FUNDING POLICY

A Translational Research Niche for Small Business Innovation Research Grants

Karl Handelsman

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The United States Congress will decide the future of the Small Business Innovation Research program in the coming months. Essential changes needed in the program and its unique role in translational research are discussed.

Fig. 1. More is better. Scientists seek funding to translate basic discoveries.

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MONEY, IT'S A HIT

In 2008, Regis Kelly, director of Quantitative Biology 3 (QB3)—an institute formed as a cooperative effort among three campuses of the University of California and private industry (*1*)—surveyed the QB3 faculty needs for translational research project funding. The survey results were striking: Almost 20% of these basic scientists suffered from a shortage of funds required to move their basic discoveries along the continuum to practical application (Fig. 1). Kelly noted that funding for such efforts might come from the National Institutes of Health (NIH) Small Business Innovation Research (SBIR) grant program. From an academic director's standpoint, increasing the pace of the SBIR funding process and expanding the fraction of funded requests would be welcome changes. The U.S. Congress has extended the SBIR program twice since it expired in July 2009 and will decide its future in the coming months (*2*). Here I discuss essential changes needed in the program and its unique role in translational research.

FUNDING TRANSLATION'S FIRST STEPS

Practical problems associated with the SBIR program have fueled the search for alternative funding mechanisms by basic-cum-translational investigators. For example, QB3 bolsters budding entrepreneurs by providing them with incubator space in its Garage facility, a collection of small-project lab space rentals complete with full access to top-of-the-line large lab equipment. There are now 16 nascent companies incubating at the University of California San Francisco's Mission Bay campus (*3*).

This funding gap between translational research and commercialization efforts is driven by the difference between robust academic science and the types of data that attract capital directed at creating products. Basic biomedical or bioengineering discoveries born at academic institutions or small companies must be advanced enough in their feasibility to grab the attention of either private investors or corporate sponsors. This feasibility is measured by comparing the risk/reward (success) ratio of a given venture with those of other competing projects. Most competing projects will be directed at improving established products and thus have a clear (less risky) commercial path. Small companies often pursue riskier, more innovative projects than do established businesses by recruiting highly focused teams and attracting funding from investors and granting agencies.

The advantage of grants is that they are non-dilutive; that is, they minimize the dilution of stakes held by existing investors. Indeed, a company funded solely by grants can remain wholly owned by the startup team. Not so for companies buoyed by funds from investors, who include individual "angels," corporate sponsors, and firms that focus on private equity, such as venture capital. In return for their investments, these financiers expect to be granted partial ownership of the company. This ownership, via equity, must be sufficient for the possible rewards of success to overcome the investor's fear of the risk of failure. It is not uncommon for the so-called sweat equity of the knowledge workers (high-level company employees and advisors) to be valued at a dollar amount that requires the company to sell half of its equity shares to the investors, even at an early stage of development. The availability of grants allows small companies to either go it alone for a time or sell less of the company to investors and thus retain more control over the company's destiny. Furthermore, investors view the acquisition of grants by a potential investment target as both validation of the business's promise and a force for risk reduction, because each investor dollar can be stretched further when combined with grant money.

SBIR SNAFUS

Created in 1982, the NIH's SBIR program has the potential to play more of a leadership role in the starting and sustaining of embryonic biomedical business ventures. For example, SBIR grants could help fill the early-stage funding gap between basic discoveries and commercially enabled health care technologies. This role would be a natural one for the SBIR program, because early-stage, commercially directed research and development (R&D) is complementary to the NIH-funded basic research conducted in academic labs and is a necessary stage of the translation of basic biological knowledge to product commercialization.

In 2008, the SBIR program gave grants totaling more than $2 billion to fund R&D projects in small businesses, and NIH accounted for more than $600 million of this total (Fig. 2). Although this is a welcome source of capital for academic researchers who are attempting to translate their research into solutions for patients, unfortunately, the SBIR program redefined "small" in 2001 to exclude venture capital–backed companies. In fact, in most cases, if a start-up company accepts any significant venture capital investment, it no longer qualifies as

Managing Director, CMEA Capital, San Francisco, CA 94111, USA. E-mail: karl@cmea.com

a small business eligible for SBIR grants, even if the company consists of fewer than 20 employees.

There have been proposals to set aside 8 or 18% of SBIR funds for venture-backed small companies. This is an illogical compromise, because early-stage, venture-backed companies certainly are small businesses in every sense of the word and deserve the opportunity to compete for SBIR grants on an equal footing with other small businesses. It is impossible to develop a perfect grant-selection system for early-stage projects, because they are by their very nature risky and unproven. However, the contributions of the SBIR program to future health care innovations can be enhanced substantially by allowing the participation of early-stage companies and technologies that have attracted investment from the venture community. In addition, this participation has not been detrimental to the goals of the SBIR program. As Sally J. Rockey, acting deputy director for Extramural Research at NIH, testified on 23 April 2009 before the U.S. House of Representatives, "Throughout the SBIR program's history, small businesses, including those companies with venture capital funding, have applied for and received SBIR funding in areas that help to advance our mission. The National Research Council's study found no evidence that participation of companies with multiple venture capital ownership was harmful to the program or that other small businesses have ever been crowded out by the participation of small businesses that are majority-owned by [venture capital companies] (*4*)."

