Translational Research for Cardiovascular Diseases at the National Heart, Lung, and Blood Institute
Moving From Bench to Bedside and From Bedside to Community

Michael S. Lauer, MD; Sonia Skarlatos, PhD

Thanks to the dedicated involvement of the communities it serves, the National Heart, Lung, and Blood Institute (NHLBI) completed development of a scientific working strategic plan in 2007 to guide its activities and initiatives over the next 5 to 10 years. The plan outlines a cross-cutting strategic plan in 2007 to guide its activities and initiatives (NHLBI) completed development of a scientific working group of 3000 biomedical researchers based at 50 universities who have been presented previously in this series.2,3

What is Translational Research?
The ultimate goal of biomedical research is to improve individual and public health by discovering new effective strategies for the maintenance of wellness and for the prevention and treatment of disease. The Institute of Medicine Clinical Research Roundtable identified 2 “translational blocks,” or obstacles, to the realization of tangible health benefits derived from original research.4 The first block, or T1, is “the transfer of new understandings of disease mechanisms gained in the laboratory into the development of new methods for diagnosis, therapy, and prevention and their first testing in humans.” The second block, or T2, is “the translation of results from clinical studies into everyday clinical practice and health decision making.” Some authorities divide T2 into 2 components: T2 includes guideline development, meta-analyses, and systematic reviews, whereas T3 includes dissemination and implementation research.5 Some commentators have argued that the National Institutes of Health (NIH) disproportionately funds T1 compared with T2/T3 and that there is a need for increased national commitments to T2/T3 (from this point referred to as T2).6,7 A recent survey of >3000 biomedical researchers based at 50 universities who received relatively large sums of NIH support found that 9.1% of researchers focus primarily on T1 translation and 9.0% focus on T2.7 T2 researchers were more likely to have no funding compared with T1 or basic researchers (47% versus 23% versus 12%, respectively).7

The NIH recently demonstrated its strong interest in translational research through the launching of its Clinical and Translational Science Award program.8 Detailed descriptions of the program have been posted.9 Briefly, the NIH is funding 46 major academic centers with 5 goals in mind: building a national clinical and translational research capacity, providing opportunities for training and career development, enhancing consortium-wide collaborations, improving community health through research, and advancing T1 to accelerate the translation of basic science discoveries to clinical testing.10

The NHLBI’s strategic plan1 explicitly recognizes the critical value of both T1 and T2. Goal 2 of the strategic plan recognizes as an explicit challenge the need to “accelerate the translation of basic research findings into clinical studies”; goal 3 calls for “an improved understanding of the processes involved in translating research into practice and use that understanding to enable improvements in public health.” NHLBI also recognizes that translation is not unidirectional. Discoveries made in the clinic or in populations often stimulate new ideas among bench laboratory researchers.

Connecting Basic and Clinical Research (T1)
The clinical and translational research goals in the strategic plan emphasize transmission of knowledge between basic and clinical research so that findings in 1 arena rapidly inform and stimulate research in others. Remarkable advances are being made in understanding the molecular, genetic, and cellular bases of disease, and opportunities now exist to uncover practical uses for this new knowledge. The application of this new understanding to the prevention and management of cardiovascular diseases will call for creative insights into possible relationships and implications. In particular, success in this arena will require a concerted effort to identify, measure, and validate targets and pathways that have been detected in basic studies.

Several potentially fruitful areas for such bench-to-bedside translation are highlighted in the NHLBI plan. Regenerative biology, for instance, stands to benefit greatly from recent developments in understanding the molecular, genetic, and cellular bases of disease, and opportunities now exist to uncover practical uses for this new knowledge.
advances in stem cell biology and tissue engineering. In addition, the evolving field of nanotechnology promises to play a key role in drug delivery and therapeutics, molecular imaging, diagnostics and biosensors, and tissue engineering and biomaterials. Biomedical research has generated volumes of data from advances in “-omic” technologies, and an overwhelming amount of new information can be expected from such developments as affordable individual genome sequencing and real-time metabolomics. The challenge will be to integrate, analyze, and widely share enormous quantities of complex genotypic and phenotypic data to realize their full potential.11

Our strong focus on bench-to-bedside translation is reflected in many activities underway (the Table). We are conducting an in-depth reexamination of each of our programs of Specialized Centers of Clinically Oriented Research (SCCOR).12 The SCCOR provides rich environments in which findings from basic science drive clinical research directions and, in turn, clinical needs inform new basic investigations. However, they are funded only via periodic NHLBI requests for applications in specifically identified directions and, in turn, clinical needs inform new basic investigations. However, they are funded only via periodic NHLBI requests for applications in specifically identified areas of scientific interest; we now support 15 awards as a result of solicitations on cardiac dysfunction, pediatric heart development and disease, and vascular injury, repair, and remodeling. Thus, access to these avenues for translational research is constrained. In our reassessment of the program, we are looking for innovative ways to facilitate access to resources by investigators from many disciplines across the country and, in particular, to expand training opportunities in translational research.

