



NEWSLETTER Winter 2014–15

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GTRP Collaborations with Other NIH Institutes and Centers

The Gene Therapy Resource Program (GTRP), funded by the National Heart, Lung, and Blood Institute (NHLBI), provides services through applications submitted by investigators conducting gene therapy research that is within the mission of the NHLBI. Over the past seven years, the GTRP has fulfilled more than 140 requests for service. In addition, researchers funded by other Institutes and Centers (ICs) of the National Institutes of Health (NIH) can take advantage of the services provided by GTRP Core Laboratories. Other ICs may transfer funds to the NHLBI to support the specific GTRP service requested. Additionally, the GTRP can consider providing services to investigators with Small Business Innovation Research (SBIR) funding and to investigators with Small Business Technology Transfer (STTR) funding.

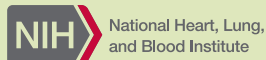
In fact, both intramural and extramural investigators from several ICs have been able to access GTRP and other program services to move promising gene therapy projects along the translational pathway, with several projects having reached the clinical trial stage. Specifically, the NHLBI GTRP has thus far collaborated with: the National Eye Institute (NEI); the National Institute of Neurological Disorders and Stroke (NINDS); the National Center for Advancing Translational Sciences' (NCATS) Bridging Interventional Development Gaps (BrIDGs) Program; the NHLBI Production Assistance for Cellular Therapies (PACT) Program; the NHLBI Center for Fetal Monkey Gene Transfer for Heart, Lung, and Blood Diseases; and the National Cancer Institute (NCI). These collaborations are described below.

X-Linked Retinoschisis. The NEI was the first of the other ICs at the NIH to tap into GTRP resources. In 2012, then-NEI intramural investigator Peter Colosi, PhD, received a Good Manufacturing Practice (GMP) process-comparable AAV8 vector for pivotal pharmacology/toxicology/biodistribution studies. With the preclinical studies complete, NEI Director Paul Sieving, MD, PhD, requested production of clinical-grade vector for use in the planned clinical trial. Vector was produced by the GTRP AAV Vector Production Core Laboratory at The Children's Hospital of Philadelphia (CHOP) and will be provided to Dr. Sieving following the completion of the vector release testing.

Parkinson's Disease. The BrIDGs Program (<http://www.ncats.nih.gov/research/rare-diseases/bridgs/bridgs.html>) and the NINDS supported the request of Krystof Bankiewicz, MD, PhD, for GMP process-comparable AAV vector (AAV2-GDNF) production from the GTRP AAV Core Laboratory for use in a pharmacology/toxicology study. Following completion of the preclinical work and submission of an IND, the GTRP produced the clinical-grade vector for the NINDS-sponsored clinical trial (ClinicalTrials.gov identifier NCT01621581). This Phase I clinical trial employing the AAV2-GDNF vector opened to enrollment in May 2012 at the NIH Clinical Center in Bethesda, Maryland. John Heiss, MD, is the principal investigator (PI) of this trial that is ongoing and recruiting. More information about this trial can be found at ClinicalTrials.gov (<http://www.clinicaltrials.gov/ct2/show/NCT01621581?term=gene+therapy+for+Parkinson%27s+disease&rank=6>).

Osteoarthritis. The GTRP Pharmacology/Toxicology Core Laboratory at Lovelace Biomedical and Environmental Research Institute recently completed a study using an AAV2 vector in an osteoarthritis model for Christopher Evans, PhD, an extramural investigator funded by the National Institute of Arthritis and Musculoskeletal and Skin Diseases (NIAMS). This study was supported by the NIH BrIDGs Program (<http://www.ncats.nih.gov/research/rare-diseases/bridgs/bridgs.html>).

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Hemophilia A. David Wilcox, PhD, requested and received GMP process-comparable lentivirus vector for use in a study to assess a protocol for cell transduction procedures. The protocol is being developed through the PACT Program (<http://www.pactgroup.net/>).

Hemophilia. Gerald Lipshutz, MD, requested preclinical vector production through the GTRP for studies to be conducted through the NHLBI's Center for Fetal Monkey Gene Transfer for Heart, Lung, and Blood Diseases (<http://www.cfmgt.ucdavis.edu>).

