The National Heart, Lung, and Blood Institute Small Business Program

A Comprehensive Ecosystem for Biomedical Product Development

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SUMMARY

Small companies working to develop products in the cardiovascular space face numerous challenges, from regulatory, intellectual property, and reimbursement barriers to securing funds to keep the lights on and reach the next development milestone. Most small companies that spin out from universities have the scientific knowledge, but product development expertise and business acumen are also needed to be successful. Other challenges include reduced interest in early-stage technologies and limited deal flow for cardiovascular products. The National Heart, Lung, and Blood Institute (NHLBI) small business program is a comprehensive ecosystem designed to address these critical challenges and to provide resources and expertise to assist early-stage companies developing cardiovascular and other products within the institute’s mission. This article describes steps that NHLBI has taken to enhance our small business program to more effectively translate basic discoveries into commercial products to benefit patients and public health, including enhancing internal expertise and developing nonfinancial resources to assist small businesses as they develop their products and seek private sector investment and partnership. (J Am Coll Cardiol Basic Trans Science 2016;1:660–5)

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THE NHLBI SMALL BUSINESS ECOSYSTEM

The federal government Small Business Innovation Research (SBIR) and Small Business Technology Transfer (STTR) programs represent the largest seed-stage funding sources for companies in the world, totaling more than $2.2 billion each year. The SBIR/STTR Reauthorization Act of 2011 (P.L. 112-81) has increased the funding that federal agencies must spend on small business programs from 2.8% of extramural research spending in 2010 to 3.65% in 2017 (Figure 1). In fiscal year 2015, the National Institutes of Health’s (NIH’s) small business programs invested $785 million in health and life science companies.

In addition to increasing overall funding for small businesses, the Reauthorization Act allowed agencies to use a small portion for administrative purposes, thus catalyzing the institute’s ability to implement a more comprehensive ecosystem to support the program. The National Heart, Lung, and Blood Institute (NHLBI) small business ecosystem consists of 3 interconnected components: 1) funding support; 2) educational and commercialization assistance programs; and 3) staff within the NHLBI Office of Translational Alliances and Coordination (OTAC) with expertise in biomedical technology development and commercialization (Figure 2). These components are designed to provide the financial support companies need, prepare them for success through education,
advice, and mentorship, and help transition them to the private sector.

**SMALL BUSINESS FUNDING MECHANISMS**

In fiscal year 2015, the NHLBI distributed $91 million to small businesses to perform research and development on products within our mission, encompassing the areas of cardiovascular, pulmonary, blood diseases and resources, and sleep. The NHLBI currently supports 166 companies working on 189 projects, including therapeutics, devices, diagnostics, health information technology, and research tools (Figure 3). Forty-six percent of these projects are for cardiovascular indications. The NHLBI funds small businesses with projects ranging from pre-clinical research to clinical trials.

The NHLBI supports small businesses using both the SBIR and STTR programs. These 2 programs have subtle, but important, differences that are highlighted in Table 1; however, this article focuses on the elements common to both programs. The NHLBI small business program consists of 3 phases, termed Phase I, Phase II, and Phase IIB (Figure 2). Phase I is designed to support projects at the earliest stages of development, often only a concept, and does not require any preliminary data, although it can help convince peer reviewers of the project’s merit. The goal of Phase I projects is to demonstrate proof-of-concept in about a year with a relatively small budget, suggested to be $150,000 to $225,000. Phase I applications should focus on the research plan, although it is beneficial for the applicant to briefly address business issues, such as the market size, intellectual property, regulatory strategy, and company management. Phase II is designed to support additional research and development of successful Phase I projects. Phase II projects are generally 2 years with suggested budgets of about $1.5 million and applications require an extensive commercialization plan. For both Phase I and Phase II projects, applicants can request longer durations and higher budgets for projects if warranted by the research aims. Applicants are strongly encouraged to contact NHLBI staff to discuss both the research and commercialization components of their applications, as well as proposed budgets. Additional information about the programs can be found at: `http://www.nhlbi.nih.gov/research/funding/sbir/about-program.htm#structure`

