Special Article

National Heart, Lung, and Blood Institute and the Translation of Cardiovascular Discoveries Into Therapeutic Approaches

Zorina S. Galis, Jodi B. Black, Sonia I. Skarlatos

Abstract: The molecular causes of ≈4000 medical conditions have been described, yet only 5% have associated therapies. For decades, the average time for drug development through approval has taken 10 to 20 years. In recent years, the serious challenges that confront the private sector have made it difficult to capitalize on new opportunities presented by advances in genomics and cellular therapies. Current trends are disturbing. Pharmaceutical companies are reducing their investments in research, and biotechnology companies are struggling to obtain venture funds. To support early-stage translation of the discoveries in basic science, the National Institutes of Health and the National Heart, Lung, and Blood Institute have developed new approaches to facilitating the translation of basic discoveries into clinical applications and will continue to develop a variety of programs that create teams of academic investigators and industry partners. The goal of these programs is to maximize the public benefit of investment of taxpayer dollars in biomedical research and to lessen the risk required for industry partners to make substantial investments. This article highlights several examples of National Heart, Lung, and Blood Institute–initiated translational programs and National Institutes of Health translational resources designed to catalyze and enable the earliest stages of the biomedical product development process. The translation of latest discoveries into therapeutic approaches depends on continued federal funding to enhance the early stages of the product development process and to stimulate and catalyze partnerships between academia, industry, and other sources of capital. (Circ Res. 2013;112:1212-1218.)

Key Words: cardiovascular ■ National Heart, Lung, and Blood Institute ■ National Institutes of Health ■ programs resources ■ translational

The molecular causes of ≈4000 medical conditions have been described, yet therapies exist for only ≈200 of these. Developing a new drug from discovery to approval requires billions of dollars and takes many years, which decreases enthusiasm for investment risk.1 Because fewer new medical entities are being approved by the Food and Drug Administration (FDA) and expiring patents limit the profits made by companies, which have invested in development of new agents, the pharmaceutical industry and venture capitalists are reluctant or unable to invest in early-stage translational science. Limiting the financial risk and legal liability make industry more willing to invest. The need is even greater for rare diseases with presumably small market potential. One example of the time required to develop a potentially curative treatment for a rare condition is Pompe disease, an autosomal-recessive disorder caused by a deficiency in a lysosomal enzyme (acid α-glucosidase). Early onset of the disease is characterized by progressive cardiac and skeletal myopathy, culminating in cardiorespiratory failure and death within the first 2 years of life. A mouse model, developed at the National Institute of Arthritis, Musculoskeletal, and Skin Diseases in the 1990s, was instrumental in expediting drug development for Pompe disease.2 A series of studies in the animal model3 and early human studies4 established the basis for treatment of this previously fatal inherited cardiосkeletal myopathy. Limited drug approval (Myozyme) was achieved after 6 years of clinical studies and followed by approval for late-onset disease in 2006. The advent of enzyme replacement therapy defined a new clinical course, which has now led to an era of next-generation therapy using gene transfer. A phase I/II study of adeno-associated virus (AAV)-mediated gene transfer for Pompe disease was recently begun with support from the National Gene Vector Labs5 and the National Heart, Lung, and Blood Institute (NHLBI) Gene Therapy Resource Program (Smith BK, submitted 2012). The early studies with local and regional dosing will lead the way to systemic dosing strategies that are expected to have a broader impact on global function. Gene transfer for cardiopulmonary disease is an opportunity...
to design highly specific treatments for many rare conditions in need of a personalized therapy.