In line with these objectives, we developed a new initiative, the Cardiac Translational Research Implementation Program,13 to supersede the SCCOR program in Cardiac Dysfunction and Disease, which is drawing to the end of its 10-year cycle. The goal of the Cardiac Translational Research Implementation Program is to accelerate translation of prom-

<table>
<thead>
<tr>
<th>Title</th>
<th>Funding Announcement Web Link</th>
<th>No. of Awards and Budget</th>
</tr>
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<tbody>
<tr>
<td>Cardiac Translational Research Implementation Program (P20)</td>
<td><a href="http://grants.nih.gov/grants/guide/rfa-files/RFA-HL-10-001.html">http://grants.nih.gov/grants/guide/rfa-files/RFA-HL-10-001.html</a></td>
<td>NHLBI expects to commit $9 million/y to support up to 12 2-y stage 1 grants and 4 subsequent stage 2 grants</td>
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<tr>
<td>NHLBI Pediatric Cardiogenics Consortium (U01)</td>
<td><a href="http://grants1.nih.gov/grants/guide/rfa-files/RFA-HL-09-003.html">http://grants1.nih.gov/grants/guide/rfa-files/RFA-HL-09-003.html</a></td>
<td>NHLBI expects to commit $25.4 million over 6 y; a total of 5 awards were funded</td>
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<td>Pediatric Heart Network</td>
<td><a href="http://grants.nih.gov/grants/guide/rfa-files/RFA-HL-05-010.htm">http://grants.nih.gov/grants/guide/rfa-files/RFA-HL-05-010.htm</a></td>
<td>NHLBI committed $30 million for a 5-y period; a total of 9 awards were funded</td>
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<td>NHLBI Progenitor Cell Biology Consortium</td>
<td><a href="http://grants.nih.gov/grants/guide/rfa-files/RFA-HL-09-004.html">http://grants.nih.gov/grants/guide/rfa-files/RFA-HL-09-004.html</a></td>
<td>NHLBI committed $70 million for a 6-y period; a total of 17 awards were funded</td>
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<td>Cardiovascular Cell Therapy Research Network</td>
<td><a href="http://grants.nih.gov/grants/guide/rfa-files/RFA-HL-06-001.html">http://grants.nih.gov/grants/guide/rfa-files/RFA-HL-06-001.html</a></td>
<td>NHLBI committed $29.9 million for 5 y to fund 5 clinical centers and 1 Data Coordinating Center</td>
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<tr>
<td>Science Moving Towards Research Translation and Therapy</td>
<td><a href="https://www.fbo.gov/index?s=opportunity&amp;mode=form&amp;id=eb9754c73b37ace85b11054a8e31b033&amp;tab=core&amp;_cview=1">https://www.fbo.gov/index?s=opportunity&amp;mode=form&amp;id=eb9754c73b37ace85b11054a8e31b033&amp;tab=core&amp;_cview=1</a>, <a href="https://www.fbo.gov/index?s=opportunity&amp;mode=form&amp;id=777f42404cd025f1d193ad879f779f7731&amp;tab=core&amp;_cview=1">https://www.fbo.gov/index?s=opportunity&amp;mode=form&amp;id=777f42404cd025f1d193ad879f779f7731&amp;tab=core&amp;_cview=1</a>, and <a href="https://www.fbo.gov/index?s=opportunity&amp;mode=form&amp;id=b7cf99a712babadb5a05697e302b8a0&amp;tab=core&amp;_cview=1">https://www.fbo.gov/index?s=opportunity&amp;mode=form&amp;id=b7cf99a712babadb5a05697e302b8a0&amp;tab=core&amp;_cview=1</a></td>
<td>NHLBI expects to commit $32 million for 6 y to fund 1 coordinating center and 3 production facilities</td>
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<td>Translating Basic Behavioral and Social Science Discoveries Into Interventions to Reduce Obesity, Centers for Behavioral Intervention Development (U01)</td>
<td><a href="http://grants.nih.gov/grants/guide/rfa-files/RFA-HL-08-013.html">http://grants.nih.gov/grants/guide/rfa-files/RFA-HL-08-013.html</a></td>
<td>NHLBI committed $25 million for a 5-y period; a total of 5 awards were funded</td>
</tr>
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<td>Demonstration and education research grants (R18)</td>
<td><a href="http://www.nhlbi.nih.gov/funding/policies/d&amp;eguide.htm">http://www.nhlbi.nih.gov/funding/policies/d&amp;eguide.htm</a></td>
<td>Program renewed on advice of NHBLI Council in 2009</td>
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<td>Interventions to Improve Hypertension Control in African Americans (U01)</td>
<td><a href="http://grants.nih.gov/grants/guide/rfa-files/rifa-hl-04-007.html">http://grants.nih.gov/grants/guide/rfa-files/rifa-hl-04-007.html</a></td>
<td>NHLBI committed $17.5 million for a 5-y period; a total of 5 awards were funded</td>
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<td>NHLBI Centers for Cardiovascular Outcomes Research (U01)</td>
<td><a href="http://grants.nih.gov/grants/guide/rfa-files/RFA-HL-10-008.html">http://grants.nih.gov/grants/guide/rfa-files/RFA-HL-10-008.html</a> and <a href="http://grants.nih.gov/grants/guide/rfa-files/RFA-HL-10-018.html">http://grants.nih.gov/grants/guide/rfa-files/RFA-HL-10-018.html</a></td>
<td>NHLBI has committed $19.8 million to fund 3 outcomes centers and 1 Coordinating Center</td>
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<td>Cardiovascular Research Network (U01)</td>
<td><a href="http://grants.nih.gov/grants/guide/rfa-files/RFA-HL-07-001.html">http://grants.nih.gov/grants/guide/rfa-files/RFA-HL-07-001.html</a> and <a href="http://www.cvrn.org">http://www.cvrn.org</a></td>
<td>NHLBI has committed $7.5 million for a 5-y period; a total of 1 award was funded; &gt;$14 million for 7 ancillary grants have been awarded</td>
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is ing new fundamental research discoveries for the treatment and prevention of heart failure and arrhythmias through well-designed clinical trials that demonstrate efficacy and safety. This program has 2 stages: stage 1 provides 2 years of funding for pilot studies to plan phase 1 and 2 trials; and stage 2 provides 5 years of funding for phase I and II trials.