NIH funding through Phase I and Phase II, although significant, is generally insufficient to advance most biomedical projects, especially those requiring Food and Drug Administration (FDA) clearance, to a milestone that would make the company attractive to private sector investors; however, due to the linear structure of the program, small businesses must transition from NHLBI to private sector support. As a result, in 2012, the NHLBI developed a Phase IIB program to better address the transition from government funding to private sector investment. Small businesses applying to the NHLBI Phase IIB program are expected to include a well-supported plan to raise significant third-party funding. This unique programmatic structure brings advantages to the company and project from both the public and private funders. The NHLBI provides substantial nondilutive funding, reducing risk to third-party investors, while the private sector contributes industry-style due diligence, project management, and access to downstream capital. The Phase IIB program is implemented through 2 Funding Opportunity Announcements and supports projects with up to $3 million for up to 3 years. The Small Market Award (`http://1.usa.gov/1v0Wxn1`) is designed to support projects focused on pediatric or rare disease indications requiring FDA clearance. The NHLBI expects that companies will include a fundraising plan in their application outlining how they will acquire private sector investment totaling at least one-third of the budget they request from the NHLBI (e.g., if the small business requests $3 million from the NHLBI, they must have a comprehensive and verifiable plan to raise at least $1 million from non-federal sources). The Bridge Award (`http://1.usa.gov/1q9yTyP`) is designed to support all other projects requiring FDA clearance and requires a fundraising plan detailing how the company will acquire private investment that matches or exceeds their requested budget from the NHLBI (e.g., if they request $3 million from the NHLBI, they must provide a plan to raise $3 million from the private sector). Applications received through the NHLBI Phase IIB program undergo a substantially modified peer review process that focuses on both scientific merit and commercial potential. The Funding Opportunity Announcements detail the review criteria and the study sections are empaneled with experts in regulatory, intellectual property, reimbursement, investment, and product development issues, in addition to scientific domain experts.

The NIH offers 2 programs to save small businesses time and reduce their administrative burden, and the NHLBI participates in both. The Fast-Track program allows applicants to submit a single application that combines both Phase I and Phase II proposals into a single application. If the application is selected
for funding, then the NHLBI will perform an administrative review between phases, rather than a competitive peer review. This process usually only takes several weeks, as opposed to several months. To enable an appropriate administrative review, applicants must submit clear quantitative milestones for the Phase I portion of a Fast-Track application. In addition, because applicants must submit a Phase II proposal with their application, they must be able to generate a compelling commercialization plan. Fast-Track applications are often scored poorly as a result of inadequate Phase I milestones or unconvincing commercialization plans. The Direct to Phase II mechanism allows applicants to submit a Phase II application for projects for which they have already demonstrated proof-of-concept. Applicants must include a description of the proof-of-concept work and demonstrate that they have achieved an important feasibility milestone. Other than this difference, a Direct to Phase II application follows the format of a Phase II proposal, including the requirement for a commercialization plan. The Fast-Track and Direct to Phase II mechanisms are most suitable for experienced companies with clear and compelling research and commercialization plans for their project, but if they are appropriate, these mechanisms can save significant time. Because of their unique elements, applicants considering Fast-Track or Direct to Phase II submissions are strongly encouraged to contact NHLBI staff.

Traditional NIH funding mechanisms are designed to support research, but not the administrative, regulatory, and commercial work (e.g., market research and FDA documentation) that small businesses must perform to develop early-stage technologies. In addition, standard small business support mechanisms restrict the amount of work that can be subcontracted to generally <50%, which can cause significant challenges for companies that need technical assistance from contract resource organizations or consultants. As a result, the NHLBI participates in the recently published NIH Commercialization Readiness Pilot (CRP) (link to solicitation: PAR-16-026 [http://grants.nih.gov/grants/guide/pa-files/PAR-16-026.html]). Through this pilot program, the NHLBI will provide up to $50,000 to Phase II awardees to perform work not normally allowed under standard NIH mechanisms. Appropriate work under the CRP program includes, but is not limited to, preparation of documents for an FDA submission, development of an intellectual property strategy, planning for a clinical trial, technical assistance with manufacturing, and market research. Companies are allowed to outsource a significant portion of the work, provided it is appropriate and well justified.

These funding mechanisms have been developed in response to the needs of the small business community. The Fast-Track and Direct-to-Phase II programs are reducing the time between awards, and the CRP program is adding much needed support for the commercialization activities that early-stage biomedical companies need to perform. Finally, the NHLBI Phase IIB program is catalyzing the move from government support to the private sector, a transition that will be necessary for the commercialization of most life science products. Additional information on funding can be found in Table 2.