The mission of the National Institutes of Health (NIH) is to seek fundamental knowledge about the nature and behavior of living systems and the application of that knowledge to enhance health, lengthen life, and reduce the burdens of illness and disability (http://www.nih.gov/about/mission.htm). To achieve these ambitious goals, the NIH and NHLBI (http://www.nhlbi.nih.gov/index.htm) have long been and continue to be committed to supporting a diverse portfolio that includes basic, translational, and clinical research. Historically, many of the basic science discoveries enabling successful new therapies originated in academia. Lefkowitz and Kobilka, the 2012 Nobel Laureates in Chemistry, were rewarded for their pioneering work in discovering and understanding the function of G-protein–coupled receptors, a large family of molecules that control many important pathways in the body, which have since become the targets of >40% of all medications used today. Both researchers are academics and both received NIH support for their basic research that has engendered so many drug development efforts. Transitioning academic discoveries through the product development process was traditionally conducted by large pharmaceutical companies with powerful research and development engines and with investment from other sources of private capital. However, the process of translating fundamental biomedical discoveries into new or better clinical applications to enhance public health has become an increasingly complex, costly, and risk-laden endeavor. Recent estimates indicate an average 10-year development process for a new drug at an average cost of $2 billion. Despite increased investments, the number of FDA-approved drugs has decreased over the past decade with the exception of last year. Although cardiovascular disease (CVD) remains the leading cause of death, the pharmaceutical industry has lost interest in pursuing innovative treatments because of the increased investment requirement and risk traditionally associated with the development of new CVD therapies. The failure of Torcetrapib, one of the most scrutinized failed drug development stories, provides an example of investment risk. Development, which began in the early 1990s, culminated in a widely publicized halting of a mega-phase III trial in 2006 because of increased mortality in the treatment group (receiving Torcetrapib and atorvastatin, also known as Lipitor). Overnight, Pfizer’s valuation plummeted by $21 billion, leading them to discontinue development of the compound and terminate all cardiovascular drug development efforts. Other pharmaceutical companies developing similar cholesterylester transfer protein inhibitors followed suit. The failure of the Torcetrapib trial was touted to signal the demise of the blockbuster.

The current state of the industry and the overall economic environment create a responsibility and a great opportunity for the NIH to become a key partner in the process of developing therapeutic approaches. The NIH is uniquely positioned to assist in identifying the medical needs, scientific opportunities, resource gaps, and challenges to enable the early phase of translation of scientific ideas into interventions by encouraging collaborations across all disease topics and research specialties, enabling and providing access to specific resources needed for clinical applications and the development of biomedical products, and enhancing training in the relevant disciplines. NHLBI is leading the translational efforts in the area of CVD.

Current Major Areas of Translation Focus at the NIH

The NIH is the primary, and often the sole, supporter of basic biomedical research. Its role in drug development varies with circumstances. In general, industry—not the NIH—develops markets and distributes new pharmaceuticals. The NIH takes an active role in facilitating drug development in areas of high public health need in which industry needs support or facilitation to invest because the product may not have an attractive market. The NIH is focusing on specific areas of public health with the greatest need of support as identified by the grantees, the public, and industry. With regard to translational research, a group of NIH initiatives specifically targeting the early phase of product development are being developed to enable basic research findings to cross the so-called valley of death. This is the crucial early phase in which scientific breakthroughs, including those funded by the NHLBI, languish and frequently succumb because of scarcity of support (funding and expertise) needed to enter into the process of product development. The current and future NIH initiatives aim at providing funding for the research and the infrastructure needed to obtain a proof of concept, build a prototype, assess toxicology and pharmacodynamics, and, overall, to reduce the amount of investment risk associated with unproven solutions. Addressing disease conditions commonly neglected by industry because of lack of perceived potential for high commercial return is also driving the development of several NIH translational programs. Such efforts can obtain orphan drug or Humanitarian Use Device status from the Office of Orphan Products Development of the FDA. This evaluates therapies or diagnostics intended to diagnose, prevent, or treat rare diseases, which are defined as affecting <200,000 people in the United States or not expected to recover the costs of developing and marketing a treatment drug, even if affecting >200,000 persons in the United States, and devices that benefit <4000 individuals. Interestingly, the view of the industry on rare and neglected diseases recently has been changing with several major companies working with academic or government laboratories to repurpose drugs or acquire rights to develop products aimed at niche markets, as also demonstrated by the high number of orphan products approved by the FDA in 2011. Many new orphan products

<table>
<thead>
<tr>
<th>Nonstandard Abbreviations and Acronyms</th>
</tr>
</thead>
<tbody>
<tr>
<td>CVD</td>
</tr>
<tr>
<td>FDA</td>
</tr>
<tr>
<td>GTRP</td>
</tr>
<tr>
<td>NCAI</td>
</tr>
<tr>
<td>NCATS</td>
</tr>
<tr>
<td>NHLBI</td>
</tr>
<tr>
<td>NIH</td>
</tr>
<tr>
<td>SBIR</td>
</tr>
</tbody>
</table>
were for cancer, likely reflecting scientific and technological progress enhancing our ability to tailor therapies to specific patients. The new commercial interest in the development of therapies for a variety of orphan diseases seems to be in concert with the provisions of the new Affordable Care Act. These eliminate the limits on life-long insurance coverage for children with preexisting conditions (http://www.healthcare.gov/law/full/index.html). Many of these conditions represent rare diseases, and thus the new therapies become commercially viable products despite their limited market size. As part of its continued commitment to translational research, and following President Obama’s signing of a related bill,17 the NIH recently created the National Center for Advancing Translational Sciences (NCATS; http://www.ncats.nih.gov/), whose mission is to catalyze the generation of innovative methods and technologies that will enhance the development, testing, and implementation of diagnostics and therapeutics across a wide range of human diseases and conditions. In this role, NCATS will serve as a national hub that will strive to identify and overcome hurdles that slow the development of effective treatments and cures. To achieve this, NCATS plans to work closely with the other dedicated NIH Institutes and Centers and regulatory, academic, nonprofit, and private sectors.18

