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Partnering/Licensing

Published online: 28 December 2005, doi:10.1038/bioent895

Beyond patents and royalties: the perception and reality of doing business with the NIH

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Young biotech startups can benefit hugely from the US National Institutes of Health (NIH), not least because of the agency's non-dilutive funding, guidance, and opportunities for collaboration. Increasingly, however, there is a fair bit of misunderstanding about what the NIH can and *cannot* do for a biotech entrepreneur.

Introduction

The NIH licensing landscape has changed significantly during recent years with increasing industry consolidation, large pharmaceutical firms are no longer looking to directly license early stage technologies for commercialization, and the number of NIH licenses signed with small and medium-sized biotech companies is on the rise. Unlike five to ten years ago, when all or most of the high revenue products based on NIH licenses came from large pharmaceutical firms, a majority of the latest success stories tend to be from biotech or other nonpharma companies. Some examples are Kepivance (palifermin) from Amgen, Velcade (bortezomib) from Millennium, Synagis (palivizumab) from Medimmune and Taxus Express (paclitaxel-eluting coronary stent system) from Angiotech[1].

Several other products are being developed by younger firms with the help of the NIH. The new reality is that commercial partners, especially small, innovative ones, are essential to the NIH's role of helping to facilitate the formation of novel healthcare products for the public. From new or invigorated activities in technical assistance to technology licensing to financial considerations, the NIH has an extensive menu of options at NIH that bioentrepreneurs can use in their product development efforts.

Recent NIH licensing practices have been adapted and expanded to take advantage of these new realities. This is reflected in the sharp increase in corporate licensing activity from NIH over the past two years—now in excess of 300 transactions per year—with a particular focus on smaller firms.

Many groundbreaking technologies emanating from NIH laboratories are of a basic research nature and considered early stage, and they provide a wealth of untapped opportunities for bioentrepreneurs (see Box 1). In this article we will try to provide a functional guide to bioentrepreneurs about the various access points for doing business with NIH. We'll review some of the unique features of the NIH licensing program, discuss financial issues like grants and contracts, and use examples of successful collaboration with industry to demonstrate how working with the NIH can help bioentrepreneurs in terms of finance, technology transfer, product development and validation, access to investigators and know-how. We'll also try to dispel some of the myths surrounding NIH's ethics policies (see Table 1).

Show me the money

As most entrepreneurs already know, the NIH can provide startups with nondilutive funding through the Small Business Innovation Research (SBIR) and Small Business Technology Transfer (STTR) Programs[2]. The NIH SBIR program is the most prolific funding source in the Federal Government for a bioentrepreneur, and as an added bonus, it comes with virtually no strings attached.

The SBIR program was established in 1982 by the *Small Business Innovation Development Act* to increase the participation of small, high technology firms in federal R&D activities. Under this program, departments and agencies with R&D budgets of $100 million or more are required to set aside 2.5 percent of their R&D budgets to sponsor research at small companies.

In 2005 NIH's combined SBIR and STTR grants will total $640 million. As a major mechanism in achieving the NIH roadmap goals of enhancing public-private partnership, the SBIR and STTR grants present an excellent funding source for small biotech companies. Recently a spirited debate is underway in the research and venture capital communities on whether it is appropriate for SBIR awards to be given to small companies in which venture capital has controlling interest (that is, more than 51% stake)[3]. The Small Business Administration (SBA) has yet to make a final ruling on this issue.

Phase I grant support, also known as a feasibility study, is normally funded at $100,000 for 6 months (SBIR) or $100,000 for 12 months (STTR). Phase II support is available to Phase I recipients and provides two-year awards of $750,000 (SBIR) or $500,000 (STTR). To foster the best quality applicants, the NIH SBIR program provides prospective applicants with a wealth of information, including advice documents[4], free workshops and conferences[5], and easy access to the program officials who can answer more in-depth questions[6]. Those who hope to receive an SBIR grant from the NIH must convince the agency that the proposed research is unique, creates value for the general public at large through advancements in knowledge and treatment of disease, and is relevant to the overall goals of NIH. It is important to contact the program officials ahead of time within the particular component of NIH from which funding is sought to determine whether the proposed research plan fits these criteria.

Applications are evaluated by a peer group of researchers drawn from industry and academia. It is, therefore, important that applicants do not include proprietary information. The success rate for well-written SBIR grants is ~25–30%. More than the mere funding, SBIR-funded projects have earned the seal of approval from a panel of expert peer reviewers, which will facilitate further fund-raising efforts. Unlike private financiers who evaluate a business plan for its economic returns, NIH reviewers determine whether an SBIR grant application to NIH is significantly aligned with the agency's public health mission. However, like any other attempt by a biotech startup that seeks funds, an SBIR proposal should describe a sound and innovative approach to solving an unmet medical need, and applicants must prove that a committed R&D team that can successfully achieve its objectives is in place.