**PREPARING COMPANIES FOR SUCCESS**

Funding alone is frequently insufficient for early-stage small businesses developing biomedical products to achieve the appropriate milestones that will result in private sector follow-on funding. The NHLBI provides a suite of resources to assist companies that includes comprehensive customer-discovery programs, webinars focused on specific topics, and full-time staff available to provide expert advice on regulatory, business development, intellectual property, and entrepreneurship issues.

One of the major challenges facing all early-stage companies is understanding their customers, value proposition, and path to market. Small businesses developing biomedical products must also understand
the complex regulatory and payment reimbursement environment. In 2014, the NIH launched the I-Corps at NIH program to help promising SBIR/STTR awardees overcome the commercial challenges of biomedical product development. Based on the successful National Science Foundation I-Corps program, the I-Corps at NIH curriculum is focused on teaching scientist-entrepreneurs how to get out of the laboratory and talk to stakeholders who can inform a startup company’s understanding of its customer segments, value proposition, partners, development path, and regulatory and reimbursement environments. The NHLBI has supported 7 Phase I companies to participate in the I-Corps at NIH program, helping them develop a sound business strategy. Future opportunities to participate in the I-Corps at NIH program will be announced on our website (http://www.nhlbi.nih.gov/research/funding/sbir/).
In addition to customer discovery, value proposition, and regulatory issues, there are myriad other topics important to small businesses and entrepreneurs. The NHLBI SmallBiz Hangouts are a series of webinars addressing entrepreneurship and biomedical technology development. Topics are expanding and include regulatory, business development, intellectual property, and reimbursement. The events feature NHLBI staff and guest experts offering insights into challenges facing early-stage biomedical companies and providing case studies in overcoming them. Popular webinars in the series include How Pharma Evaluates New Treatment Opportunities (http://bit.ly/SBHangout-PharmaEval), IP for the New Biomedical Innovator (http://bit.ly/IPbasics), and Identifying and Connecting With Your Customer. These webinars are archived on the NHLBI YouTube channel (http://bit.ly/SmallBizHangouts-YouTube).

Companies developing the most innovative medical devices are often blazing a new regulatory path and they face significant risks trying to identify the appropriate regulatory requirements. The NHLBI developed the Pilot Program to Provide Regulatory Support to SBIR/STTR Awardees Developing Medical Devices (Diagnostics and Therapeutics) (PPRS) (link to solicitation: PA-16-335 [http://grants.nih.gov/grants/guide/pa-files/PA-16-335.html]) in collaboration with the FDA Center for Devices and Radiological Health to provide early FDA access to awardees developing and testing technologically innovative or substantial risk medical devices. The PPRS provides an early meeting with FDA to validate the company’s development plans and help ensure they follow the appropriate regulatory strategy to minimize costly mistakes.

Perhaps the greatest commitment that the NHLBI has made to small businesses is the investment in full-time staff with business expertise to augment the usual scientific expertise associated with the NIH. This expertise complements the scientific expertise of program officials and includes a small business coordinator, a business development advisor, a regulatory specialist, an entrepreneur-in-residence, and an investor-in-residence. These individuals are available to speak with small business applicants and awardees, as well as other translational scientists, about the business and commercialization challenges that are often faced by academic investigators and early-stage small businesses. For example, the small business coordinator can help companies identify the most appropriate funding mechanisms and help new applicants navigate the complicated registration and application process. The business development advisor assists companies in understanding the key elements of their Phase II commercialization plans and the importance of synergizing the research and business strategies. The NHLBI regulatory specialist advises on the appropriate regulatory strategy and assists with navigating the FDA. For contact information, see our website (http://www.nhlbi.nih.gov/research/funding/sbir/contact-us.htm).

**Hand-Off to the Private Sector**

The primary goal of the NHLBI small business program is to provide funding and resources to help
companies reach the key milestones that will enable them to transition to private sector support so they can ultimately bring new products to market to benefit patients and public health. In addition to the Phase IIB program described in the preceding text, the institute has dedicated significant resources to assisting companies with this transition.