The NCATS programs are designed to address unmet needs, so they will complement, not compete with, the private sector and the other NIH Institutes, which continue to support a diverse research portfolio that includes basic, translational, and clinical sciences focused on specific organ systems and related disease conditions. NCATS will reinforce the commitment of NIH to basic science research by creating opportunities to continue the development of new concepts and testing their potential utility to improve human health.18 Operationally, NCATS is currently coordinating the consolidation of several large existing NIH programs and offices into an integrated scientific enterprise, previously housed in the National Center for Research Resources and several NIH Institutes. This entails coordinating the administration of a varied portfolio of approaches and activities considered to be essential in research translation. This coordination includes the administration of the Clinical and Translational Science Award program (https://www.ctsacentral.org/), a national consortium of academic center–associated research bastions focused on the translation and the training of the next generation of academic medicine researchers, as well as administration of several NIH–based resources available to support extramural and intramural requests for assistance with drug development, including the Molecular Libraries Probe Program (http://www.ncats.nih.gov/research/reengineering/ngce/mlp/mlppc.html), Bridging Interventional Development Gaps (http://www.ncats.nih.gov/research/rare-diseases/bridges/bridges.html), Theraeutics for Rare and Neglected Diseases (http://www.ncats.nih.gov/research/rare-diseases/trnd/trnd.html), the Cures Acceleration Network (http://www.ncats.nih.gov/funding-and-notices/can/can.html), and the NIH Office of Rare Diseases (http://www.ncbi.nlm.nih.gov/research/rare-diseases/ordr/ordr.html; Table). The NCATS has engaged other government agencies, including the FDA, the Environmental Protection Agency, and the Defense Advanced Research Projects Agency, along with pharmaceutical and medical device industry, to be able to provide additional tools that allow testing compounds with therapeutic potential, including approved and investigational drugs, which might be rescued or repurposed for new indications. NCATS also offers support and guidance for building new types of assays and access to medium throughput screening for physiological and toxicological effects of investigational compounds (http://www.ncats.nih.gov/research/tools/preclinical/preclinical-research-tools.html).

NHLBI Resource Programs Available for CVD Translational Research

New NHLBI translational programs seek to address the needs of patients by focusing on disease conditions that were traditionally neglected by industry and removing barriers to inventors developing potential breakthrough clinical interventions.

More than 70% of the NHLBI award portfolio currently supports investigator-initiated studies focused on novel intervention discovery. However, the investigator-initiated RO1 grants are typically (and unavoidably) limited in scope because of their hypothesis-driven paradigm and are thus poor enablers of the product development process. Transferring viable basic science discoveries to the market can pose the greatest challenge to innovators, and many abandon potentially fruitful discoveries because of lack of know-how and access to the specific support needed to develop them into medical products that would benefit the patient.19 The NHLBI recognized that new paradigms were needed to address the problems that hinder the critical early steps necessary to translate novel scientific advances and discoveries into commercially viable diagnostics, devices, therapeutics, and tools that improve patient care and advance public health. Thus, the NHLBI convened working groups with expertise in either disease-specific or process-specific areas, which collectively identified barriers and gaps that hinder the critical early steps necessary to translate novel scientific discoveries into commercially viable diagnostics, devices, therapeutics, and tools that improve patient care and advance health. They suggested creating NHLBI programs that provide or develop the following: (1) funding for the nonhypothesis-driven scientific feasibility studies (proof of concept, prototype development) required to define the product; (2) access to coordinated expertise in areas required for early-stage technology development, including scientific, regulatory, business, legal, market research, and project management; (3) processes to better-leverage and integrate existing NIH and NHLBI resources designed to enable preclinical technology development (eg, Bridging Interventional Development Gaps, Therapeutics for Rare and Neglected Diseases, Clinical and Translational Science Award, or the Science Moving Toward Research Translation and Therapy, program); (4) novel partnerships that help to strengthen existing alliances between stakeholders, including public, private, nonprofit, and academic sectors; (5) training and hands-on experience in entrepreneurship; and (6) cultural and systemic changes by providing the necessary resources to proactively and more rapidly move from breakthrough innovations to products with impact on health, economy, and society. Many of these hurdles are also frequently highlighted in the popular press20 and were discussed by the National Advisory Council on Innovation and Entrepreneurship.19 As a result, a portfolio of varied cardiovascular translational programs was created...
at the NHLBI to address needs in the area of specific disease conditions and to overcome barriers identified by the working groups, potential grantees, and other stakeholders. A more detailed description of several of the programs focused on CVD was published previously.21

