The NHLBI SMARTT Program
A Novel Approach to Facilitate Translational Research for Heart, Lung and Blood Diseases

Ray F. Ebert, Narasimhan S. Danthi, Marc F. Charette, Manjit Hanspal, Traci H. Mondoro, Patricia J. Noel, Michelle Olive, Antonello Punturieri, Timothy M. Moore

The National Heart, Lung, and Blood Institute (NHLBI), one of 27 institutes/centers within the National Institutes of Health, has a strong interest in promoting translational research. This can be traced to its mission statement, which reads in part: “The National Heart, Lung, and Blood Institute stimulates basic discoveries about the causes of disease, enables the translation of basic discoveries into clinical practice, fosters training and mentoring of emerging scientists and physicians, and communicates research advances to the public” (http://www.nhlbi.gov/about/org/mission). Each year, the NHLBI invests more than $3 billion to support research, training, and education programs to promote the prevention and treatment of heart, lung, and blood diseases and sleep disorders. More than two thirds of this investment is allocated to investigator-initiated research, spanning the continuum from discovery through preclinical and clinical studies.

For more than a decade, the need for targeted programs to foster translational research, including investigational new drug (IND)–enabling research activities, has been recognized by the National Heart, Lung, and Blood Institute (NHLBI) leadership. As summarized in Table 1, the first of these was initiated in 2004 to provide production assistance for regenerative cell preparations (Production Assistance for Cellular Therapies). A second program was launched in 2007 to support gene therapy research (Gene Therapy Resource Program), and these were followed by additional programs to support translation of promising discoveries from laboratory to clinic: Science Moving Towards Research Translation and Therapy (SMARTT) in 2010; National Institutes of Health Centers for Accelerated Innovations in 2011, and Vascular Interventions/Innovations and Therapeutic Advances in 2013. Then in 2014, (1) the Centers for Advanced Diagnostics and Experimental Therapeutics in Lung Diseases was funded to accelerate the development of novel products to treat lung diseases and sleep-disordered breathing; and (2) the Center for Translation Research and Implementation Science was formed to address gaps in late translation research that fosters the adoption of effective interventions and identifies gaps in translation research knowledge.

Others from NHLBI have emphasized the importance of supporting a diverse mix of basic and applied research and found “a generally well-balanced distribution of NHLBI funds among clinical and nonclinical projects across topics and funding mechanisms.” This diversity is reflected in the broad array of services and capabilities available from the NHLBI-sponsored translational research programs summarized in Table 2.

SMARTT began in November 2010 under the direction of the late Dr Sonia Skarlatos and in the setting of increasing NHLBI investments in translational research. The program was funded via a 5-year contract mechanism with a total value of $31.6 million. The organizational structure of SMARTT is shown in Figure 1. Program staff (the NHLBI SMARTT team) consists of representatives from the Division of Cardiovascular Sciences, the Division of Blood Diseases and Resources, and the Division of Lung Diseases and Sleep Disorders. Services are provided by 3 contractors: RTI International (Research Triangle Park, NC) for coordinating center and regulatory affairs support, SRI International (Menlo Park, CA) for pharmacology–toxicology and nonbiologic small-molecule manufacturing, and Advanced Bioscience Laboratories (Rockville, MD) for biologics manufacturing. An independent investigator, Dr Terry Matsunaga (University of Arizona), chairs the SMARTT Steering Committee and an external Scientific Review Board consisting of 88 members representing a broad range of scientific disciplines assists in evaluating applications.

The mission of the SMARTT program is to accelerate translation of research from demonstration of efficacy in vivo to submission of an IND application to the Food and Drug Administration (FDA). To accomplish this, SMARTT provides regulatory affairs support and manufacturing and pharmacology–toxicology services for qualified projects. It is important to note that the minimum requirements for SMARTT services are that the proposed project is aligned with the NHLBI mission...
and that proof of concept has been demonstrated in at least one relevant animal model. SMARTT does not provide continuous support throughout the preclinical development process. Rather, SMARTT support is designed with handoff end points in mind. Thus, SMARTT operates within a slice of the translational research continuum between preclinical proof of concept and IND submission. Drug candidate selection studies and clinical trials are not within scope for SMARTT funding.