A Conversation with Dr. Dwight Koeberl



Dwight D. Koeberl, MD, PhD, is an Associate Professor in Pediatrics and in Molecular Genetics and Microbiology at Duke University School of Medicine. He is currently exploring the use of an AAV8 vector with a liver-specific promoter and human acid alpha-glucosidase to achieve correction of heart and skeletal muscle in patients with late-onset Pompe disease.

Dr. Koeberl received GMP process-comparable AAV8 vector and toxicology and biodistribution testing services from the GTRP. These services were provided at no cost to Dr. Koeberl. The results of the definitive toxicology and biodistribution studies in mice were published in *Molecular Therapy — Methods & Clinical Development* (June 2014).

During a recent interview conducted by the GTRP Clinical Coordinating Center, Dr. Koeberl provided his thoughts on the value of being able to access multiple resources, including GTRP services, to move research along the translational pathway.

Having received the services noted previously from the GTRP, how would you describe your experience working with the Program? The GTRP is a unique resource for the clinical translation of gene therapy. The GTRP has an extremely collaborative and responsive staff, which provided professional service in support of our pharm/tox study that would simply not be available to an academic researcher otherwise. From the initial drafting and revision of our proposal to the pre-IND meeting with the FDA, through the design and completion of the protocol and analysis of the data, the GTRP was incredibly helpful and devoted to the successful execution of our study.

Dr. Fraser Wright at the GTRP Clinical AAV Vector Production Core Laboratory at CHOP was extremely helpful during the planning and preparation of clinical-grade vector for the study.

B-cell Leukemia and Lymphoma. The GTRP Lentivirus Vector Core Laboratory at Indiana University is producing clinical-grade vector for an NIH intramural investigator. The National Cancer Institute's PI, James Kochenderfer, MD, will use the GTRP-produced clinical grade lentivirus vector in multiple clinical trials. Dr. Kochenderfer anticipates that the clinical trials will open to enrollment in September 2015.

Drs. Janet Benson and Gensheng Wang at the GTRP Lovelace Pharm/Tox Testing Core Laboratory collaborated with me and my Regulatory Affairs Office to plan the pharm/tox study and participated in the discussion at our pre-IND meeting.

During the early phases of preclinical development of your investigational product (e.g., supporting proof-of-concept studies), what services or products were you able to access from various resources?

An NHLBI R01 grant allowed me to develop AAV vector-mediated gene therapy for Pompe disease, and an administrative supplement allowed generation of mice for my pharm/tox study.

Knockout mice with Pompe disease were provided to me by Dr. Nina Raben of the National Institute of Arthritis and Musculoskeletal and Skin Diseases (NIAMS).

A Muscular Dystrophy Association grant allowed me to evaluate tissue-specific regulatory cassettes within our vectors, which were kindly provided by Dr. Steve Hauschka (University of Washington) and Dr. Inder Verma (Salk Institute).

GAA enzyme for validation of assays and anti-GAA antibody were provided to me by Genzyme Corporation (now Sanofi).

I received AAV capsids from AAV packaging plasmids from Dr. Jim Wilson (University of Pennsylvania) and GAA cDNA from Dr. Y. T. Chen (former division chief at Duke University, now at Academia Sinica in Taiwan).

As you readied your project for a definitive pharmacology/toxicology study, what types of regulatory resources did you access and from whom?

The Regulatory Affairs Office at the Duke Translational Medicine Institute (Director Dr. Bruce Burnette and Associate Director Dr. Erin O'Reilly), specifically assisted with preparation of my letter to CBER, FDA requesting a pre-preIND meeting and later a pre-IND meeting to guide the design of the pharm/tox study.

Point of Interest

NIH Director, Frances Collins, MD, PhD, provided a statement in May 2014 about the Institute of Medicine's (IOM) assessment of the role of the Recombinant DNA Advisory Committee. Dr. Collins noted that "NIH will move forward with implementing the IOM recommendations and will be issuing a proposed revision to the NIH Guidelines for Research Involving Recombinant or Synthetic Nucleic Acid Molecules for public comment in the coming months." The full statement from Dr. Collins is available on the NIH website (http://www.nih.gov/about/director/05222014_statement_iom_rac.htm).