We briefly describe 4 NHLBI programs that exemplify the variety of opportunities created in support of research translation into therapeutic approaches (Figure).

**A Translational Success Story: The Gene Therapy Research Program**

The Gene Therapy Resource Program (www.gtrp.org) was launched in March 2007 to address major research challenges identified by the NHLBI Gene Therapy Working Group held in June 2005. Gene Therapy Research Program (GTRP) has already moved the field of gene therapy ahead by providing the vectors needed for preclinical studies and the pharmacology/toxicology studies critical for an investigational new drug application. In addition, its support of phase I clinical trials, with several GTRP studies being completed to date and some still ongoing, made a big difference in rare diseases, including Fabry disease, pneumocystis carinii pneumonia, duchenne muscular dystrophy, cystic fibrosis, Pompe disease, α-1 antitrypsin deficiency, and Wiskott-Aldrich syndrome. These results demonstrate that the GTRP program has successfully addressed its goal challenges, including producing large-scale, well-characterized viral vectors under current good manufacturing practices for use in clinical trials conducting pharmacology and toxicology studies in small and large animal models and meeting the regulatory requirements of the FDA, Institutional Biosafety Committees, Institutional Review Boards, NIH Recombinant DNA Advisory Committee, and Data and Safety Monitoring Boards.22 The GTRP provides services through several cores. A preclinical vector core produces research-grade AAV, lentivirus, and recombinant adenovirus vectors and immunology testing services on preclinical specimens, whereas the pharmacology/toxicology core performs toxicology and biodistribution studies in rodents, dogs, pigs, and nonhuman primates as a prerequisite for use of vector in clinical studies and prepares final study reports for investigational new drug submission. Clinical cores provide clinical-grade lentivirus and AAV vectors using good manufacturing practices processes, as well as chemistry, manufacturing, and controls, and a certificate of analysis. A clinical coordinating center supports program infrastructure, provides regulatory assistance to investigators, and manages disbursement of clinical trial funds.

More than 89% of requests received for support were approved. Specific GTRP accomplishments to date include more than 80 preclinical vectors (viral and nonviral) in production, 5 pharmacology/toxicology studies for heart failure and cystic fibrosis, 4 good manufacturing practices AAV productions (heart failure), 4 good manufacturing practices lentivirus productions (thalassemia), 7 immunology services, 3 clinical trials supported, and 9 instances of regulatory assistance.

The variety of gene therapy clinical trials that have received support from GTRP demonstrate the program’s breadth of clinical applications and include a multisite phase I/II trial in heart failure testing safety and potential efficacy of intracoronary delivery of Ad5.hAc6, a single-site phase I/II trial testing the safety and potential efficacy of bilateral diaphragm delivery of AAV acid α-glucosidase for Pompe disease, and the safety of a lentivirus vector encoding Wiskott-Aldrich syndrome cDNA using transduced T-cell delivery for Wiskott-Aldrich syndrome in a single-site pilot and feasibility study. The GTRP is also an example of a program being housed in the NHLBI, which is engaged in trans-NIH collaborations to meet the needs of applicants, working with the National Eye Institute, the NIH Rapid Access to Intervention Development Program, and the National Institute of Neurological Disorders and Stroke.

