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Leveraging Public Private Partnerships to Innovate Under Challenging Budget Times

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Abstract

The National Institutes of Health (NIH), academic medical centers and industry have a long and productive history in collaborating together. Decreasing R&D budgets both the private and public sector have made the need for such collaborations paramount [critical?] to reduce the risk of [further?] declines in the number of innovative drugs reaching the market to address pressing public health needs. Doing more with less has forced both industry and public sector research institutions (PSRIs) to leverage resources and expertise in order to de-risk projects. In addition, it provides an opportunity to envision and implement new approaches to accomplish these goals. We discuss several of these innovative collaborations and partnerships at the NIH that demonstrate how the NIH and industry are working together to strengthen the drug development pipeline.

Keywords

collaboration; de-risking; drug repurposing; drug rescue; public private partnerships; technology transfer; translational

Background

The National Institutes of Health (NIH), academic medical centers and industry have long and productive history in collaborating together. Support for these collaborations received a boost with the implementation of legislation in 1980, the Bayh Dole Act and the Stevenson Wydler Act, as amended by the Federal Technology Transfer Act of 1986,¹ by creating a stronger incentive for academic and government institutions to engage with industry in research collaborations and public private partnerships. With the advent of these new legislative authorities public sector research institutions (PSRIs)--academic medical centers and federal labs such at the NIH-- were able to own the intellectual property they created with federal funding and license it for commercialization according to terms they negotiated. PSRIs have shown that technology transfer and commercialization programs have been effective in building innovative partnerships and licensing inventions, many made with Federal support, to commercial partners. As a result, many new technologies have been

diligently and successfully introduced into the market to public benefit. A study conducted in 2011 showed that in the past 40 years, 153 new FDA approved drugs, vaccines, or new indications of existing drugs reached the market based on inventions made by PSRIs. Historically, PSRIs did not play a major role in applied phase of drug discovery, but with the legislative Acts of 1980 and the emergence of biotechnology tools, such as recombinant DNA and monoclonal antibodies, PSRIs were able to create and patent biologic drug candidates and small molecule drugs.ⁱⁱ While the New Drug Applications (NDA) filed with the FDA for these drugs between 1990 and 2007 represented only 9% of the total NDAs, they represented 19% of those receiving priority review--a designation given by FDA to those drugs likely to have a disproportionately important clinical effect. The number of drugs that reached the market as a result of significant collaborations with PSRIs is certainly much higher as this study only examined drugs for which PSRI inventions were licensed for use in the commercial product. A few examples that have reached the market based on collaborations with NIH but not government inventions include: FluMist® an influenza vaccine, Istodax® (romidepsin) a chemotherapeutic for chronic lymphocytic leukemia, Ketalar® (ketamine) for depression and bipolar disorder, and Xeljanz (tofacitinib) for rheumatoid arthritis.

Changing Landscape

In the past, R&D spending by industry grew predictably year to year, but that is no longer the case. In 2012, Burrill and Company reported that several drug companies sought to cut R&D expenses. Additionally, a survey by the National Venture Capital Association has found the nearly 40% of life sciences venture capital firms plan to invest less in the sector for the next several years.ⁱⁱⁱ A corollary can be seen at the NIH with its flat budget in recent [just a suggestion] years due to the Federal budget climate.^{iv} Even so, collaborations with the private sector and licenses to inventions made with government funding continue to shape the type and the manner in which drugs and vaccines are brought to the market by the private sector. In addition, diminishing R&D budgets in the private sector have inspired new paradigms for partnerships to strengthen the drug pipeline. Recognizing the important role federal labs play in providing the private sector with unique expertise, technology and facilities, President Obama issued a memorandum to federal agencies requiring greater efforts in “Accelerating Technology Transfer and Commercialization of Federal Research in Support of High- Growth Businesses”.^v In response, agencies submitted five-year plans for increasing the rate and number of effective collaborations with industry.^{vi} As a result of these external needs and expectations, the role of the traditional technology transfer or commercialization office within PSRIs is changing. Whereas its role had been to primarily out-license technology, the current expectation is for various parts of an organization to work more effectively together to develop collaborations that bring in much needed resources and expertise to further translate the institution's own research more efficiently and provide resources to the public and private sectors to advance their proprietary drugs into new cures and therapies.