Therapeutic drug candidates that are not intended for treatment of heart, lung, or blood diseases or for which efficacy in an animal model has not been demonstrated are not eligible for SMARTT services. Also, medical devices, diagnostic tests (except for diagnostic imaging agents requiring an IND), projects involving gene or cell therapy, and exploratory research aimed at identifying lead therapeutic candidates are not within the scope of SMARTT services.

Application Process
SMARTT accepts requests from academic institutions, non-profit organizations, and small businesses. The 2-phase application process begins with completion of an online application that asks for a general description of the project and services being sought. If the project is within the NHLBI mission (ie, related to treatment of heart, lung, and blood diseases or sleep disorders) and capabilities of SMARTT facilities (Figure 1), investigators are invited to complete a more detailed Request for Services Application (RSA), which is evaluated by a panel of external reviewers familiar with the field of study. Evaluation criteria include significance, feasibility, soundness of the overall approach, investigator readiness, and freedom to operate based on intellectual property considerations. Successful applicants collaborate with the relevant SMARTT facility to develop a project schedule and budget, which undergoes a final approval step by NHLBI before initiation of the work. The application and review process is designed to be completed within 3 to 6 months, assuming that all eligibility and scientific merit criteria are met.

Program Performance Metrics
By the end of its fifth year, SMARTT had received 181 RSAs; of which, 117 (65%) met the eligibility criteria and were invited to submit more detailed applications for specific services (ie, Regulatory affairs support, pharmacology–toxicology studies, and manufacturing services). Reasons for exclusion from further consideration included (1) requested services outside of SMARTT capabilities; (2) requested services outside of NHLBI’s mission; (3) failure to identify a specific disease target or drug candidate; (4) inadequate proof of concept for efficacy in a relevant animal model via the intended route of administration; and (5) failure to have had a pre-IND meeting with the FDA as a prerequisite to receive Good Manufacturing Practice (GMP) or Good Laboratory Practice (GLP) services. Approximately half (52%) of initial applications to SMARTT were from investigators at academic institutions, with most of the remaining requests (46%) from small businesses. Applications also were

<table>
<thead>
<tr>
<th>Program</th>
<th>Description</th>
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<tbody>
<tr>
<td>PACT</td>
<td>PACT was initiated in 2004 to provide clinical grade cell therapy products for early phase clinical trials in the heart, lung, and blood diseases. The program was renewed in 2009 and closed on January 14, 2015. However, in May 2015, a presolicitation notice was published and a new 5-year award is expected in 2016. Additional information is available at <a href="http://www.pactgroup.net">http://www.pactgroup.net</a>.</td>
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<tr>
<td>GTRP</td>
<td>GTRP was initiated in 2007 to facilitate translation of gene therapy research to clinical interventions by providing resources for manufacture, preclinical, and pharmacology–toxicology studies aimed at supporting IND applications. The program was renewed in 2012 through May 2017, and additional information is available at <a href="http://www.gtrp.org">http://www.gtrp.org</a>.</td>
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<tr>
<td>SMARTT</td>
<td>SMARTT was initiated in 2010 to accelerate translation of research from bench to bedside by providing manufacturing services for biologic and nonbiologic drug products, pharmacology–toxicology and formulation studies, and regulatory affairs guidance and support. The program ends on November 7, 2015 but is expected to be renewed in early 2016. Additional information is available at <a href="http://www.nhbismartt.org">http://www.nhbismartt.org</a>.</td>
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<tr>
<td>NCAI</td>
<td>NCAI was initiated in 2011 to provide a novel infrastructure for translation of discoveries into commercially viable products that improve patient care and advance public health. It consists of 3 Commercialization Centers and three Research and Innovation hubs. Additional information is available at <a href="https://ncai.nhlbi.nih.gov/ncai/">https://ncai.nhlbi.nih.gov/ncai/</a>.</td>
</tr>
<tr>
<td>VITA</td>
<td>VITA was initiated in 2013 to enable and accelerate development of promising diagnostic and therapeutic modalities for unmet and underserved medical needs. Additional information is available at <a href="http://www.nhlbi.nih.gov/research/resources/vita">http://www.nhlbi.nih.gov/research/resources/vita</a>.</td>
</tr>
<tr>
<td>CADET</td>
<td>CADET was initiated in 2014 to accelerate development of novel products for the treatment of lung diseases and sleep-disordered breathing. CADET supports preclinical, milestone-driven research on therapeutic products for which the target has been validated, focusing on support for that portion of drug development between target validation and IND application filing.</td>
</tr>
<tr>
<td>CTRIS</td>
<td>CTRIS was initiated in 2014 and is focused on T4 phase translation to promote rapid and sustained adoption of effective interventions. Additional information is available at <a href="http://www.nhbiscris.org/about/org/ctris">http://www.nhbiscris.org/about/org/ctris</a>.</td>
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Table 1. Translational Research Programs at the National Heart, Lung, and Blood Institute

