The advent of gene therapy holds great promise but the field is still in its infancy. Advances have been made but the translation of gene therapy from the bench to the clinical application has been slow. Relatively few clinical trials of gene therapy have been initiated for heart, lung, and blood disorders, and very few are currently ongoing.

The future of gene therapy depends on our ability to translate basic research studies into clinical applications. These “translational studies” are expensive and complex, but necessary if we are to develop gene-based treatments that treat or prevent cardiovascular, lung and blood diseases. This article describes the National Heart, Lung, and Blood Institute’s (NHLBI) current gene therapy programs which have been created to help support academic research efforts to successfully translate gene therapy into viable clinical applications.

Challenges and Barriers for Gene Therapy
NHLBI convened an expert Working Group in June 2005, to better understand the issues that impede progress in gene therapy research. The group was asked for their expert advice as to the status of gene therapy research and to identify critical resources needed by academic investigators to speed clinical translation of gene therapies for heart, lung, and blood diseases.1

The Working Group Identified Three Major Research Challenges

Producing Good Manufacturing Process Vectors Reliably and Efficiently
The ability to undertake gene therapy clinical trials will require large scale production of safe and well-characterized vectors. The choices for viral vectors for many gene therapy applications are adenovirus, adeno-associated virus (AAV), retrovirus and lentivirus. Each requires dedicated facilities and technical expertise. To date, the availability of designated facilities to produce good manufacturing process (GMP)-grade vectors has been cost-prohibitive for academic investigators.

Conducting Pharmacology/Toxicology Studies
Before initiating a gene therapy trial, extensive toxicology and pharmacology studies are required in small and large animal models to understand vector dosing, related toxicity and vector dissemination. These experimental prerequisites are extremely labor intensive and expensive for individual investigators, which has slowed the pace for clinical gene therapy translation.

Lengthy and Complex Oversight and Regulatory Processes
Gene therapy clinical trials receive a high level of scrutiny and evaluation by many separate oversight and regulatory bodies. The oversight and regulatory processes involve not only the FDA, but also Institutional Biosafety Committees and Institutional Review Boards, the NIH-Recombinant DNA Advisory Committee, and the NHLBI Data and Safety Monitoring Board.

The vast array of requirements from each of these entities represents a veritable gauntlet for investigators. Each committee is capable of preventing a study from being conducted.

Providing a resource to help investigators obtain information and assistance into the oversight and regulatory processes, could greatly facilitate transfer of clinical gene transfer research into clinical practice and will have widespread applicability in the treatment of heart, lung, and blood diseases.

The NHLBI has responded to the Working Group’s recommendations by investing and establishing the following resources to facilitate the translation of gene therapy into beneficial clinical treatments to treat or prevent heart, lung and blood diseases.

NHLBI Resources and Programs
Gene Therapy Resource Program
The objective of the NHLBI Gene Therapy Resource Program (GTRP) is to provide resources in areas such as the production of preclinical and GMP grade vectors and the conduct of pharmacology/toxicology studies. In addition, the program includes resources for regulatory processes to initiate clinical trials. The program was initiated on March 12, 2007, and includes the following five components: 1) a clinical coordinating center that oversees and coordinates the logistics of the core laboratories and provide regulatory assistance for clinical trials (Social & Scientific Systems, Silver Spring, Md); 2) a preclinical-grade vector production
core laboratory (University of Pennsylvania); 3) a clinical-grade vector production core laboratory for adeno-associated virus (Children's Hospital of Philadelphia); 4) a clinical-grade vector production core laboratory for lentivirus (Indiana University); and 5) a pharmacology/toxicology core laboratory (Lovelace Biomedical Laboratories, Albuquerque, NM).

As an additional effort to promote the translation of basic research to the clinic, this program also provides funds for a maximum of two phase I/II gene transfer clinical trials per year that have successfully met all regulatory requirements and are ready to enroll patients within 12 months of application approval.

An application process for investigators to obtain services is being developed in the next couple of months (Figure 1). A Scientific Review Board composed of extramural investigators will be created to review each application. A Steering Committee will oversee the whole process. It is expected that services may be available in September 2007. A website is being created and will be available shortly at www.gtrp.org.

Fetal Non-Human Primates Gene Transfer Center

In November 2006, the NHLBI renewed the Fetal Non-Human Primate Gene Transfer Center at University of California, Davis, which has been in operation since 2000. This Center has been very successful in providing unique nonhuman primate expertise, services, and resources to NHLBI-funded investigators who wish to evaluate their viral and nonviral gene transfer strategies in monkeys. In the prior 5 years, 25 projects have taken place at this facility, all involving gene delivery using a variety of vectors (AAV, lentiviral, nonviral, etc) into nonhuman primate fetal lungs, diaphragm, heart, liver, and hematopoietic stem cells.

Each year, the center invites applications that are evaluated for scientific merit, compatibility with the center’s mission, and feasibility. Examples of services (Figure 2) include: direct in vivo fetal gene transfer using systemic and organ-targeting approaches; imaging-related techniques and procedures (ultrasound, microPET, optical imaging); cell and tissue processing and cryopreservation; flow cytometry and

Center for Fetal Monkey Gene Transfer for Heart, Lung, and Blood Diseases

**Services offered to grantees:**

- Study development and design
- Gene transfer (all age groups-systemic and organ-targeting)
- Transplant models (autologous, allogeneic, xenogeneic)
  - *In vivo imaging* (ultrasound, microPET, optical)
  - Physiologic assessments
  - Tissue harvests (collect, process, analyze)
- Laboratory (e.g., molecular, immunophenotyping, immunoselection, morphology, morphometry, laser capture microdissection)
immunoselection; real-time RT-PCR and laser capture microdissection; morphometry and morphology; and postnatal assessments focusing on the cardiovascular, pulmonary, and hematopoietic systems.

The Center continues to organize an annual gene therapy symposium focusing on state of the art technologies for gene therapy. Information on services, applications and meetings can be found at www.CFMGT.ucdavis.edu.

New Approaches to Nonviral Systems for Gene Transfer Applications for Heart, Lung, and Blood Diseases

In 2006, the NHLBI issued a Program Announcement with Review (PAR 06 to 243) entitled “New Approaches to Non-Viral Systems for Gene Transfer Applications for Heart, Lung, and Blood Diseases” with application receipt dates for the next 2 years. This funding opportunity uses the combined Exploratory/Development Grants and Exploratory/Developmental Grants Phase II (R21/R33) grant mechanisms that offer a seamless transition between the exploratory and the development phases of a project. Additional information can be found at http://www.nhlbi.nih.gov/funding/its/index.htm#pa.

The purpose of this program is to stimulate research on developing new and efficient nonviral vectors that can be used in gene therapy clinical trials. For example, studies may explore the cellular barriers that prevent efficient delivery of DNA, factors controlling stability, pharmacokinetics, and biodistribution of nonviral vectors. Studies may also include more tissue-specific and site-specific integrating or self replicating vectors. Emphasis on delivery methods is also included such as electroportation, lipofection, gene gun, ultrasound, and nanoparticles.

Summary

The NHLBI is committed to supporting basic, applied, and clinical research in gene therapy for heart, lung and blood diseases. Continued research and further development of vector systems are critical to the future success of gene transfer in treating conditions that affect millions.

Additional information regarding the research supported by the NHLBI can be found at www.nhlbi.nih.gov.

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Disclosures

None.

References


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