Strengthening the Pipeline for Innovation in Cancer Research: The National Cancer Institute's Program for Innovative Molecular Analysis Technologies

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*The viewpoints expressed here are not necessarily those of the National Cancer Institute or the US Government, nor do they reflect any actions that will be taken on the part of either. These viewpoints are the sole opinions and findings of the primary author as an AAAS Science and Technology Policy Fellow at the NCI, to whom inquiries can be addressed, mdl128@yahoo.com

***Abstract* - The declining value of the dollar and the evolving shape of the economy are affecting the value and availability of the funds that support the development and commercialization of novel cancer technologies. This conservatism goes against the forward advance of translational science, which is beginning to show its greatest promise for the pursuit of innovation and the dissemination of emerging technologies. Cancer technology development is nearing a tipping point in which these countering trends may result in a decline of the United States' ability to encourage and foster innovation. The National Cancer Institute's Innovative Molecular Analysis Technologies (IMAT) program is attempting to address this rapidly changing environment to ensure that innovation is not stifled. Discussed is an overview of the IMAT program, identified bottlenecks for innovation, and a proposed strategy for engaging new partners to strengthen the pipeline for innovative cancer technologies.**

I. INTRODUCTION

The recent decade has witnessed a transformation in the practice and study of medicine, catalyzed by an increase in the methods and tools available to a clinician for determining a patient's health and treating disease. Enabled by the development and use of various "-omics" based technologies (genomics, proteomics, metabolomics, etc.), a more personalized medicine promises to provide the clinician with the ability to make better informed decisions through information generated by the molecular analysis of a patient's specimen. The resulting readout provides a specific description about a patient's nature of disease and could be used to guide the prescription and dosage of therapeutics, allowing for immediate optimization of treatment aided by real-time measurements of therapeutic efficacy. This information could also be used to design more specific pharmaceuticals that minimize adverse side-effects while maximizing therapeutic response.

The integration of innovative technologies into the biomedical research and clinical communities is a product of the efforts being made in the physical sciences to push the limits of detection in their own disciplines, which are then translated into novel tools capable of directly observing molecular interactions in the human body. This focus on team-based translational medicine has advanced our understanding of the basic elemental processes occurring in the body as they relate to health and disease, and is part of a cycle that continually challenges innovators to incorporate newfound knowledge into applications that benefit the health of our society.

In 1998, the National Cancer Institute (NCI) created the program for Innovative Molecular Analysis Technologies (IMAT, http://innovation.cancer.gov) as an investment in the potential of innovation to revolutionize its mission for reducing the burden associated with cancer. The mission of the program is to support out-of-the-box approaches towards technology development that at the time of inception are considered innovative and high risk, but if successful would have high-payoffs in advancing research and medicine. IMAT is the primary trans-divisional technology development program offered by the NCI, allowing individual innovators to access the resources at the NCI and better direct the application of their technologies in the areas of basic cancer biology, cancer prevention, cancer therapy and detection, or cancer control and epidemiological sciences.

IMAT supports the inception and development of both innovative and emerging technologies. The former describes those that are built from the ground up, in which there exists no current comparison, and the latter are those technologies whose development has not reached demonstrated feasibility in its intended use, including those created by redirecting a currently existing technology for a novel application. As shown in Figure 1, IMAT's philosophy for supporting innovation divides the development of technologies into two broadly defined and sequential stages. The first step is the demonstration of feasibility through strategic pilot studies and IMAT utilizes an NIH R21 funding mechanism for this exploratory stage of technical development. Applications submitted to this funding opportunity are not required to have preliminary data and

external reviewers base their judgment on the technical soundness of the applications as well as potential impact and current need. The second stage of development is supported through an NIH R33 funding mechanism for the maturation of an innovative technology through scale-up and validation.

