



### NEWSLETTER Spring 2013

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## The GTRP Advances Gene Therapy Research

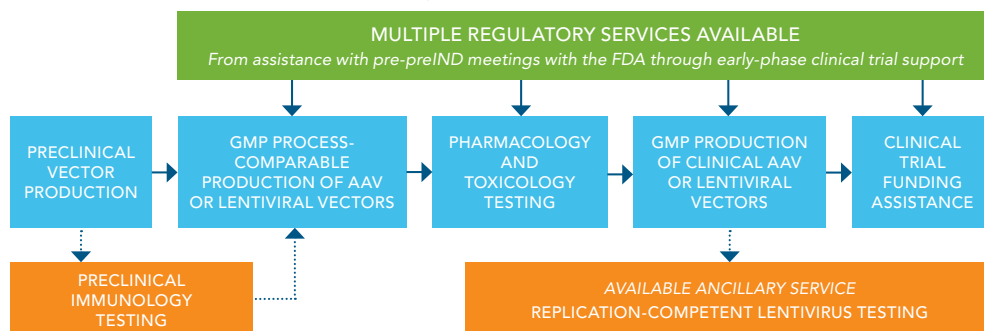
Since its inception in 2007, the National Heart, Lung, and Blood Institute (NHLBI) Gene Therapy Resource Program (GTRP) has been providing resources at no charge to U.S.-based investigators researching gene therapy for heart, lung, and blood diseases.

The GTRP, directed by the NHLBI Gene Therapy Group (GTG) under the leadership of Sonia Skarlatos, PhD, consists of four core laboratories and a clinical coordinating center. The GTG receives program oversight advice from the GTRP Steering Committee. The Scientific Review Board, a panel composed of experts in various aspects of gene therapy and disease-specific fields, provides written evaluations of investigators' requests for services on an ad hoc basis at the request of the NHLBI GTG. Clinical trials that receive GTRP funding assistance are reviewed and followed by the NHLBI Gene and Cell Therapies Data and Safety Monitoring Board (DSMB).

The Core Laboratories are: Preclinical Vector Core Laboratory at the University of Pennsylvania; Pharmacology/Toxicology Testing Core Laboratory at the Lovelace Biomedical and Environmental Research Institute; Clinical AAV Core Laboratory at The Children's Hospital of Philadelphia; Clinical Lentivirus Vector Core Laboratory at Indiana University; and the Clinical Coordinating Center (CCC) at Social & Scientific Systems, Inc.

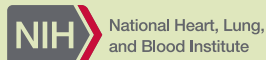
GTRP resources offered to U.S.-based investigators include: preclinical and clinical-grade vector production; pharmacology/toxicology testing; immunology testing; regulatory affairs support; and partial funding for clinical trials—all at no cost to the investigator. The services provided by the GTRP span the product development spectrum as shown below.

### The GTRP Offers Services Along the Entire Product Development Spectrum



Investigators may request one or more services, as needed, to expedite their translational research. Investigators not funded by NHLBI, or those who are researching conditions outside of the NHLBI Mission (<http://www.nhlbi.nih.gov/about/org/mission.htm>), may still be eligible for some GTRP services. Researchers funded by other Institutes and Centers at the NIH are encouraged to speak to their respective NIH Program Officers, and those not funded by the NIH may contact the GTRP Clinical Coordinating Center at [gtrpccc@s-3.com](mailto:gtrpccc@s-3.com).

In order to request Program services, investigators must first be approved and registered in the GTRP system. At present, there are 125 investigators registered in the GTRP and over 200 service requests have been submitted, approximately 89% of which have been fulfilled. To register and apply for resources, investigators should visit the GTRP website at [www.gtrp.org](http://www.gtrp.org) or email the GTRP Clinical Coordinating Center.



## A Conversation with Dr. Sissel Lund-Katz



Sissel Lund-Katz, Ph.D., is a biophysicist at Children's Hospital of Philadelphia and the University of Pennsylvania. She is currently collaborating with Drs. Michael C. Phillips and Daniel Rader (University of Pennsylvania) to explore the use of AAV8 vectors to express human apoE in apoE-deficient mice.