The Regulatory Affairs Office also assisted with preparation of the clinical protocol, Institutional Biosafety Committee protocol, Institutional Review Board protocol, Investigator's Brochure, and Manual of Operating Procedure, as well as the application to the Recombinant DNA Advisory Committee (RAC).

If an investigator is unaware or does not have regulatory support through his/her institution, how would you advise him/her to proceed? Talk with colleagues having similar interests; talk with your Dean of Research and departmental contacts. I learned of our Regulatory Affairs Office from a collaborator and colleague.

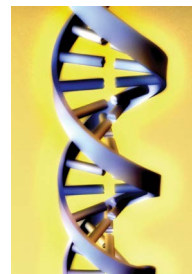
Did you collaborate with colleagues at the early preclinical and/or definitive pharmacology/toxicology testing phases? We are a center for Pompe disease research and, therefore, I had access to resources very relevant to the planning and execution of the pharmacology/toxicology study conducted through the GTRP.

We have an extremely valuable resource in the form of a clinical laboratory specializing in Pompe disease, the Duke Pediatric Biochemical Genetics Laboratory, which is supervised by Dr. Deeksha Bali—an expert in glycogen storage disease diagnosis and Dr. Sarah Young—an expert in clinical testing with mass spectrometry. These colleagues provided specialized testing in support of the pharm/tox study that also validated the biochemical endpoints for the future clinical trial.

In preparing to conduct a clinical trial, what type of support are you receiving for the various associated activities? We were very fortunate to receive a clinical trial planning grant from NIAMS, a U34 grant that supported preparation of the clinical protocol, investigator's brochure, manual of operating procedures, consent form, institutional biosafety protocol, and institutional review board protocol. I contacted the program director regarding that grant opportunity and was encouraged to apply because Pompe disease, in addition to being related to the NHLBI mission, is also related to the NIAMS mission.

NHLBI GTRP Hosts Translational Resource Session at 2014 ASGCT Meeting

On Wednesday, May 21, 2014, the Steering Committee (SC) of the GTRP hosted the evening session, "Translational Resources—What We Have and What We Need," at the American Society of Gene and Cell Therapies (ASGCT) annual meeting.



Cheryl L. McDonald, MD, Director of the GTRP, opened the evening session with a brief overview of NIH and FDA translational research resources.

GTRP SC members Janet Benson, PhD, DABT, and Charles Bridges, MD, ScD, facilitated the portion entitled "NIH Resources for and Perspectives from NIH-Funded Researchers." Two GTRP investigators, Dwight Koeberl, MD, PhD, and John Forsayeth, PhD, gave interesting and informative presentations on how they capitalized on NIH resources to move their research along the translational pathway.

The third part of the session, "From the Public Sector to the Private Sector," was hosted by GTRP principal investigator and SC member, James Wilson, MD, PhD. This portion opened with a presentation by Steven Gould, MD, Executive Director of the organization Chicago Innovation Mentors ([CIM] www.chicagoinnovationmentors.org/). Dr. Gould presented CIM's history and the CIM model for helping academic investigators bridge the knowledge and resource gaps along the translational pathway. This was followed by a panel discussion, "Perspectives from Private Sector Leaders." Panelists included: Thomas Chalberg, Jr, PhD (Avalanche Therapeutics); Steven Gould, MD (CIM); Jeffrey Marrazzo, MBA, MPA (Spark Therapeutics); Philip Reilly, MD (Third Rock Ventures); and Samuel Wadsworth, PhD (Dimension Therapeutics). Dr. Wilson and the panelists discussed interactions between the public and private sectors in cell and gene therapy product development, including issues involved in private-sector partnering with academic investigators. Audience members asked several thought-provoking and insightful questions, and a lively discussion ensued. It was clear that this topic was of keen interest to many, and the GTRP SC will consider hosting another session at the 2015 ASGCT annual meeting.