Early market intelligence

Another valuable NIH resource for bioentrepreneurs is the CRISP[7] (Computer Retrieval of Information on Scientific Projects). This is a searchable database of federally funded biomedical research projects conducted at universities, hospitals and other research institutions. CRISP can be queried to find prospective collaborators or scientific advisors from a universe of prequalified, NIH-funded group of researchers.

For a small company with limited scientific depth, this list can provide the comfort of NIH-reviewed investigators, and provide insight into funded research plans and strategies that are being contemplated for the next three to five years. The database can be queried based on institutions, disease indications, names of primary investigators, type of grants and state. Thus, when properly used, it can provide a wealth of information regarding NIH-funded projects in a specific area.

CRISP provides a heads-up about promising new areas of research, and indicates the scientists whose work should be monitored. It can also be used by biotechs to identify potential customers or key contacts.

Flexible IP licensing terms

Contrary to the perception that the NIH is only interested in working with academics, the NIH affords favorable treatment to small businesses and

creates an attractive playing field for them to get into new areas of product development. For example, startups can negotiate to have patent prosecution of licensed technologies managed by the NIH. This is particularly useful for small firms that may not yet have internal counsel or the resources to retain a top intellectual property (IP) law firm.

Another feature of the NIH licensing program is that unlike many university-based license agreements, the NIH licenses do not require sponsored research agreements. Typically, this requirement may add significant costs to R&D programs which can impose a burden on cash-strapped small companies.

When licensing technologies from the NIH, entrepreneurs should also be aware that equity dilution will not be part of the negotiations. This feature becomes important as companies try to raise capital through additional rounds of financing. Likewise, biotech startups entering license agreements with NIH do not give up any co-marketing rights, nor do they forsake any downstream developmental rights. Research tool licenses negotiated through the NIH carry no grant-backs or reach-through rights. For instance, when a research tool technology is licensed to a company by NIH, the licensee is not required to grant back any usage rights to the improvements that it may develop subsequent to the license agreement. Also the licensee is not required to share with NIH any future profits that may be made as a result of improvements to the original discovery. In other words, IP derived from new discoveries made with NIH-licensed tools will remain clear and unencumbered.

The overlooked role of OTT

The NIH licensing program represents one of the largest and most successful technology transfer efforts in the US biomedical field, having entered into almost 2,500 license agreements in the previous 18 years (FY 1988 to FY 2004), and having generated more than $500 million in royalty revenues[8]. Recently we undertook a market research study to better understand the profile and needs of NIH licensees. The main focus areas of that study were an examination of the different ways by which potential licensees became aware of the NIH technologies that were available for licensing, and whether there were any particular mechanisms of interaction that were preferred by different customer segments.

One interesting observation that came out of this study related to how small companies scout for new licensing opportunities from NIH. Although large companies (with bigger resources) were found to rely more on their familiarity with inventors' publications and their personal contact with the inventor community, small businesses relied more on the marketing messages that originated from the NIH Office of Technology Transfer (OTT)[9].

The marketing messages from NIH that were found most useful by potential licensees consisted of brief one-page summaries of the new NIH inventions available for licensing. The NIH disseminates this information in a timely fashion through our website[10],[11] and our electronic Listserv[12]. In addition to getting up-to date information from these sources about the NIH licensing opportunities, biotech startups can also get in touch with individual licensing specialists in our office whose areas of licensing practice may be most closely related to the company's focus areas[13]. Indeed the role of OTT in technology transfer ranges from invention disclosure, patenting, and technology marketing to license negotiations and postlicensing communications with licensee companies. Bioentrepreneurs have many points of access to NIH licensing professionals at several of these stages of technology transfer.

Free advice and training

Outreach to prospective bioentrepreneurs is important to the NIH. Many postdoctoral fellows, who are concluding their scientific training at the NIH may have the passion to start a biotech company, but usually lack the required business expertise. Scientists can exploit some of the NIH programs that target prospective bioentrepreneurs.

These programs include training in technology transfer through internships and fellowships offered at the Office of Technology Transfer[14], graduate-level courses in technology transfer and in business development, where scientists can develop their business plans based on NIH technologies, and discussion groups such as the Bioscience Business Interest Group that help entrepreneurs with career development and networking[15].

The NIH could be your first customer

Among the little known facts about doing business with the NIH, few are more overlooked than the commercial role that NIH plays as customer to a vast and growing number of biotech firms. With an intramural staff of about 17,000 employees, laboratories spread across the nation (with the Bethesda campus housing a majority of the labs), and an annual intramural budget of about $2.7 billion (FY 04), the NIH is perhaps the largest US consumer of bioscience research reagents and instruments. A variety of mechanisms for selling products and services to the NIH are possible, including stocking in government storerooms.