CADET indicates Centers for Advanced diagnostics and Experimental Therapeutics in Lung Diseases Stage II; CTRIS, Center for Translation Research and Implementation Science; GTRP, Gene Therapy Resource Program; IND, investigational new drug; PACT, Production Assistance for Cellular Therapies; NCAI, National Institutes of Health Centers for Accelerated Innovations; VITA, Vascular Interventions/Innovations and Therapeutic Advances; and SMARTT, Science Moving Towards Research Translation and Therapy.
received from each of two other National Institutes of Health institutes, plus one from the National Institutes of Health intramural program, one from a nonprofit foundation, and one from an investigator used by a SMARTT contractor.

The 117 applications that advanced to the second phase of the application process produced a total of 174 individual RSAs (Figure 2): 38% for regulatory affairs support, 28% for pharmacology–toxicology studies, 24% for nonbiologic small-molecule manufacturing services, and 10% for biologic molecule manufacturing services. Of these 174 requests, 58 (33%) were approved: 62% for regulatory affairs support, 12% for pharmacology–toxicology studies, 17% for nonbiologic small-molecule manufacturing services, and 9% for biologic molecule manufacturing services (Figure 3). Approvals were based mainly on reviews by independent experts who considered soundness of the overall approach, significance of the work, feasibility, investigator readiness, and freedom to operate within intellectual property rights. Most of the approved requests (55%) originated from academic institutions, and small businesses accounted for 38% of funded requests.

Overall, the SMARTT program funded a total of 58 projects for 40 different investigators. These projects targeted a broad range of diseases, with the majority related to lung and blood diseases (34% and 33%, respectively), 24% to heart disease, and 9% to other diseases (Figure 4). All funding was incremental and based on successful achievement of milestones in a mutually agreed on project plan. As expected, project costs varied significantly, with the least expensive projects associated with regulatory affairs support and the most expensive associated with pharmacology–toxicology studies and manufacturing of biologic drug products.

**Accomplishments**

The core mission of the SMARTT program is to support IND-enabling research, and therefore, one of the most important measures of success is the number of IND applications (INDs) filed by SMARTT-supported investigators. The first IND was submitted in February 2013—early in the third year of the program. During the fifth year, 6 additional INDs were submitted for a total of 7 INDs during the initial 5 years of the program. During the next 3 months, 3 additional INDs were submitted, 1 of which was a resubmission. Thus, a total of 10 IND applications representing 9 new clinical trials were supported by the SMARTT program during its first 5 years.

Other SMARTT-assisted interactions with FDA also reflect programmatic success, and the regulatory support team has participated in a total of 7 pre-IND meetings and 4 successful Orphan Drug Applications. In addition, 19 investigators received planning support in the form of clinical development plans, gap analyses, or both. A summary of regulatory affairs support during the past 2 years is shown in Online Figure I.