With therapies currently only existing for ~200 of the ~4000 conditions with molecular causes^{vii}, the opportunities for collaboration at the NIH and other PSRIs are quite rich. NIH programs such as the National Center for Advancing Translational Sciences (NCATS)

Therapeutics for Rare and Neglected Diseases Program (TRND) and Bridging Interventional Development Gaps (BrIDGs),^{viii} as well as the National Institute of Neurological Disorders and Strokes' (NINDS) NeuroNext Program^{ix} provide drug development resources for investigators at both for-profit and non-profit institutions by de-risking their technologies. These programs focus on providing resources and expertise for a variety of human diseases. For example, the TRND Program offers an opportunity to partner with TRND researchers and gain access to rare and neglected disease drug development capabilities, expertise, and clinical/regulatory resources in a collaborative environment with the goal of moving promising therapeutics into human clinical trials. Each TRND collaboration is unique, since potential therapeutics and biologics come into the program at various stages of development. TRND makes sure that all partners understand that it is a collaborative program, rather than a grant funding program, because TRND employees are closely involved in the management of the project such that the possibility for new intellectual property and data generation is great. As such, TRND collaborators have access to jointly developed intellectual property and data through a Cooperative Research and Development Agreement (CRADA), which provides an option for an exclusive or non-exclusive license to inventions made under the scope of the CRADA.

Focusing on the translational research arena, we can look to NIH's recent establishment of the National Center for Advancing Translational Sciences (NCATS), whose unique 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 diseases and conditions."^x NCATS looks to complement translational research being conducted at other NIH Institutes as well as the public and private sectors. NCATS is developing innovative partnership and collaborations with panoplies of partners to further specific NCATS collaborations and provide resources to the scientific community. An example of the latter is an NCATS and Eli Lilly and Company partnership, established last March, that will generate a publicly available resource to profile the effects of thousands of approved and investigational medicines in a variety of sophisticated disease-relevant testing systems. Through the collaboration, NCATS will have its pharmaceutical collection of 3,800 approved and investigational medicines screened using Lilly's state-of-the-art Phenotypic Drug Discovery (PD2) panel. This panel features assays that are designed to reveal novel mechanisms or pathways of potential medicines and, as part of this collaboration, approved medicines as well. As such, the panel is expected to provide new insights for drug discovery.^{xi}

In the drug repurposing area, the NCATS program Discovering New Therapeutic Uses for Existing Molecules is a collaborative pilot designed to develop partnerships between pharmaceutical companies and the biomedical research community to advance therapeutic development. This innovative program matches researchers with a selection of molecular compounds from industry to test ideas for new therapeutic uses, with the ultimate goal of identifying promising new treatments for patients. NCATS is collaborating with eight pharma partners who have agreed to make 58 of these compounds available for the pilot program. The compounds have undergone significant research and development by the pharma partners, including the generation of clinical data, providing a strong starting point for scientists and permitting the process to move more rapidly. One of the unique aspects of

the program is the template agreements that were developed to streamline the legal negotiation and administrative implementation of these collaborations. Because of the quick turnaround time (11 weeks) to develop a research plan with the pharma partner and submit the grant to the NIH, a template collaboration agreement for each company to use with each of its partners was essential not to delay this important research^{xii}. NCATS will be studying whether the template agreements provided a framework for efficiently establishing partnerships in this area. The NCATS is planning to make awards for this program in June 2013.^{xiii}

Elements of a successful partnership

For each one of these partnerships, it was important for the partners to recognize that there is not a “one size fits all” approach to establishing collaborations. Each one is unique and requires a significant amount of discussion around three areas. For each one of the NCATS partnerships mentioned above, there was a significant amount of time spent answering these questions.