Since its establishment, IMAT has supported the development of many technologies that are currently ubiquitous in clinical research and practice. One example is the Affymetrix chip, a technology that can quantitatively measure the expression levels of specific genes. At its inception, the concept of a gene chip was unheard of and possibly deemed unrealistic. Now, this technology is routinely used to understand the genetic effects of biochemical perturbations, providing the knowledge needed to understand the mechanism of disease formation and progression, and thus accelerating the discovery of gene-based drug and diagnostic targets. IMAT has also supported the inception and development of a life-sciences technology created by a team of physicists. Raindance Technologies' platform combines microfluidics with water-in-oil separation and one application has recently entered the commercial market (March 2009). The RDT-1000 has pushed the limits of polymerase chain reaction's (PCR) ability to duplicate targeted copies of DNA by increasing its speed and precision. The potential for this technology goes beyond improving PCR and Raindance Technologies continues to expand this platform to address other unmet needs.

Even with these success stories, the majority of IMAT grantees face several bottlenecks that complicate the dissemination of their technologies. The NCI has a responsibility to ensure that the investment in the research and development of these technologies are not wasted by ensuring their dissemination. To limit the scope of the discussion, this manuscript is focused on issues related to pre-tech transfer innovation, or the inception stage of technology development. The "tech-transfer" milestone, as defined in this manuscript, is considered the stage of development in which proof-of-principle and/or feasibility of a given application has been demonstrated and thus should be eligible for intellectual property protection. The bottlenecks at the tech-transfer and post-tech transfer stages of technology development are also complex, but have already been widely discussed in other forums.

Presented in this paper are the findings made from assessing the needs of some of the IMAT grantees and a proposed solution to those needs. It is hoped that the subsequent roundtable discussion at the Atlanta Conference on Science and Innovation Policy will result in insight to help ensure that IMAT continues to be a resource for innovation in cancer research and medicine.

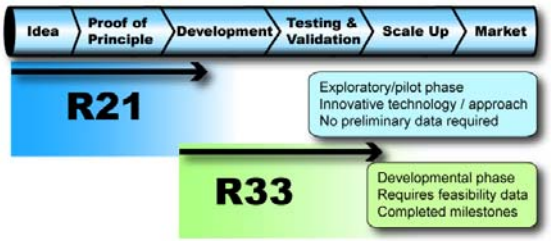

Fig. 1. IMAT's mechanisms to support the pipeline for innovation

II. BOTTLENECKS FOR DEVELOPING INNOVATIVE TECHNOLOGIES

A. Forming the scientific team

Many scientist-innovators lack the comprehensive training and expertise to advance their technologies to the commercial market, while at the same time, many business development experts lack the rigorous training in the sciences to recognize promising avenues for scientific discoveries. There are several bottlenecks for translational science that can be envisioned by presenting a scenario typical of many innovators. In this scenario, an initial scientific breakthrough is made in a life-science laboratory associated with a traditional "research one" university. While many basic discoveries are also made in an industrial R&D setting, the majority of the discoveries reported in the literature typically derive from academic efforts. The strength of most commercial efforts, instead, is more weighted on the application of knowledge, rather than its discovery. In the laboratory described in this scenario, scientists used traditional molecular biology tools to discover and validate that the presence of proteins X and Y are undoubtedly correlated with a particular disease. Although the data supporting the discovery and correlation of these biomarkers are solid in this scenario, the academic environment is one that traditionally encourages the pursuit of additional studies aimed at elucidating the exact mechanisms and pathways responsible for this correlation, for the goal of many academic scientists is to expand the knowledge base through publication of their research results. The pursuit of a patent is sometimes considered as a by-product of their efforts, rather than an emphasis. This environment could lead to additional years and possibly decades of research before an application is synthesized, assuming that no other tangents are made by the additional discoveries along the way. This is the first bottleneck; recognition by scientists that they have a discovery that could be translated to a broader-use application in the laboratory or clinic. In this instance, the technology could be either a diagnostic device or a therapeutic target for the disease that proteins X or Y indicate. This bottleneck is further constrained by the dearth of business development experts who have the time and/or training to monitor the

scientific literature for findings that could lead to an application with commercial potential.

Continuing with this scenario, passing through this first bottleneck requires recognition of the potential application for the discovery, whereupon the second bottleneck is the identification of collaborators and convincing them of the potential promise of an innovative technology. Most scientists have extensive expertise in their field of study, but due to the traditional discipline-based silos of academic departments and minimal cross-disciplinary overlap, many lack the training and insight to effectively utilize another discipline's approach and tools. This is where the "translation" of science is important and the first step for the scientist is to define the type of collaboration that is needed to effectively pursue the development of an application. In this instance, a collaborator could be an engineer to design and fabricate the device, or a chemist to synthesize and characterize the drug. Other collaborators on the scientific end of this project include biostatisticians to design the experiments and interpret the data, and clinicians to help narrow and define its medical impact.

