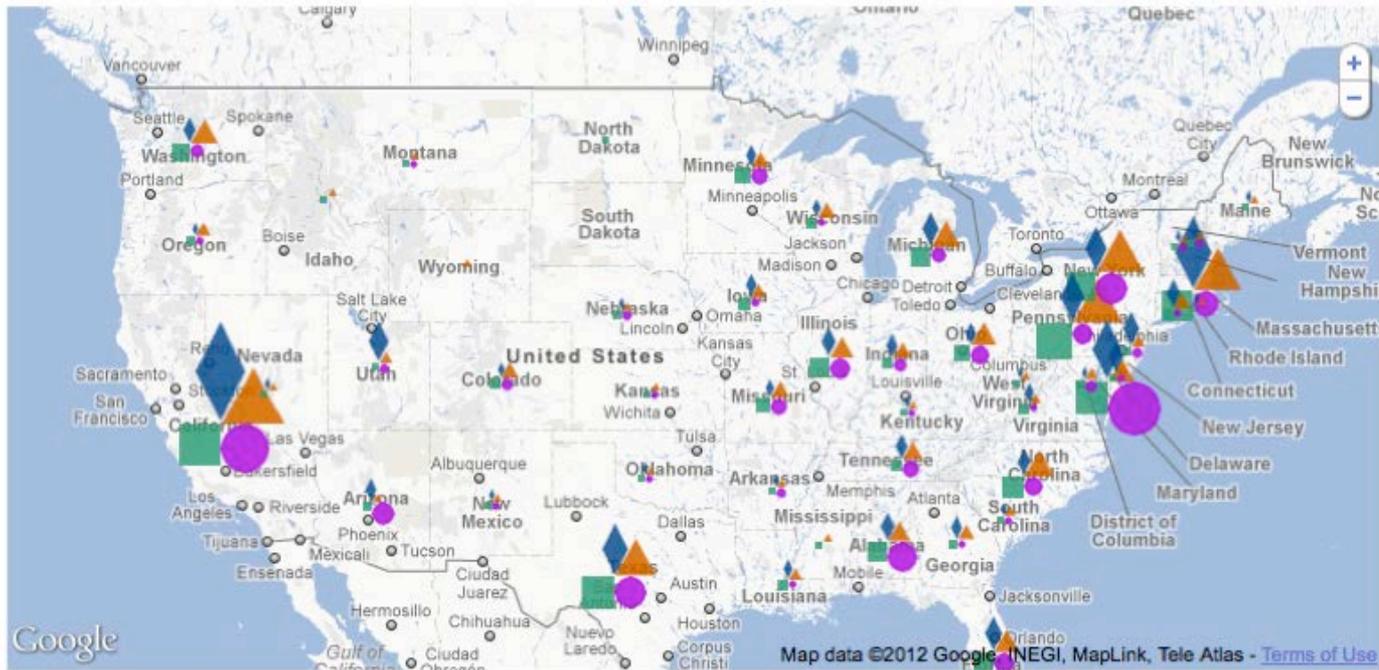
Gene Symbol:	Evi1
Gene Location:	intron 1
Identity:	100.0
Strand:	-
Closest End (kbp):	443.4
Gene ID:	NM_007963.1
Human Ortholog:	EVI1

Sequence
Original Sequence
 GCTTGGTCCGAGCTCCGATCCACTAGTAAACGCCGCCAGTGTGCTGGAATCCGCCCTCCATGCCCTGCCA
 AAATGGCGTTACTGCAGCTAGCTTGCCAACTACAGGTGGGCTTTTCAGTAGTGTATCAACTGAGAT
 AACCCAGAATCATTTTCTATATCTCCAGGGCAGGCCCCACAGTGAGGTGTTTAGAACCTGGTCTTCT
 CCAGAGAATCACCACGGCTGCCNTAAGANGNGGGCAATTCTGCTGCAGATTTCNCATCCACACTGGGGCG
 GCNGCTCGAGCATGCATCTAAGGGGCCAANTTCGCCCTATAGTGAAGTCTATTACAATTCACCTGCCNGT
 CNTTNTACACNNTCNTGACNGGAAAAAAA

Vector Removed Sequence
 GCTTGGNN
 NNN
 AACCCAGAATCATTTTCTATATCTCCAGGGCAGGCCCCACAGTGAGGTGTTTAGAACCTGGTCTTCT
 CCAGAGAATCACCACGGCTGCCNTAAGANGNGGGCAATTCTGCTGCAGATTTCNCATCCACACTGGGGCG
 GCNGCTCGAGCATGCATCTAAGGGGCCAANNNNNNNNNNNNNNNNNNNNNNNNNNNNNNNNNNNNN
 CNTTNTACACNNTCNTGACNGGAAAAAAA

Repeat Masked Sequence
 GCTTGGNN
 NNN
 AACCCAGAATCATTTTCTATATCTCCAGGGCAGGCCCCACAGTGAGGTGTTTAGAACCTGGTCTTCT
 CCAGAGAATCACCACGGCTGCCNTAAGANGNGGGCAATTCTGCTGCAGATTTCNCATCCACACTGGGGCG
 GCNGCTCGAGCATGCATCTAAGGGGCCAANNNNNNNNNNNNNNNNNNNNNNNNNNNNNNNNNNNNN
 CNTTNTACACNNTCNTGACNGGAAAAAAA

Welcome to the Gene Therapy Data Map



- ▲ Funding ?
- NIH
- NSF
- Publications ?
- Medline
- Clinical Trials ?
- ◆ Patents ?
- USPTO

From year to year

Search by:



Maps
Detail
Data
About

About

Gene therapy seeks to offer new therapeutic options to patients suffering from a wide range of diseases. This work combines the insights into human illness illuminated by the human genome project with advances in gene transfer technology. The field is highly interactive involving basic scientists, engineers, bioethicists, and clinicians. As the methods of gene transfer are a new paradigm, the novel therapies are of significant interest to patients, regulators and the press.

Please consult the National Gene Vector

Cost to Investigator for NGVB Resources

<u>Resource</u>	<u>Cost</u>
Reagents	FREE to academic investigators
Pharm/Tox Database Information	FREE to all
Archiving Services	FREE to academic US investigators
SeqMap	FREE to all
Insertion Site Analysis (e.g. LAM-PCR)	FREE to academic investigators
RCR/RCL Testing Post-Trial Monitoring	FREE to academic investigators

NGVB Contact Information

NGVB Biorepository Manager

Lorraine Matheson
Phone: 317-274-4519
ngvbcc@iu.edu

Mailing Address

National Gene Vector Biorepository
Dept. of Medical and Molecular Genetics
980 West Walnut Street, R3 C602
Indianapolis, IN 46202

16th Annual ASGCT Meeting (May 15-18, 2013)

Salt Lake City, Utah

“The GTRP: Perspectives of an Investigator and the Program Cores”

Date: Thursday, May 16, 2013

Time: 10:30am-12:30pm

Location: Room 150ABC, Salt Palace Convention Center

Agenda:

- Guest Speaker: Dan Rader
- GTRP Project Director: Sonia Skarlatos
- Core Labs: Respective PIs

GTRP Booth

NGVB Booth #412



National Heart, Lung,
and Blood Institute