Moving discoveries with therapeutic potential out of the basic science lab and along the translational pathway into clinical applications is the goal of the GTRP. Teamwork and effective collaborations among basic science researchers and experienced clinical investigators can be invaluable in creating and implementing an effective product development plan. Such teamwork can also make optimal use of the available financial and intellectual capital. Dr. Lund-Katz has successfully partnered with colleagues and the GTRP to further her apoE research along the translational pathway.

A major step in translation is moving a product from the bench to pharmacology/toxicology testing in animals. It can take years to identify the best combination of genes/vectors/promoters that will make a product candidate with the most favorable profile. The GTRP plays a pivotal role in this process by providing preclinical gene vectors. Although the GTRP does not support preclinical vector production for purely mechanistic studies, it has allowed several investigators to identify product candidates with the potential for clinical significance.

Via three separate Request for Service Applications (RSAs), the GTRP Preclinical Vector Core produced AAV8 vectors with 14 different genes for Dr. Lund-Katz. In her most recently completed RSA, Dr. Lund-Katz noted that "once an 'enhanced apoE' molecule has been developed and evaluated in mice (including effects on atherosclerosis), Dr. Rader will use the AAV8 vector expressing this 'enhanced apoE' variant to develop procedures for correcting hypercholesterolemia in human subjects."

In a recent interview with the GTRP Clinical Coordinating Center, Dr. Sissel Lund-Katz offered insights into her experience with the GTRP; the dissemination of her research outcomes on the apoE project; and her thoughts on collaborative efforts in translational science.

**How did you initially learn about the NHLBI Gene Therapy Resource Program?** Daniel Rader and Ms. Dawn Marchadier from Dr. Rader's laboratory told me about the NHLBI program and the services they provide.

**How would you describe your experience working with the GTRP?** The GTRP provided excellent advice and service with three RSAs and had very good follow-up support. The UPenn Vector Core was very productive; all vectors were produced on time as stated by the core and the AAV8 products were well characterized. The Director [Dr. Julie Johnston] and her staff were very helpful with explanations and suggestions.

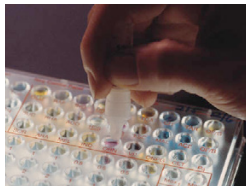
**Have you been able to share information garnered from the completed research with the research community?** Yes, our work was recently published in *Arteriosclerosis, Thrombosis, and Vascular Biology (ATVB)*, Vol. 33, April 2013. Additionally, our work was previously presented at the following two meetings:

1. "Comparison of the Structure-Function Relationships of Human ApoE3 and ApoE4: From in vitro Structural Studies to in Vivo Mouse Studies"; American Heart Association Workshop on HDL, Chicago, IL, April 2011.
2. "ApoE3 and ApoE4 Polymorphism: Mechanistic Basis for Differential Isoform Effects on Serum Cholesterol Levels and Lipoprotein Profiles"; Workshop 22, Recent Advances in Cardiovascular Disease Assessment, XVI International Symposium on Atherosclerosis, Sydney, Australia, March 2012.

These two presentations generated quite a bit of interest. Subsequently, Dr. Michael Phillips and I were invited, as a team, to present our work at the American Society for Pharmacology and Experimental Therapeutics meeting in Boston, April 21-25, 2013. During the Symposium: "Apolipoprotein E: A Protein at the Intersection of Vascular and Neurodegenerative Disease," Dr. Phillips gave a session entitled, "Molecular basis for differential effects of apolipoprotein E isoforms on lipoprotein metabolism."

**As a biophysicist involved primarily in basic research, how did you establish your collaborative research relationship with an experienced clinician?** We have a long standing collaboration with Dr. Rader on HDL metabolism, so it was easy to extend our collaboration to apoE. Dr. Rader's clinical expertise in translational research provided us with an opportunity to apply new mechanistic knowledge about apoE to clinical applications. Collaborations are essential to conducting a project that spans biochemistry, biophysics, molecular biology and animal physiology. I highly recommend collaborations so that more complex research questions can be addressed.

## Valuable Immunology Testing Offered to Gene Therapy Investigators

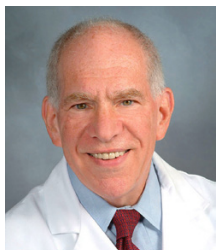


The University of Pennsylvania (UPenn) Vector Core began offering immunology testing services related to the use of preclinical-grade vectors to GTRP investigators in 2008.

