Granting you success

David Beylin, Cara J Chrisman & Michael Weingarten

Non-dilutive funding from government programs can help startups move forward.

Securing funding is always a critical step for an early stage life sciences company. If you are a founder seeking to get your venture up and running, the Small Business Innovation Research (SBIR) and Small Business Technology Transfer (STTR) programs run by the US National Institutes of Health (NIH) offer the possibility of accessing a unique source of funding. Unlike venture capital investments, this funding is particularly useful as it does not dilute share ownership (the US government does not take equity in companies).

In the following article, we lay out the process of applying for SBIR and STTR grants. Although 11 US government agencies provide this type of funding, we refer specifically to the programs run by the US National Cancer Institute (NCI) and illustrate the steps you must take in applying for funding and following receipt of an award, if your application is successful. We also discuss the ways in which these programs can help nascent companies build the relationships critical to their businesses and, most importantly, develop products and technologies that will ultimately benefit both the cancer community and overall public health.

Box 1 International money

Several government programs around the globe can help life science entrepreneurs raise public capital for their companies. Some programs have structures that are in many respects similar to those of US Small Business Innovation Research (SBIR) and Small Business Technology Transfer (STTR) programs; for example, the Small Business Innovation Research Initiative (SBIRI) in India and the UK's Small Business Research Initiative (SBRI). In the European Union, the Seventh Framework Programme (FP7) provides several mechanisms to support R&D conducted by small and medium enterprises (SMEs). It is a good idea for entrepreneurs to search for the programs accessible to their companies through central and local governments in geographies where their companies operate (**Table 1**).

Table 1 Government programs around the world supporting SMEs

Name	Description	URL
UK's SBRI	Relaunched in April 2009, the program aims to use government funds to drive innovation through short-term development contracts.	http://www.bis.gov.uk/policies/innovation/procurement/sbri
EU's FP7 private company information	FP7 runs until 2013. According to their website, they aim "to strengthen the innovative capacity of mainly medium to low tech SMEs and their contribution to the development of new technology based products and markets."	http://cordis.europa.eu/fp7/sme_en.html
India's SBIRI	Initiated in September 2005, SBIRI receives applications from SMEs in the areas of health care, agricultural applications, industrial product and process development, and environmental biotechnology.	http://india.gov.in/sectors/science/sbiri.php

Letters and numbers

With more than $2 billion in funding made available to thousands of small businesses each year, the SBIR and STTR programs have a critical impact on US-based technology and life science companies. The US Congress established the SBIR and STTR programs through legislation requiring certain federal agencies to set aside 2.8% of their extramural R&D budgets for small, US-based companies. The funding is provided for R&D that has the potential for commercialization, within the missions of the participating federal agencies. For a biomedical enterprise, this encompasses a wide range of activities, from developing a medical device prototype or generating a lead drug candidate to performing preclinical studies or clinical trials required for US Food and Drug Administration (FDA) approval.

Internationally, similar programs supporting small business are offered by a number of nations (**Box 1** and **Table 1**), but in order to be eligible for SBIR and STTR funding in the US, the company must be a US small business concern. This is defined as a for-profit enterprise, majority-owned by US individuals, with fewer than 500 employees. The key difference between the SBIR and STTR programs is that STTR projects must include a partnering nonprofit research institution.

SBIR and STTR projects are required to proceed in phases. Phase 1 funding is used to prove the feasibility of a new idea, whereas phase 2 funding supports further development of a product or technology. Phase 3 refers to the eventual commercialization of that product or technology and must be funded by outside sources. Per guidelines issued by the Small Business Administration, phase 1 SBIR awards are generally up to $150,000 and SBIR phase 2 awards are generally up to $1 million (additional guidelines are provided for STTR award sizes). Companies can exceed these guidelines with proper justification,

David Beylin is program director, Cara J. Chrisman is project manager and Michael Weingarten is director, National Cancer Institute Small Business Innovation Research Development Center, Bethesda, Maryland, USA. e-mail: ncisbir@mail.nih.gov

and individual federal agencies are empowered to set their own budget policies, leading to some variation in award sizes.