The NHLBI Innovation Conference (http://bit.ly/NHLBIshowcase) is an annual event that brings together small businesses, angel investors, venture capitalists, strategic partners, and business leaders from the biotech, pharmaceutical, and medtech industries focused on the NHLBI mission, including cardiovascular indications. The conference features presentations by top NHLBI-funded small businesses with innovative and commercially relevant technologies, expert keynotes and panels addressing topics relevant to early-stage companies, and opportunities for networking. Because of this event’s unique focus on cardiovascular, pulmonary, blood, and sleep indications, it attracts investors with a targeted interest in the NHLBI mission space, maximizing relevant networking opportunities for NHLBI-funded small businesses. In addition to the NHLBI Innovation Conference, the institute supports 15 to 20 NHLBI-funded small businesses to attend other industry and investor conferences. Events such as the BIO International Convention, AdvaMed, and the Redefining Early Stage Investment conferences provide domain-relevant platforms for small businesses to present their technologies to potential partners and investors.

Recognizing that many early-stage companies are not prepared to present a pitch that will attract potential investors and partners, every company selected for NHLBI support to present at an investor showcase event is coached on their presentation by an experienced team of entrepreneurs and investors. In addition, the company is mentored on how to speak with potential investors and partners, and on their partnering strategy at the event. This mentoring process is routinely lauded by both participants and investors and is an example of our commitment to providing the key support beyond funding that is necessary to our portfolio companies’ success. More information on showcase opportunities and coaching is available on our website (http://www.nhlbi.nih.gov/research/funding/sbir/ric/index.htm).

**CONCLUSIONS**

The NHLBI views the small business program as an engine of innovation to translate early-stage technologies into life-saving products. Since 2010, we have transformed how we support early-stage biomedical companies by developing a comprehensive ecosystem to provide funding, resources, and expert advice. One recent participant in the I-Corps at NIH program stated, “OTAC’s staff and resources provided [us] with tools to understand the fundamentals of our business model. During I-Corps, our team was able to rapidly focus, refine, and validate our business model through customer interviews—learning in seven weeks what may have otherwise taken us well over a year.” For more information on any of the programs mentioned in this article or to discuss a potential application, please visit our website (http://www.nhlbi.nih.gov/research/funding/sbir/).

**TABLE 2 Accessing NHLBI Funding for Small Businesses**

Although the NHLBI primarily funds small businesses by supporting investigator-initiated grant applications received through general funding opportunity announcements termed Omnibus solicitations, the institute does publish targeted grant funding opportunities (program announcements and RFAs) and Topics of Special Interest. RFAs typically have a targeted area of focus, special review criteria, and money set aside to support applications in response to the solicitation. Topics of Special Interest are meant to highlight research areas that NHLBI deems high priority. Although no money is set aside, the NHLBI does provide additional consideration to applications in these areas when making funding decisions. Topics of Special Interest can change at any time, so applicants are encouraged to check the website (http://www.nhlbi.nih.gov/research/funding/sbir/funding-opportunities/omnibus_grant_solicitation.htm) frequently for updates and sign up for the listserv (http://bit.ly/NHLBI-SBIR-Updates) to be notified of new funding opportunities. In addition, the NHLBI supports a limited number of small business contracts each year.

Examples of recent cardiovascular topics addressed by NHLBI RFAs and Topics of Special Interest

- Bioreactors for reparative medicine
- Biocompatible fluid sealant for paravalvular leaks
- Smartphone apps to increase accessibility and evaluation of the latest educational materials and trial research on cardiovascular, nutritional, and physical activity information
- Technology that enables immediate, user-friendly measures of average daily sodium intake
- New animal models for the study of chronic venous insufficiency and post-thrombotic syndrome
- Development of mechanical circulatory support devices for individuals with congenital heart disease and single ventricle physiology after Fontan surgical palliation
- Innovative technology and/or service delivery model or design targeted at increasing the adoption, uptake, and sustainability of evidence-based guideline recommendations
- New and improved methods to assess, monitor, or predict cardiovascular toxicity of therapeutic agents

For links to current funding opportunities covering all aspects of the NHLBI mission, please visit our website (http://www.nhlbi.nih.gov/research/funding/sbir/funding-opportunities/).

NHLBI = National Heart, Lung, and Blood Institute; RFA = request for application.

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