To accelerate translational research in the health and care of patients with congenital disease, we recently launched an innovative pediatric cardiovascular translational program, the Bench to Bassinet Program. This program will create a critical mass of collaborative research across 3 interacting consortia (see Figure 1). The Cardiovascular Development Consortium will link 4 seasoned research teams using complementary animal models to drill deeply into the details of the transcriptional regulatory networks that govern cardiac development. Investigators from 5 sites in the Pediatric Cardiac Genomics Consortium will recruit children into a common protocol to speed the discovery of causative genes and to evaluate the effects of genetic variation on short- and long-term outcomes in congenital heart disease patients. These 2 consortia will align with the Pediatric Heart Network, a multicenter clinical research enterprise initiated by the NHLBI in 2001. All 3 programs will pursue their individual lines of research but will also interact with each other on multiple levels to ensure that important discoveries in 1 component will be rapidly evaluated and tested by the disciplines and technologies of the others.

We have initiated the Progenitor Cell Biology Consortium, which will identify and characterize progenitor cell lines, direct the differentiation of stem and progenitor cells to desired cell fates, and develop new strategies to address the unique challenges presented by the transplantation of these cells. This consortium will assemble multiple independent research projects, each with a multidisciplinary team of principal investigators, core research support facilities, and skills development components to establish synergistic virtual hubs focused on progenitor cell biology. The consortium will complement the Cardiovascular Cell Therapy Research Network, which was established by the NHLBI in 2006 to promote and accelerate clinical research in the evaluation of novel cell therapy treatment strategies for individuals with cardiovascular disease (see Figure 2).

In another effort to accelerate translational research, we will seek to provide the community access to resources and technologies that are otherwise unattainable by NIH investigators. A new program, Science Moving Towards Research Translation and Therapy, will be starting in the fall of 2010 to assist in the translation to the clinic of new synthetic, natural, or biological interventions for the treatment of heart, lung, and blood diseases. This 6-year program will fund 1 coordinating center and 3 facilities to provide resources of preclinical and clinical-grade production and testing for biologics, nonbiologics, and small molecules in accordance with good manufacturing practices and in the conduct of pharmacology and toxicology studies. Regulatory assistance will be available to investigators. This program will be similar to the Rapid Access to Interventional Development program of the National Cancer Institute, which provides contract services to expedite translation to the clinic of potential new therapeutic agents originating in academia.