Ownership is a function of capital structure—the way a company funds its internal programs through a variety of mechanisms, including equity—and this is driven by the risk/reward ratio needed to attract investor capital. However, in the first round of funding for a company, the percentage of ownership is not related to the risk or merit of each early-stage project. In fact, the ownership percentages may be based entirely on the group's lead project and not a promising but earlier-stage effort within the company, which is a perfect match for SBIR grant funding. Defining "small" based on the company capital structure eliminates some of the most promising opportunities for grant funding leading to commercialization.

Policy-makers need to ensure that companies that are awarded SBIR grants remain true to the "small" part of the SBIR mission. However, it is certainly true that the present guidelines eliminate many promising projects from consideration because a dozen employees have accepted investment from venture capitalists on the order of 5 or 10 million dollars. Often these creative scientists, toiling away together over long hours on the primary focus of the company, jointly inspire each other to envision alternate approaches or applications that have great potential but are riskier than the lead project. These side projects can languish in the extremely capital-constrained world of early-stage venture-funded companies. This is a common situation in which venture capital and SBIR funds can effectively leverage each other to unlock value in a context in which innovative technology may most rapidly be transformed into novel products. There are numerous examples of these early-stage research programs evolving into economically important spinoffs. For example, pharmaceutically focused Affymax developed early-stage DNA chemistry to a point at which it was spun off as the DNA microarray company Affymetrix (*5*). Symyx Technologies, a company that develops industrial chemistry solutions, spun off a pharmaceutical company called Illypsa, which was later acquired by Amgen for over $400 million (*6*).

The NIH SBIR and STTR* programs

Total grants in millions by year

Year	$ Million
1994	125
1995	173
1996	188
1997	249
1998	268
1999	314
2000	362
2001	418
2002	498
2003	542
2004	613
2005	627
2006	621
2007	640
2008	656

*STTR, Small Business Technology Transfer; data from http://grants.nih.gov/grants/funding/award_data.htm

Fig. 2. Grants grow. NIH's SBIR grants could greatly enhance translation from bench to bedside.

A NATURAL NICHE

Companies founded on translational medicine platforms offer an extraordinary opportunity to deploy SBIR grants in a highly leveraged manner. These early-stage companies bring together talented teams with deep expertise around a particular disease, biological process, biochemical pathway, or proprietary technology, and often these ventures focus heavily on the lead application. Frequently the core expertise and opportunity resident in the company apply to multiple promising applications. In such an arena, SBIR grants can do much more than stretch venture investment funds: They can allow greater flexibility to exploit the core technology and apply it in creative new ways.

A typical example of such a scenario involves Andrew G. Myers of Harvard University, who developed chemistry that led to the formation of a small company called Tetraphase (*7*), which recently started its first clinical trial of an antibiotic based on a tetracycline compound. However, there are many publications that support the promise of the tetracycline chemical scaffold in other areas of clinical medicine, such as inflammation and oncology. Tetraphase has created a talented team, with custom reagents and techniques funded by venture capital to work primarily on antibiotics. The expertise around this chemistry created by Tetraphase enables thousands of unique new compounds, which could be more rapidly assessed for utility in oncology and inflammation with the supplement of SBIR grants. This incremental grant money leverages the company's talent and assets created by a much larger investment secured primarily to advance the lead program. In this way SBIR grants could be a key input to expand, not displace, venture capital investment by amplifying the breadth of commercial applications. This example is replicated across many small companies with and without venture funding. Grant money enables efficient expansion into additional opportunities, because these elite teams are already assembled to exploit the lead technology.

The SBIR program awards grants in phases. Unfortunately, these award sizes have not been adjusted since 1992 (*8*). Phase I grants currently are limited at $100,000, and phase II grants at $750,000. It may be wise to double these amounts, even at the expense of halving the number of grants.

SBIR GRANTS SEED COMMERCIALIZATION

A final issue that warrants comment is whether there should even be an SBIR program. Detractors of the program have called it a "$1 billion tax on R&D funds" (*9*), and there is one economic analysis that suggests that a tax credit would be more cost-effective (*10*). In the coming months, the U.S. Congress will determine the long-term future of the program and thus whether SBIR grants can continue to serve as an important input to encourage commercialization of scientific breakthroughs (*2*). Although they alone cannot fill the bench-to-business funding gap, the SBIR program can be part of the health care solution by financing small biomedical companies in a way that stokes their translational engines to the benefit of patients worldwide.

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11. Competing interests. K. Handelsman is on the board of directors of Tetraphase, and CMEA Capital is an investor.

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