Selling to NIH can be seen as a daunting task for biotechs because of the US Government's complex acquisition process. However, there are a few simple steps that companies can take, such as establishing a blanket purchase agreement with NIH and getting their goods and services into the NIH stockroom. Once these steps are completed, it is much easier for

NIH scientists to buy from such companies, and if the quality of goods and services provided by a particular biotech company is superior, an NIH scientist can justify buying from that source.

Companies that provide products and services to NIH laboratories can not only generate cash flow and revenues to fuel R&D, but also begin to demonstrate their commercial acumen to would-be partners and investors (see Box 2).

The annual NIH Research Festival is an excellent starting point for companies hoping to sell products to the NIH[16]. This event is held every fall at the Bethesda campus and during spring on the Ft. Detrick campus. Part scientific, part social, part informational and part inspirational, this three-day event draws a variety of small-to-medium-sized bioscience companies. These events attract almost 6,000 NIH PhDs, many of whom come to these gatherings to buy the latest research tools.

Biodefense in your future?

Firms capable of developing products and services that focus on medical countermeasures to chemical, biological or radiological threats can receive grant or contract money through Project Bioshield. This project, which was signed into law on July 21, 2004, aims to protect the American public from various weapons of bioterrorism. Over the next 10 years, ~$6 billion will be committed to these efforts.

Awards granted through project Bioshield are not limited to academia. In fact, out of the ten grants and two contracts recently awarded by the National Institute of Allergy and Infectious Diseases (NIAID), totaling ~$27 million, five grants and two contracts were awarded to private companies.

These first grants and contracts, which range in duration from 12 to 18 months, respond to a key objective of the NIAID biodefense research agenda that emphasizes the development of new and improved medical products against 'Category A' agents—those biological agents considered by the Centers for Disease Control and Prevention to pose the greatest threat to national security.

Can NIH scientists work with biotechs?

There is a perception among many industry professionals that the implementation of new ethics rules at NIH means that NIH researchers can no longer interact with the private sector.

Although it is true that NIH investigators cannot engage in outside consulting with biotech and pharmaceutical companies in their personal capacity, without prior approval, the fact is that technology transfer activities are actually among the official duties in which NIH scientists are encouraged or required to participate. These activities may include the reporting of new inventions from the lab, and assisting technology transfer staff with patenting, marketing and licensing interactions with companies. NIH scientists can also officially collaborate with industry scientists through Cooperative Research and Development Agreements (CRADAs), Clinical Trial Agreements (CTAs), and Material Transfer Agreements (MTAs).

In a CRADA arrangement, which could last for several years, NIH scientists and company scientists can engage in mutually beneficial joint research where each party provides unique resources, skills and funding, and where either partner may not be able to solely provide all the resources for successful completion of the project. In such an arrangement, the scope of the research work to be carried out and the license options granted to discoveries emanating from the joint research are clearly spelled out.

A CTA would typically involve a compound or therapeutic modality, which is proprietary to a company that desires the clinical trial infrastructure that NIH possesses. NIH generally enters into these agreements only in cases where such trials would be difficult or impossible to run in other places. The NIH is also particularly interested in clinical trials involving orphan diseases that affect 50,000 or fewer people each year. An MTA is a popular mechanism for exchanging proprietary research reagents, which is used by scientists worldwide. NIH scientists actively use this mechanism to share reagents with scientists in other nonprofit organizations.

Of the three collaborative mechanisms described above, a CRADA is perhaps the most comprehensive and far-reaching. Such agreements can facilitate financial support for an NIH lab, while providing the collaborating company with preferential access to the NIH scientist's future work and expertise during the research or clinical collaboration. The easiest way for a bioentrepreneur to begin to access this expertise is to simply approach the agency officially through the various technology development coordinator offices located in the individual institutes within NIH[17].

Working with the NIH from abroad

Although a US-based government agency, the NIH's technology-licensing activities increasingly have a worldwide scope. Patent protection is sought in major non-US markets for discoveries made in NIH laboratories with license agreements to non-US firms now representing more than one out of every six licenses signed. Of particular note is the emerging biotech industry and entrepreneurial culture in countries such as India and China, which has also led to the growth of licensing activity in those areas by NIH for such products as vaccines that substantially serve those regional needs and markets (see Box 3).

To facilitate this effort, the NIH has added international technology transfer professionals, who focus their outreach and training efforts on non-US

biotech and R&D organizations.

Conclusion

The NIH realizes that for its work to have full impact, the research findings generated in its laboratories must be translated into goods and services that benefit society by improving public health and by reducing the burdens of disease. Clearly this cannot be done without active partnerships with private industry.