The Sonia I. Skarlatos Public Service Award of the American Society of Gene and Cell Therapy (ASGCT)

On May 22, 2014, at the 17th annual ASGCT meeting held in Washington, DC, James Wilson, MD, PhD, announced that the ASGCT Distinguished Service Award has been renamed *The Sonia I. Skarlatos Public Service Award*.

Sonia Skarlatos, PhD (from the National Heart, Lung, and Blood Institute) and Catherine McKeon, PhD (from the National Institute of Diabetes and Digestive and Kidney Diseases) were the inaugural recipients of the ASGCT Distinguished Service Award at the 2013 Annual Meeting in Salt Lake City. Sadly, Dr. Skarlatos passed away on August 6, 2013.

Dr. Wilson described Dr. Skarlatos as "...a valued champion of gene and cell therapy from its very early days." He noted that the NIH-sponsored programs she managed "...played a huge role in the clinical successes we are currently witnessing."

Translational research was championed by Dr. Skarlatos, and she was instrumental in creating three major research programs at NHLBI that reflect this passion. In addition to the establishment of the Gene Therapy Resource Program (GTRP) in 2007, Dr. Skarlatos was instrumental in the founding of the Cardiovascular Cell Therapy Research Network (CCTRN) also in 2007, and the Science Moving Toward Research Translation and Therapy Program (SMARTT) in 2010.

Also in Dr. Skarlatos' honor, the ASGCT established an endowment fund that will support young investigators in the fields of gene and cell therapy. Details related to this fund can be found on the ASGCT website (<http://www.asgct.org/donate/sonia-i-skarlatos-phd-public-service-award>).

Professor's Program Progresses



Charles R. Bridges, MD, ScD, is a Professor of Cardiovascular Surgery at Sanger Heart and Vascular Institute at Carolinas HealthCare System in Charlotte, North Carolina. He is the first investigator to move his research project from the proof-of-concept phase to GLP pharmacology/toxicology testing all within the GTRP.

Dr. Bridges initially received preclinical vector production and immunology testing services through the GTRP in 2009. With proof-of-concept studies complete, Dr. Bridges recently requested and received assistance from the GTRP in preparing and submitting his pre-preIND and pre-IND meeting packages to the Center for Biologics Evaluation and Research, Food and Drug Administration. This involved a collaborative effort among the investigator, the GTRP's Clinical Coordinating Center, and two GTRP Core Laboratories. Dr. Bridges has GTRP approval to receive GMP process-comparable vector for use in efficacy and pharmacology/toxicology studies. He is in the process of submitting a request to the GTRP for pharmacology/toxicology testing services for this project.

Dr. Bridges noted, "I have thoroughly enjoyed my interactions with all members of the GTRP staff and GTRP investigators. Without their support, our progress toward clinical translation would not have been possible. The GTRP provides a critical link allowing investigators to navigate the 'valley of death' and most efficiently and safely move promising therapeutic modalities into the clinic to help the patients who need it most."

Dr. Bridges has an active cardiovascular surgery practice, has served as the Chairman of the Department of Thoracic and Cardiovascular Surgery, and currently is the Vice President of Cardiovascular Translational Research for Carolinas HealthCare System. He has been working to address the lack of modern, cost-effective, and efficacious therapies in the area of heart failure (HF). In that pursuit, Dr. Bridges has completed extensive pre-clinical work in the area of gene therapy for HF, exploring the use of Sarcoplasmic Reticulum Calcium ATPase (SERCA2a) in a large animal model (sheep). Although AAV.SERCA2a has been documented as a highly effective gene therapy treatment for heart failure, results from previously conducted studies suggest that problems with effective myocardial AAV delivery impact the successful transfer of the gene. In response, Dr. Bridges is proposing to address observed challenges with AAV delivery efficiency through the use of a delivery approach that results in robust cardiac gene expression while significantly reducing the amount of gene expression in unintended targets, thereby limiting collateral organ damage and enhancing this delivery method's overall safety profile.

Dr. Bridges has published numerous manuscripts and has manuscripts in press acknowledging GTRP support. In addition, GTRP support has been acknowledged in both abstract oral presentations and invited presentations delivered at the American Heart Association, the American Association for Thoracic Surgery, the Society of Thoracic Surgeons, and the American Society for Gene and Cell Therapy within the last two years.