Immunology testing is particularly important to investigators working with large animal models where even low to moderate levels of pre-existing circulating neutralizing antibodies (Nabs) can significantly impact the efficiency of gene transfer. The UPenn Vector Core offers a sensitive Nab assay to detect low levels of pre-existing Nabs to AAV, adenoviral vectors, and lentiviral vectors prior to vector administration.

The induction of T-cell responses against vector-delivered transgene(s) can result in the elimination of the transduced cells, thereby decreasing expression of the therapeutic genes. Therefore, the UPenn Vector Core also offers GTRP investigators T-cell assays including ELISpot and intracellular cytokine staining to capsid and transgenes.

## Progress in Treating Alpha-1 Antitrypsin Deficiency



Ronald G. Crystal, MD, will be presenting an abstract at the 2013 ASGCT Meeting on his project entitled "Lung-directed gene therapy for alpha-1 antitrypsin deficiency" for which he received pharmacology/toxicology testing services from the GTRP's

Pharmacology/Toxicology Core at Lovelace Biomedical and Environmental Research Institute.

The following is a preview of that presentation: *"The Department of Genetic Medicine at Weill Cornell Medical College, under the leadership of Ronald G. Crystal, MD, has developed a novel strategy to treat the pulmonary manifestations of alpha-1 antitrypsin deficiency in which an adeno-associated virus vector serotype rh.10 coding for human alpha-1 antitrypsin is administered to the pleura surrounding the lungs. In pharmacology/toxicology studies carried out by the GTRP in mice and nonhuman primates, this strategy has been shown to be safe, with human alpha-1 antitrypsin gene expression in the monkey pleura for at least 1 year. This approach is now being developed for human testing in individuals with alpha-1 antitrypsin deficiency and emphysema."*



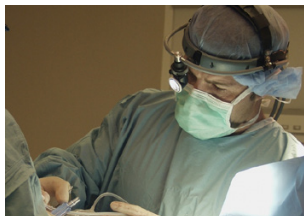
## American Society of Gene and Cell Therapy (ASGCT) Meeting, May 15-18, 2013 in Salt Lake City, UT

**GTRP Symposium** On Thursday, May 16, 2013, Daniel Rader, MD, will be the guest speaker and will open the GTRP symposium with a discussion of his experience as an investigator receiving services from the GTRP. Chairing this symposium is Sonia Skarlatos, PhD, who leads the NHLBI's Gene Therapy Group and serves as Program Director of the GTRP. Principal Investigators from the GTRP Core Laboratories and the GTRP Clinical Coordinating Center will present a series of discussions about specific GTRP services offered. This is an opportunity for both experienced and inexperienced investigators to learn more about services offered through the GTRP and to hear specific examples of services already provided to researchers. This symposium offers a rare opportunity for audience members to have all of the GTRP Principal Investigators available for questions and comments in a single setting. The NHLBI encourages investigators who have already received service through the GTRP to attend and contribute personal insights to the discussion.

**GTRP Exhibit Booths** For those attending the meeting, take the opportunity to visit the NHLBI GTRP Booth #408 in the ASGCT exhibit hall. Members of the NHLBI Gene Therapy Group and the GTRP Clinical Coordinating Center will be available at the GTRP Booth to address general and specific questions about Program services and can guide you through the online registration process.

Meeting attendees are also encouraged to visit the individual booths sponsored by the GTRP Core Laboratories. Representatives from each Core Lab will be available to address questions regarding services provided through the GTRP. The Cores Lab booths are: University of Pennsylvania (Booth #410); Children's Hospital of Philadelphia (Booth #414); Lovelace Biomedical and Environmental Research Institute (Booth #406); and Indiana University (Booth #412). Indiana University also hosts the National Gene Vector Biorepository (NGVB).

## Clinical Trials Receive Partial Funding Through the GTRP



To date, the GTRP has provided partial funding for three gene therapy clinical trials that fall within the mission of the NHLBI. The conditions under study in these three trials are: congestive heart failure (CHF), Pompe disease, and Wiskott-Aldrich Syndrome (WAS). These three trials are registered in [www.clinicaltrials.gov](http://www.clinicaltrials.gov).