Simultaneously there is a growing realization on the part of industry about the unique attributes of NIH research—attributes such as high-quality science, cutting edge discoveries in areas of research that may not be pursued in other laboratories and the agency's single-minded dedication to improving public health. Savvy bioentrepreneurs can come to NIH not only for money in the form of SBIR grants, but also for product development leads through various partnership mechanisms.

In addition, the NIH laboratories can be seen as an early adaptor customer that embraces new biomedical research products, and as a source of expertise and resources that may not be available in other places. At the same time there have been a number of myths that may have prevented some bioentrepreneurs from fully realizing the value of their interactions with NIH. Academics the world over already comprehend and appreciate the full value that NIH brings to their own work and to public health. But the full value of the NIH can only be realized if its utility is fully understood and engaged not only by academia, but also by the private sector.

Box 1: NABI biopharmaceutical's NIH link

StaphVAX, produced by North American Biologicals (NABI) Biopharmaceuticals, is a *Staphylococcus aureus* polysaccharide conjugate vaccine currently in phase 3 trials in the US. It is based on technology developed in the lab of John Robbins at the National Institute of Child Health and Human Development (NICHD), one of the NIH institutes that has a large portfolio of childhood vaccines. The vaccine technology was licensed to Univax Biologics, then a small local firm, which also recruited a postdoctoral fellow from the NICHD lab.

The platform was further used to develop additional conjugated vaccines such as the NicVax as an aid to smoking cessation. The products then proceeded to Univax, an incubator, and then further developed with a CRADA. From there, the product migrated through a merger with NABI, a publicly traded company.

Box 2: GenVec's NIH link

CRADA is a mechanism by which a company can establish a long-term relationship with NIH. When properly nurtured, such collaborations can result in substantial value creation for the company. GenVec originally signed a CRADA with the Vaccine Research Center at the National Institute of Allergy and Infectious Diseases in October 2001. This CRADA was aimed at the development of adenoviral vectors expressing modified HIV-1 genes.

As the collaboration progressed, the relationship between GenVec and the NIH expanded to include ancillary contracts with a potential value of $30 million for manufacturing adenovector-based preventative AIDS and SARS vaccine candidates for the Vaccine Research Center. “In addition to the important revenue that these contracts provide, they help companies build infrastructure, further develop technology platforms, and gain valuable experience in manufacturing, quality and regulatory functions that may be applicable to other areas of their business,” GenVec officials have stated.

Box 3: Overseas entrepreneurs and NIH

In its quest to spread the NIH technologies as widely around the globe as possible, the NIH's international license efforts have expanded beyond Canada and Europe to countries such as India, China, South Africa and Brazil. In fact, the NIH is particularly interested in non-US firms that can bring their unique strengths to the table by directly addressing their local markets, healthcare needs and diseases.

Most foreign biotechs can conduct business with the NIH Office of Technology Transfer. In fact, approximately 17% of NIH licenses now go to overseas-based companies. The key challenge to foreign firms is the US regulation, which requires that goods intended for US sales must be “substantially” manufactured domestically. Foreign businesses can meet this requirement by hiring a US contract manufacturer or corporate partner to produce the goods intended for the US market. When circumstances warrant, the NIH can grant a waiver to the US manufacturing clause as long as there is an appropriate and reasonable justification.

Table 1: Top Five Myths of Doing Business with the NIH

Myth	Reality
Small companies need not apply	For the past several years, over 50% of the NIH's license agreements and nearly all of the product commercialization deals have been with small businesses as a result of the NIH's licensing practices, which favor small companies. Increasingly, breakthrough products based on NIH discoveries emanated from working with small to mid-sized companies, entrepreneurs, venture capitalists and angel investors.
The NIH requires sponsored-research agreements	The NIH employs many flexible and creative licensing options to fit the needs of bioentrepreneurs and does not require sponsored-research agreements.
Dealing with the NIH is not for amateurs or the timid	Small companies can have consultations with NIH licensing staff at any point. This is especially useful for NIH's first-time partners who are generally not familiar with the licensing landscape. Similarly, the NIH SBIR program provides extensive customer support to grant applicants in the form of free workshops and access to program managers.
Companies cannot simultaneously obtain a license to an NIH invention and an SBIR grant	Although it is true that money received from an SBIR grant cannot be used to fund work done by NIH scientists during a CRADA project, it is perfectly acceptable to use SBIR money to further develop an invention previously licensed from NIH. In fact such use of multiple NIH resources may be an attractive way for small companies to invigorate their product pipelines.
Ethics rules now prohibit NIH scientists from working with biotechs	Translational research is one of the three pillars of the NIH Roadmap. To fulfill this commitment, the NIH needs active partnerships with industry. To achieve this, NIH scientists are encouraged to collaborate with industry scientists under official duty mechanisms.

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