Preparing your application

When does it make sense for a company to apply for SBIR funding? In many cases, successful SBIR applicants are new life science startups with scientifically sound, highly innovative and clinically and/or commercially useful technology, which needs capital for early feasibility studies. In some cases, an established company has recognized a new technology area that leverages its expertise and needs funding to pursue a new direction (although it is important to remember that innovation is a major criterion for funding). SBIR programs are not appropriate for small, incremental upgrades to an existing product or for developing a product to match a competitor's capabilities.

Typically, the first step in the process is an informal discussion with potential customers, experts in the field and other parties who will be essential to the future of your company. Throughout that process, it is useful to collect letters supporting the application. Strong applications include letters of support from all collaborators, consultants, potential customers, investors, commercial partners and key opinion leaders, as well as from other organizations involved in helping patients. If the company plans to use facilities at other research institutions, reviewers often expect a letter from the administration of the institution confirming the facilities will be available.

Building a strong, complete and engaged project team is the most important task an entrepreneur has to accomplish. NIH grant reviewers are often very critical of proposals in which the team is missing one or more types of critical expertise. For example, if a cancer drug development proposal fails to include a medical oncologist, reviewers are likely to raise concerns. Team selection begins with choosing the principal investigator who has the appropriate technical expertise and is able to direct the funded R&D effort. When the project is of a multidisciplinary nature, the NIH allows more than one principal investigator on a proposal, thus enabling the building of leadership teams that share responsibility for the project's success. For an SBIR application, the investigator selected as the contact to represent the company must spend at least half of her or his time working for the company at the time of the award. For an STTR application, the primary investigator may be employed either by the company or the partnering research institution. In either case, the qualifications and commitment of the investigators are carefully examined during peer review. It is important to note that building a strong business team, including both employees and advisors, is just as important as securing technical talent.

Many companies will have potential collaborators, including academic researchers, that will help to obtain access to research resources and provide technical feedback. They'll also serve as consultants or perform additional research in their laboratory. Fortunately, per SBIR guidelines, up to 33% of the phase 1 and up to 50% of the phase 2 research effort can be performed outside of the small business. For STTR projects, the small business must carry out at least 40% of the funded effort, and the primary nonprofit collaborator at least 30%, whereas the remaining 30% can be used for consultants and collaborators.

When to apply

Any grant or contract application must be submitted in response to a published NIH solicitation. These solicitations can be identified on the NCI SBIR website, as well as through several other resources (**Box 2**). There are two general types of solicitations: targeted solicitations and the broad-based, investigator-initiated solicitation known as the SBIR/STTR Omnibus.

The SBIR/STTR Omnibus captures a broad range of topics that are of interest to the NIH. More than 80% of all new grants awarded in fiscal year 2009 and 2010 were submitted under the SBIR/STTR Omnibus solicitation.

Targeted solicitations include NCI SBIR contracts, in which topics are developed by the NCI staff to stimulate highly promising technology areas or address specific barriers in cancer research. Each topic describes expectations for project goals and deliverables, but the choice of the specific technology implementation and the details of the experimental approach are determined by the applicant.

All published solicitations specify the application receipt dates and, in certain cases, dates for submitting a letter of intent. The NIH SBIR/STTR Omnibus solicitations currently have annual application receipt dates on April 5, August 5 and December 5. (NCI SBIR contract topics are currently published once a year in August with proposal receipt dates in early November.)

If you're working in cancer, once a project takes shape and the solicitation has been identified, it is often useful to engage with one of the NCI SBIR Development Center program directors (**Box 2**) to validate the proposal strategy. Program directors understand the grants and contracts processes and can provide information about both available funding opportunities and key criteria for a strong application. A program director will also serve as the scientific point of contact after proposals are submitted and will oversee the technical progress of funded projects.