The NHLBI has taken a leading role in obesity research, recognizing that the rapid increase in obesity prevalence among Americans threatens to reverse population improvements in life expectancy and cardiovascular risk. The NHLBI is inaugurating a new program, Translating Basic Behavioral and Social Science Discoveries Into Interventions to Reduce Obesity, which will fund 7 research teams to develop promising strategies for modifying behaviors that affect body mass. The program is funded in partnership with the National Institute of Diabetes and Digestive and Kidney Diseases, the National Cancer Institute, the Eunice Kennedy Shriver National Institute of Child Health and Human Development, and the Office of Behavioral and Social Sciences Research. The program will focus on high-risk priority populations (including children, ethnic minorities, economically disadvantaged individuals, and pregnant women) and will test a variety of individual, family, and community interventions.
Bridging Research and Practice (T2)

In its goal 3, the NHLBI strategic plan highlights the need to enhance understanding of the processes involved in translating research into practice, which corresponds to what some authorities refer to as T3, and to use that understanding to enable improvements in public health and to stimulate further scientific discovery. There is a well-recognized “quality gap” in the United States, as evidenced, for example, in a 2003 report that found that American adults receive only 55% of recommended services for a variety of chronic conditions. In cardiovascular disease, the situation is only slightly better; among adults with coronary artery disease, heart failure, and hypertension, 64% to 68% received recommended services.

The NHLBI recognizes that the processes by which evidence-based practices become widely adopted within routine care are themselves legitimate targets for research; this type of T2 research includes outcomes and health services research (see the Table). Focused behavioral and social science research may help uncover effective new approaches for communicating research findings to the public and for motivating and empowering individuals and communities to take charge of their health.

The NHLBI has for many years been a leader in this arena, facilitating the transfer of health information to physicians, patients, and the general public through support of implementation grants and through health education programs. Implementation research takes interventions that are generally accepted as beneficial and addresses their extension or adaptation to specific populations or settings, testing a variety of educational approaches, behavioral techniques, and environmental or organizational strategies. The study populations can come from a variety of settings (eg, people living in geographically defined areas, employees at work sites, schoolchildren, patients and healthcare providers in physicians’ offices, ambulatory care clinics, or health maintenance organizations) and other community settings. Examples of recently reported NHLBI-funded implementation research projects include the Activity Counseling Trial, the Rapid Early Action for Coronary Treatment trial, a trial of case management for reducing cardiovascular risk in low-income ethnic-minority neighborhoods, and a trial demonstrating the value of pharmacist collaboration for achieving blood pressure control.

The NHLBI is supporting or has recently completed supporting research programs that are specifically targeted toward improved implementation. Because poor adherence is a major obstacle to therapeutic success, the institute funded 13 randomized trials to test innovative but practical interventions to improve adherence in disadvantaged populations. Another NHLBI program is funding 11 randomized trials testing approaches to improve provider adherence to evidence-based cardiovascular guidelines. A third program is funding 5 randomized trials that test approaches to improve hypertension control in blacks. The NHLBI is about to inaugurate an ambitious program to fund centers in cardiovascular outcomes research, with each center expected to conduct at least 2 major projects and to provide high-level training to young cardiovascular outcomes researchers.

Since 2007, the NHLBI has been funding a large-scale Cardiovascular Research Network, which brings together researchers and databases from 15 integrated health plans that are members of the NIH Health Maintenance Organization Research Network. The network has access to the electronic health records of 11 million people. Three primary projects are analyzing characteristics, management, and outcomes of patients with hypertension, atrial fibrillation, and newly
implanted cardioverter-defibrillators. In the implanted cardioverter-defibrillators project, the NHLBI is partnering with the Agency for Healthcare Research and Quality and the American College of Cardiology to assess long-term outcomes and, in particular, to determine rates and determinants of implanted cardioverter-defibrillators shocks. The electronic data infrastructure and organization of the Cardiovascular Research Network offer potential for a broad array of future translational and reverse-translational research opportunities, including high-throughput mega-epidemiology technology projects, robust observational comparative effectiveness research, and large simple trials.

We are undertaking an ambitious effort to develop comprehensive, evidence-based, integrated guidelines to assist primary care physicians in helping adult patients reduce their risk of cardiovascular diseases. The integrated approach will focus on all cardiovascular risk factors to reflect the complicated clinical scenarios that patients and physicians typically face. Expert panels are being convened to review available scientific evidence and to update existing guidelines for the prevention, detection, evaluation, and treatment of high cholesterol, hypertension, and overweight/obesity. An important goal of both the integrative guidelines and the updates is to improve implementation, especially among high-risk and minority communities.

A Final Word

The NHLBI is firmly committed to pursuing excellent science both to advance scientific knowledge and to improve public health, and we believe that a strong emphasis on translation is essential to fulfilling our mission. Ensuring that the public benefits from the nation’s investment in biomedical research is, and always has been, our highest priority.

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Disclosures

None.

References


Key Words: cardiovascular diseases ± translational research ± funding ± career counseling
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