First, determine what “space” the parties will be working during the partnership

Will you be working primarily in the pre-competitive arena where all results are made widely available or are you more likely to be generating new intellectual property and proprietary data? Depending on the desired deliverables of the collaboration, it may not be necessary to focus on licensing issues when the end game of the collaboration is to develop a public resource for data. Second, determine what each party is bringing to the table. Is there a specific resource and/or expertise that the partners will need in order to move the collaboration along? Are the right partners involved in the collaboration or do others need to be included? During this discussion the partners should gain a clear understanding of the resources that each has to bring in the collaboration and how these resources and expertise will be used to achieve the desired outcomes of the partnership. Third, have a very candid discussion up-front about the potential “deal-breakers” for your organization. Are their institutional policies or laws that would preclude the parties from moving forward with the collaboration? For example, requiring a partner to indefinitely withhold publishing data and results could not be approved by institutions who are receiving NIH funding for the research. It is important to have these conversations early before time and effort have been expended in organizing the partnership. There is also much to be said for being transparent about the types of agreements you intend to use for collaborations. By example, the NIH has all its model collaboration and licensing agreements listed on a public website.^{xiv} Thus avoiding situations where potential partners are surprised by the terms and conditions found in agreements and providing assurance in advance that the terms are reasonable.

NIH has a large and effective patenting and licensing program to manage inventions made by NIH and FDA scientists, and most recently those made at the Centers for Disease Control and Prevention (CDC). In the last 20 years, 27 FDA approved products have reached the market under licenses of NIH inventions as well as hundreds of other products from NIH and FDA inventions, including diagnostics, over the counter products, research tools and laboratory equipment and reagents. While the Office of Technology Transfer (OTT) has direct responsibility for the management of patenting and licensing, it works closely with

Institutes and Centers (ICs) to ensure that the efforts of the various programs are working cooperatively toward the same goal, particularly when the IC programs take an active role in collaborations to advance the product development. For example, if an invention covers a spectrum of diseases but the IC program is particularly interested in advancing treatments for a particular indication through collaborations with industry or other internal programs, the patenting and licensing effort should support that goal.

NIH licenses patented inventions and unpatented biological materials. These licenses include internal use licenses as well as commercialization licenses. By law and policy, the preference is for non-exclusive licenses and US small businesses when the commercial goals can be achieved through those means. For technologies where significant effort and risk is required to bring the product to market, such as most FDA approved products, companies usually require the incentive of an exclusive license to make such investments. In order to ensure the greatest public good arises from our inventions, NIH tailors the scope of exclusive licenses to the needs and business plans of the licensee company. For example, if a patent on a monoclonal antibody to a cancer antigen has applications for many types of cancer, NIH works with the licensee to narrow the scope to the type of cancers and delivery modalities that the company plans to develop, leaving the remaining scope and indications for another company. In all of its licenses, NIH reserves the right to license the patent or material for internal research purposes both to industry, under a fee based license, and to non-profit institutions without an agreement unless a material is transferred under an MTA. Our invention management policies ensure that avenues for public and private research remain unobstructed even when exclusive commercial rights are given to a company to incent product development.

For biological materials, the vast majority of licenses are non-exclusive for internal research use or sale as research tools and reagents, such as mouse models, cell lines or rDNA constructs. There are however cases where a biological material has both a research and a therapeutic utility. If the material is not patented, it still can be licensed as a biological material under a commercialization license. A prime example is MedImmune's Synagis®, where the humanized monoclonal antibody is based on a mouse monoclonal antibody discovered at NIH.