Great team, great product

The SBIR program is highly competitive; thus, your application should highlight the innovative nature of the proposed product, thoughtfulness of the project plan and quality of the team (supplemented by necessary collaborators and consultants). It should also contain support from current and potential customers, investors and commercialization partners. In the end, the only material that is the peer reviewers evaluate the application, so clarity and persuasiveness are essential.

The focal point of the application is the section stating the specific aims (technical objectives) of the proposed effort. The specific aims for phase 1 should resolve key questions regarding the feasibility of the proposed innovation. The specific aims for phase 2 should build upon successful phase 1 aims and detail a step-by-step plan for eliminating technical risks and moving the product toward commercialization. Most successful proposals establish criteria for each specific aim and state them as objective, measurable milestones. For example, for a project involving ultrasensitive technology for the detection of low-abundance proteins, one of the milestones may be the ability to detect a

Box 2 NCI's online SBIR resources

Just beginning the process of preparing your grant application? There are several online resources that can provide you with information. As a starting point, the National Cancer Institute's (NCI's) Small Business Innovation Research (SBIR) main landing page (http://sbir.cancer.gov/) provides you with background information, program announcements and newsletters. For a listing of the administrative staff based in Washington, DC, key contacts are provided with a general telephone number and e-mails (http://sbir.cancer.gov/contact_us.asp). Elsewhere, you can find information on funding opportunities and different mechanisms for applying for grants (http://sbir.cancer.gov/funding/find_funding.asp) together with a detailed SF424 (R&R) SBIR/STTR application guide (http://grants.nih.gov/grants/funding/424/index.htm).

Table 2 National Cancer Institute initiatives to foster commercialization

Name	Description	URL
The Phase II Bridge Award	Unfortunately, even after completion of phase 2 research, many projects are still too risky for private sector investors, resulting in many Small Business Innovation Research (SBIR)-funded companies finding themselves in the so-called 'valley of death'. To address this problem, the National Cancer Institute (NCI) launched the Phase II Bridge Award. SBIR phase 2 awardees can apply for up to $3 million in bridge funding over a 3-year period.	http://sbir.cancer.gov/funding/phase2bridgeaward.asp
The SBIR Investor Forum	Each year, the NCI SBIR Investor Forum connects the strongest and most promising NCI SBIR–funded companies with life science investors and strategic partners. The NCI selects 10–15 of its companies to present their technologies to professional investors at this full-day conference.	http://sbir.cancer.gov/investorforum/
The Regulatory Assistance Program	Most clinical products require approval by the Food and Drug Administration (FDA), a process that can prove daunting to many small businesses. The Regulatory Assistance Program provides companies with 30 hours of consulting time with a professional FDA regulatory expert who will help draft or refine the company's regulatory plans and/or assist in the preparation of regulatory submissions including 510(k)s, PMAs, INDs and IDEs.	http://sbir.cancer.gov/resource/assistance/

certain amount of specific proteins in spiked serum, which cannot be measured with existing technologies.

The research strategy section of the SBIR proposal is important and should contain background information and provide detailed descriptions of the research activities necessary to address the specific aims. The project background needs to describe the problem addressed in the application and position the proposed product in relation to the current state of the field. Although preliminary data are not required for the phase 1 SBIR, strong applications build on what is currently considered to be state-of-the-art technology in the respective field and, whenever possible, will use experimental approaches based on commonly accepted methodologies. Unless the technology is entirely new, it is best to rely on published evaluation methods, industry standards and guidelines promoted by professional societies or government agencies. For example, if an FDA guideline document describes recommended testing for clearance of a certain class of devices, the research plan may build upon the FDA's recommendations. When the potential of a positive outcome for the research activities is uncertain, it is also useful to provide alternative plans.

The research plan must disclose sufficient technical details for reviewers to properly evaluate it. Although the desire for secrecy is understandable in an early-stage venture, you need to balance that against clearly explaining the innovation. Grant and contract applications are confidential, and reviewers are bound by federal confidentiality and conflict-of-interest rules. However, you might want to file a provisional patent application before engaging in discussions with potential collaborators and partners while preparing the application. The filing of a patent application will also demonstrate to the peer reviewers that you are being duly diligent in protecting the company's intellectual property.