**A New Translational Paradigm: The Vascular Interventions/Innovations and Therapeutic Advances**

The Vascular Interventions/Innovations and Therapeutic Advances (VITA) solicitation recently invited applications that address the need for new or better therapeutic interventions (drugs or devices) and diagnostic modalities in several medical conditions within the NHLBI mission, but have been traditionally neglected by the industry. To specifically meet the concern of academic inventors related to restrictions imposed by the Small Business Innovation Research (SBIR) and Small Business Technology Transfer mechanisms requiring the applicants to have their main appointment with a commercial entity, the VITA program does not impose any restrictions on the applicant’s type of institutional affiliation or on geographic location, as long as the primary research site is within the United States. The VITA program will offer assistance with project management, regulatory issues, and expert industry advice, and will coordinate and connect successful applicants with opportunities to leverage other existing NIH translational programs. More details can be found in the VITA solicitations (BAA-NHLBI-CSB-HV-2013-02-JS and RFP-NHLBI-CSB-HV-2013-04-JS).

The structure and overall format of the VITA program were built to be consistent with the following key management concepts about factors that enable innovation and increase accountability:

1. Successful new product development comes down to balancing of 2 important principles: managing ideas lightly while managing the process precisely. This combination allows the entry of new, including out-of-the-box, ideas and provides the support and infrastructure needed to make sure projects have the chance to proceed toward their logical conclusion (ie, new product or fast kill) while generating knowledge and learning. A recent study from the Nielsen Company concluded companies successful in developing innovative products keep senior management out of early-stage development,23 a paradigm consistent with the overall NIH approach to enabling medical science.

2. Successful innovative companies have a new product development focus of 2–3 years and maintain a formal scorecard to provide structure to organizational learning. This time frame was used to propose the length of funding within the VITA program. The Nielsen report findings further emphasize the importance of negotiating and imposing milestones and highlight the importance of creating learning opportunities in the process.
An Upcoming Resource: The NIH Centers for Accelerated Innovations

The recently published request for applications for NIH Centers for Accelerated Innovations (NCAI) represents a new approach to identifying and advancing the development of promising emerging technologies (drugs, devices, diagnostics, and tools) toward new commercial products for the prevention and management of medical conditions affecting the cardiovascular, pulmonary, and hematologic systems (http://grants.nih.gov/grants/guide/rfa-files/RFA-HL-13-008.html). This initiative is a collaborative activity that includes the NIH, the FDA, the Department of Commerce Office of Innovation and Entrepreneurship, the United States Patent and Trademark Office, and the Center for Medicaid Services. When funded, the NCAIs will solicit and select compelling innovations from research-performing institutions and offer a centralized comprehensive 1-stop shopping approach to moving basic science discoveries through the early stages of technology development in a manner consistent with enabling their subsequent commercialization. Inventors, especially those who are new to the product development process, will be provided with relevant personal training and mentoring opportunities. NCAIs will develop innovations in which commercial potential could be envisioned but are in need of additional funding and development expertise to demonstrate feasibility and to define the product. NCAIs will provide elements essential to ultimate commercial success, such as expertise in entrepreneurship and business development practices, market analysis approaches, intellectual property and other relevant legal issues, regulatory processes, and access to capital. Projects will be subjected to rigorous review and project management, which will include monitoring well-defined milestones as the basis for timely go or no-go decisions regarding whether to continue or abandon further development efforts. Together with NHLBI program staff and in cooperation with the federal agency expertise listed, the Centers will facilitate access to existing and future federal programs that can contribute to the technology development process, including the current NIH programs Science Moving Toward Research Translation and Therapy (SMARTT); and Gene Therapy Resource Program (GTRP).

Figure. National Heart, Lung, and Blood Institute (NHLBI) programs that exemplify the variety of opportunities created in support of translation using funding or assistance-type mechanisms include the following: National Institutes of Health Centers for Accelerated Innovations (NCAI); Vascular Interventions/Innovations and Therapeutic Advances (VITA); Small Business Innovation Research (SBIR); Science Moving Toward Research Translation and Therapy (SMARTT); and Gene Therapy Resource Program (GTRP).
ORDR supports and coordinates rare disease research, responds to research opportunities for rare diseases, and provides information on rare diseases.

| BrIDGs | Previously known as the NIH Rapid Access to Intervention Development program, this was launched under its new name in October 2011; BrIDGs makes available, on a competitive basis, certain critical resources (synthesis, formulation, pharmacokinetic, and toxicology services) needed for the development of new therapeutic agents | http://www.ncats.nih.gov/research/rare-diseases/bridgs/bridgs.html |
| Cures Acceleration Network | This program is to advance the development of high-need cures and reduce significant barriers between research discovery and clinical trials | http://www.ncats.nih.gov/funding-and-notices/can/can.html |
| ORDR | ORDR supports and coordinates rare disease research, responds to research opportunities for rare diseases, and provides information on rare diseases | http://www.ncats.nih.gov/research/rare-diseases/ordr/ordr.html |