As the NIH has made programmatic changes to better meet the changing environment for drug development that serves public health needs, so have we introduced new tools and strategies for transferring technologies to the private sector. These technology transfer initiatives involve both re-structured model agreements and better use of web tools. In 2011, the NIH OTT introduced an entirely web based licensing and payment system for non-exclusive licensing of non-patented biological materials for internal commercial research--the electronic Research Materials Catalog (eRMA)^{xv}. As a result, the time to process license agreements, notification to the scientists for availability and shipment, and payment by the licensee is reduced from many weeks down to as little as a few days. Also, in January of 2012 the NIH Intramural Research Program launched the Transfer Agreement Dashboard, or TAD, to streamline the transfer of NIH-developed research materials to the biomedical research community. The system reduces dramatically the transaction time for transferring NIH- developed materials. The TAD works in conjunction with Materials Transfer

Agreements, or MTAs.^{xvi} Both of these initiatives address the Presidential directive to better facilitate technology transfer and commercialization activities.

The growing role of start-up businesses, non-government organizations (NGOs), and product development partnerships (PDPs) in taking on the risk of biomedical product development provided the impetus to work with stakeholders to develop model license agreements for these purposes rather than one-off agreements for each license. The model agreements also give upfront notice to such organizations of the reasonable terms that will be offered and thereby stimulate greater interest and the transfer of more technologies for commercialization. The Start-up License^{xvii} takes into consideration the small businesses' need to conserve their limited funds for product development and the need to acquire the license quickly to attract further investment. Licensees can obtain a one-year option license for \$2,000, which they can convert to a long-term commercialization license with the submission of a commercialization plan. The significant license fees are associated with down-stream infusions of cash or stock offerings; however, NIH does not take equity in companies. This initiative has attracted more than 30 companies applying for licenses in the last year.

The NIH invention portfolio includes a strong representation of technologies to detect, treat or prevent rare and neglected diseases. As a result, OTT has licensed a number of patented inventions and unique biological materials to institutions around the world to bring these important interventions to market. NGOs and PDPs, for example PATH and Infectious Disease Research Institute (IDRI), with support from Foundations such as Gates and international bodies such as the World Health Organization have worked with us to bring new biomedical products to lower income countries. One great success was PATH's introduction of an efficacious new meningitis A vaccine (MenAfriVac)^{xviii} to sub-Saharan Africa. FDA scientists invented a protein conjugation technology; OTT licensed it to PATH, which in collaboration with the World Health Organization (WHO) contracted with Serum Institute of India to make the vaccine for delivery to Africans at risk. These experiences and discussions with NGOs and PDPs led OTT to develop a model Non-Profit License Agreement^{xix} for neglected tropical diseases, TB, HIV and malaria. The license has a \$2,000 up-front fee and minimal royalties on sales, while excluding royalties for sales to public sector institutions.

Another initiative has been to bring entrepreneurial expertise into the daily operations of technology transfer activities of invention evaluation, patenting, and licensing. Under a Partnership Intermediary Agreement, BioHealth Innovation provides OTT and the NIH ICs with access to a serial biomedical entrepreneur whose expertise strengthens our commercial due diligence analyses such that our invention management decisions are more aligned with the in-licensing needs of biotechnology companies. As we implement the five-year plan for advancing technology transfer at NIH, both at the OTT and ICs' technology transfer programs, there will be new initiatives and changes in the way we work together within NIH to expedite the rate and volume of collaborations with industry, ultimately to the benefit of public health.

Decreasing R&D budgets in both the private and public sectors have made the need for collaborations between the two groups paramount and a necessity. Doing more with less has forced both industry and PSRIs to leverage resources and expertise in order to de-risk projects. Together, academic institutions, the NIH and industry are effectively partnering to fill the drug discovery pipeline. The collective realization is that innovative partnerships and collaborations are crucial to help find therapies and cures for patients. Luckily, we have seen that when there is a desire to work together towards the same ends, there are plenty of examples of these creative public private partnerships.

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