Phase 2 applications also need a commercialization plan describing the value of the proposed product, customer base, market, competition, and financing and manufacturing plans, as well as any other issues. The commercialization plan is a critical component and needs to demonstrate the resources available to the company, including the business expertise available through the board of directors and advisors.

Other important parts of the application include the budget, biographies of senior and key personnel, and, if the company proposes the use of animals or human subjects, additional sections. It is often beneficial to have the application reviewed by collaborators and other relevant experts before submitting it to the NIH. For example, if a new radiosensitizer is proposed, a radiation biologist, radiation oncologist, medical oncologist and an industry scientist with drug development expertise should review the application. In addition, have the application draft reviewed by technically qualified laymen who are not intimately familiar with the product and company. Once the application is complete, it must be submitted by the receipt date specified in the NIH solicitation. There are several registrations that also need to be completed before a submission is made, so it is helpful to become familiar with the required steps well in advance.

Getting reviewers excited

The NIH tasks a group of external technical experts (peer reviewers) possessing relevant background to evaluate the merits of each proposal. The rosters of prior study sections are available on the NIH Center for Scientific Review website. Although the NIH has the ultimate authority over the assignment of each application to a particular study section, a preference can be expressed in the cover letter accompanying the application.

An application's priority score depends entirely on the reviewers' enthusiasm. A strong application projects a clear and exciting story about the importance of the proposed product and gives reviewers confidence in the company's ability to carry out the proposed R&D. It is important to know and study the NIH review criteria: significance, investigators, innovation, approach and environment. Detailed descriptions of the criteria are provided in the SF424 (R&R) SBIR/STTR application guide (**Box 2**). Typically, about half of all applications are not discussed and do not receive a numeric score. However, all applications will receive a summary statement, which contains the overall score, a short summary of the discussion and detailed critiques by primary reviewers.

In many cases, the initial application does not receive a fundable score and the submission of a revised application is required. In fact, about 40% of the new grants awarded in fiscal year 2010 were resubmissions. It is important to study the reviewers' feedback and address their concerns in the revised proposal. Please note, under current rules, only one resubmission is allowed.

The award and beyond

If the materials you submit receive a competitive score, the NIH will notify your company that the application is being considered for an award. Along with this notification, you will receive a request for various documents, collectively called 'just-in-time information', concerning researchers involved in the project, animal welfare, human subject protection and other administrative details. You can handle these requests with the help of the NIH staff assigned to your project—the same people who will oversee your project if the award is made.

If you receive SBIR or STTR funding from the NCI, it can take time to understand all the rules and regulations that apply to both you as a grantee and your contractors. At the NCI, the SBIR and STTR programs are managed by the NCI SBIR Development Center, which supports those conducting highly innovative R&D in cancer diagnosis, prevention and treatment. The fiscal year 2010 budget allocated to the NCI SBIR program was $110 million. It may be worthwhile to find professional consultants to help set up appropriate accounting, personnel and other company policies. It is often possible to locate experts through state and local institutions supporting small business and entrepreneurship.

Once you are using the funds for your R&D effort, you must provide the NCI SBIR program with regular progress reports. In addition to these required reports, it is also recommended that you update the SBIR staff on both technical successes and achievement of significant commercialization milestones. It is beneficial for you to maintain a dialog with your program director, as he or she can share information regarding developments in the field, provide feedback on your experimental approach or make connections with potential hires, partners and investors in his or her networks.

SBIR funding can potentially provide a company with support for many years. A successful phase 1 can be followed by a phase 2, and phase 2 can be followed by an SBIR Phase II Bridge Award (**Table 2**). To enable this progression, companies should attempt to keep the next stage in mind while working on their project.

SBIR and STTR programs provide more than funding. They can help you build your network of contacts and collaborators. Most importantly, they provide validation to other investors who might consider funding your company. Good luck with the application!