**Extending Translational Support: The NHLBI SBIR Phase IIB Bridge Awards**

Since its inception in 1982, the NIH SBIR program has provided the small business community with seed funding to support the development of a broad array of commercial products to detect, diagnose, treat, and prevent disease. It provides an important mechanism for bringing new interventions to patients and clinicians. The SBIR program is structured in 3 phases. The objective in phase I is to establish the technical merit and feasibility of a proposed research and development effort, whereas in phase II it is to continue the research and development effort for successful phase I projects. The expectation is that in phase III, a small business concern will be able to complete commercialization with non-NIH funds. However, the development of therapeutics, medical devices, and combined technologies often requires a number of years and substantial capital investments because of the costs associated with conducting clinical trials and other steps mandated by the federal regulatory approval process. Thus, despite the extensive research and development efforts during phase II projects in these areas, the results are often insufficient to attract private investments needed for the eventual commercialization of a product, and many small businesses become cash-starved before reaching the next critical milestone along the path toward commercialization. The NHLBI phase IIB Bridge Award program is designed to address this funding gap between the end of the SBIR phase II award and the point at which non-SBIR financing can be secured for the subsequent stages of product development and commercialization. The Bridge Award will facilitate partnerships between NHLBI SBIR phase II awardees and third-party investors and strategic partners by providing up to $1 million per year for 3 years to support research activities required to meet and comply with federal regulatory requirements. The level of NIH funding provided is predicated on matching funds that equal or exceed the federal investment. Because the additional NIH funding mitigates a substantial amount of investment risk, the program provides a strong incentive for third-party investors to finance projects earlier in the development process. Additionally, the probability of successful commercialization is enhanced by leveraging the expertise of third-party partners, including initial due diligence, project management, and business development.

**Conclusions**

These examples illustrate the commitment and flexibility of the NIH as it addresses the needs of patients and inventors by enabling a strong pipeline of biomedical research ideas and their successful translation into product development. Other funding opportunities are undergoing development. Those recently released can be found at NIH Funding Opportunities and Notices (http://grants.nih.gov/grants/guide/index.html) and Federal Business Opportunities (https://www.fbo.gov/). The NHLBI and the NIH are committed to facilitating the translation of basic discoveries into clinical application and will continue to develop a variety of programs that create...
teams of academic investigators and industry partners. The fiscal constraints on the NIH budget require that we be creative in identifying new efficiencies, enhance our culture of result-based accountability, continuously reassess the state of the science, and always be committed to funding outstanding science. Our goal is to work with basic scientists and with the industry, not to assume the roles properly played by investigators and the commercial sector. The future of translational research depends on how well we manage the emerging trends and new opportunities, and the availability of federal funding to enhance the early stages of the product development process and to stimulate and catalyze partnerships between academia, industry, and other sources of capital.

Acknowledgments
The authors thank Drs Susan Shurin and Michael Lauer of the National Heart, Lung, and Blood Institute and Dr Barry Byrne of the University of Florida, Gainesville for their thoughtful comments.

Disclosures
None.

References
National Heart, Lung, and Blood Institute and the Translation of Cardiovascular Discoveries Into Therapeutic Approaches
Zorina S. Galis, Jodi B. Black and Sonia I. Skarlatos

_Circ Res._ 2013;112:1212-1218
doi: 10.1161/CIRCRESAHA.113.301100

_Circulation Research_ is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231
Copyright © 2013 American Heart Association, Inc. All rights reserved.
Print ISSN: 0009-7330. Online ISSN: 1524-4571

The online version of this article, along with updated information and services, is located on the World Wide Web at:
http://circres.ahajournals.org/content/112/9/1212

Permissions: Requests for permissions to reproduce figures, tables, or portions of articles originally published in _Circulation Research_ can be obtained via RightsLink, a service of the Copyright Clearance Center, not the Editorial Office. Once the online version of the published article for which permission is being requested is located, click Request Permissions in the middle column of the Web page under Services. Further information about this process is available in the Permissions and Rights Question and Answer document.

Reprints: Information about reprints can be found online at:
http://www.lww.com/reprints

Subscriptions: Information about subscribing to _Circulation Research_ is online at:
http://circres.ahajournals.org//subscriptions/