**Congestive Heart Failure** is a debilitating condition that affects all age groups. It is estimated that over 5 million Americans are living with CHF and over 550,000 new cases are diagnosed each year. CHF accounts for more physician visits and hospitalizations per year than all forms of cancer combined. The GTRP is providing partial funding assistance for the trial, "Ad5.hAC6 Gene Transfer for CHF," sponsored by Dr. H. Kirk Hammond. This multi-site Phase I/II clinical trial is designed to determine: 1) whether gene transfer using an agent called Ad5.hAC6 (adenovirus-5 encoding human adenyl cyclase type 6) can be given safely to patients with CHF and 2) whether this agent may be of benefit in heart failure. The trial is currently enrolling.

**Pompe Disease**, classified as a rare disease, is a Type II glycogen storage disease affecting about 1 in 40,000 births. It is an autosomal recessive genetic disorder caused by a mutation in the gene that codes for the enzyme acid alpha-glucosidase (GAA). GAA deficiency leads to lysosomal accumulation of glycogen in all tissues, resulting in muscle dysfunction and profound muscle weakness. There is a spectrum of disease severity based on the degree of enzyme deficiency, but the most severely affected patients have cardiorespiratory failure, often fatal in the first two years of life if untreated. Dr. Barry Byrne at the University of Florida is receiving GTRP funding assistance for the clinical study, "Safety Study of Recombinant Adeno-Associated Virus Acid Alpha-Glucosidase to Treat Pompe Disease." This study will evaluate the safety of the intradiaphragmatic delivery of rAAV1-CMV-hGAA into individuals with GAA deficiency (Pompe disease). The study will also determine what dose

may be required to achieve improvement in measures of respiratory function. This trial is currently enrolling from across the U.S. and is nearing completion of enrollment in the second of three cohorts.

**Wiskott-Aldrich Syndrome** is a rare X-linked recessive genetic disease affecting an estimated 4 in 1,000,000 live male births. WAS is a primary immunodeficiency disease characterized by abnormal T- and B-cell lymphocyte functioning and micro-thrombocytopenia. Clinical manifestations include recurrent infections, frequent and hard-to-control bleeding, eczema, and a high incidence of autoimmune manifestations and lymphoid malignancies. There are some milder forms of WAS, but more severe forms need treatment as early as possible to prevent life-threatening complications due to bleeding, infection, and malignancies.

Allogeneic hematopoietic stem cell transplantation can be curative, but its success is limited by the availability of an HLA-matched donor and the age of the patient (ideally <5 years). Researchers are exploring gene transfer as an alternative treatment option for WAS that is independent of HLA-donor availability and one that should avoid complications such as graft-versus-host disease or rejection.

The GTRP is providing partial funding support for a study entitled, "Pilot and Feasibility Study of Hematopoietic Stem Cell Gene Transfer for the Wiskott-Aldrich Syndrome (WAS)." This study is sponsored by Dr. David A. Williams, and the Principal Investigator is Dr. Sung-Yun Pai, at Boston Children's Hospital.

This open-label, non-randomized study employs autologous CD34+ cells transduced ex vivo with the w1.6\_hWASP\_WPRE(VSVg) lentiviral vector containing the human WAS gene. The primary objectives of this study are 1) to assess the safety of administration of the lentiviral vector encoding human WAS cDNA in Wiskott-Aldrich patients without an HLA-genotypically identical bone marrow donor, and 2) to assess the achievement of engraftment of WASP-expressing transduced T-cells. The study is currently recruiting participants.

## Points of Interest

**NEW Journal** The premier issue of *Human Gene Therapy Clinical Development*, launched April 2013, includes an article entitled, "Advancing Translational Research Through the NHLBI Gene Therapy Resource Program."

**Revised NIH Guidelines** The revised *NIH Guidelines for Research Involving Recombinant or Synthetic Nucleic Acid Molecules* became effective March 2013. The revised Guidelines are available on the NIH-OBA website (<http://oba.od.nih.gov>).

**Helpful References and Guidance Documents** Gene Therapy researchers can find select guidance documents and links to other helpful resources under the "Information Center" on the GTRP website ([www.gtrp.org](http://www.gtrp.org)).