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**Table 2. National Heart, Lung, and Blood Institute Translational Research Programs**

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<thead>
<tr>
<th>Program</th>
<th>Cell Therapy</th>
<th>Gene Therapy</th>
<th>Therapeutics</th>
<th>Diagnostics</th>
<th>Manufacturing Services</th>
<th>Pharmacology–Toxicology Services</th>
<th>Regulatory Affairs Services</th>
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<td>VITA</td>
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<td>CADET</td>
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CADET indicates Centers for Advanced diagnostics and Experimental Therapeutics in Lung Diseases Stage II; GTRP, Gene Therapy Resource Program; IND, investigational new drug; PACT, Production Assistance for Cellular Therapies; NCAI, National Institutes of Health Centers for Accelerated Innovations; VITA, Vascular Interventions/Innovations and Therapeutic Advances; and SMARTT, Science Moving Toward Research Translation and Therapy.
Finally, we note that the SMARTT program provided services to 2 projects sponsored by other institutes at National Institutes of Health, and many projects were complimentary to or represented extensions of other NHLBI programs and grants. This illustrates the cross-functional nature of the program and the need for translational research platforms to augment the government’s investments in health-related research.

Important Features of the SMARTT Program

Several features built into the SMARTT program likely contributed to program effectiveness. The application and review process was integrated into the SMARTT website and designed for rapid turnarounds, with initial reviews for eligibility typically completed within 2 weeks and responses to the more detailed RSA occurring within 3 to 6 months. The program was positioned as a platform for engaging investigators in translational research projects with customer-focused service provision. Project funding was incremental and milestone based, with go/no-go decision points designed to assess feasibility and ensure focus on meeting FDA standards and requirements for IND submissions. Projects were managed in a collaborative environment, with project teams consisting of contractors, principal investigators and their staff/collaborators, with oversight from NHLBI Contracting Officer Representatives and the SMARTT Steering Committee.

Another feature important to program success was provision of comprehensive regulatory affairs support services, which included assistance with creation of clinical development plans and gap analyses, as well as preparation of pre-IND briefing packets and IND applications. At the discretion of the principal investigator, SMARTT regulatory affairs staff often attended meetings with the FDA for projects they supported.

A culture of continuous improvement was promoted by insertion of customer satisfaction surveys after completion of key process steps or project milestones. After completing a project with the SMARTT program, several investigators elected to create separate contracts with SMARTT service providers for continued support on the translational pathway. This was viewed as an additional advantage of the SMARTT program, which facilitated the process of moving a promising therapeutic agent into the clinic.

Future Directions

The NHLBI has funded a 3-year extension of the SMARTT program, which began in March 2016. As before, the program was funded via a contract mechanism with a total of $16.3 million. Because of lessons learned during the first 5 years of the SMARTT program, resources allocated for GLP studies and GMP manufacturing projects will be expected to include cofunding from investigators during the extension period. This means that under certain conditions, investigators will be required to identify additional financial resources to enable completion of their projects.
In view of decreased funding available during the extension period, several other changes have been implemented. The application process has been reduced to a single submission, and the review process has been reduced to 1 or 2 cycles per year (versus continuously). This will minimize the burden on staff resources and improve the ability to rank/prioritize applications and manage project schedules against a more limited capacity. Finally, prioritization factors will be broadened to include investigator aptitude for managing the complexities of preclinical research, availability of cofunding for large projects, programmatic balance, and consideration of risk factors associated with achieving the objective of an IND submission.

In summary, during its initial 5 years of funding, from 2010 to 2015, the SMARTT program has enabled research translation from preclinical to clinical studies for 40 investigators. On the basis of the number and quality of service requests, we conclude that the SMARTT program plays an important role by providing IND-enabling services to investigators of heart, lung, and blood diseases. With the current round of NHLBI funding through February 2019, we anticipate that the program will continue to fulfill its mission of accelerating translation of research from demonstration of efficacy in vivo to submission of INDs to the FDA. Additional information is available at http://www.nhlbismartt.org.

Sources of Funding
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Disclosures
None.

References
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Online Figure I: Regulatory affairs support activities from 2013-2015.