Paralleling this scenario is another one from the viewpoint of an academic scientist who has the expertise and tools to develop a technology. These scientists are traditionally trained in more physical-science oriented disciplines such as chemistry, physics, materials sciences and engineering. In pursuit of their respective department's academic aims, they continue to expand the knowledge base and capabilities by synthesizing, characterizing, and fabricating technologies that push the limits of size, speed, and function. While the science that they discover might revolutionize their own field of study, many of these technologies fail to find a direct application and their utility remains isolated within their discipline. This is the bottleneck faced by this type of innovator; the inability to find a direct application of their technologies, or a lack of direction about how to tune their technologies for broader impact. As with the scenario previously presented, this scientist also needs to seek collaborators representing potential users of a technology, giving the innovator access to the expertise and evaluation needed to ensure its application in a real-world setting.

It is then up to either the first scientist to translate the importance and impact of their biomarker discovery to the other scientists, or for the second scientist to translate the capability of their technology, in a grassroots effort to convince potential collaborators for a commitment of time and resources. This is no small feat in consideration of other complications outside of the scope of this manuscript, which include reduced overall funding, the need for additional grant applications to compensate for reduced funding in an increasingly competitive arena, the need to meet the requirements for academic tenure, and the need to continue publishing in one's area of expertise.

The Government, as a principal source of research funding, continues to shape science by establishing funding mechanisms to catalyze multi-disciplinary research. In addition to IMAT, the NIH has other funding mechanisms aimed at supporting team-science approaches toward biomedical problems, including initiatives for "Bioengineering Research Partnerships" and the "Alliance for Nanotechnology in Cancer", as well as partnerships with other agencies such as the National Science Foundation.

Some universities have also taken their own initiative to address these bottlenecks by eliminating the silos inherent with academic departments. For example, UCSF's new research campus in Mission Bay, San Francisco, is interdisciplinary in design, with the overall appearance of a unified unit without any segregation in space or focus on a particular discipline. There is minimal isolation of laboratories into discrete spaces as the physical layout of the buildings lack walls between different investigators, and their groups also share common areas such as lounges, dining areas and conference rooms. In addition, the principle investigators/faculty also share common office space – all with the goal of maximizing the potential for collaboration by putting the researchers and faculty in close proximity.

But an intimate physical space may not enough to accelerate an idea past the first bottleneck – identification of an application from a basic discovery. Some recent state-, regional- and university-level initiatives have emerged to address this hurdle, recognizing that innovation is an important economic driver and metric for reputation. The state of California established four institutes of innovation through its University of California system that are focused on different themes: the biomedical sciences, information technology, nanosystems, and telecommunications. The first theme is addressed by the California Institute for Quantitative Biosciences (QB3), a cooperative effort involving the basic physical and life-science strengths of UC Berkeley and UC Santa Cruz with the biomedical emphasis of UC San Francisco. In addition to establishing trans-university laboratories on each of the campuses, it also employs "knowledge brokers" to help accelerate investigator-level innovation. These "knowledge-brokers" are scientists who have an understanding of business development and market forces, or are venture capitalists who appreciate the potential for early-stage scientific discoveries. They are tasked with pro-actively engaging the faculty through discussions of their research, with the hope of identifying potential applications. If a potential technology is identified from these conversations, QB3 has a second level of venture capital and clinical mentors dedicated to helping the faculty member create a business plan outlining the development and dissemination of an innovative technology. As with the MIT's Deshpande Center, which has a similar mission and mechanism as QB3, these knowledge brokers are considered to work in the realm of "pre-tech transfer".

Post-tech transfer knowledge brokers are also used to "incubate" and accelerate a technology to market. Many of these are knowledge brokers are part of "innovation centers" that are established to promote regional economic development and job creation; examples include St. Louis' Center for Emerging Technologies, the Austin Technology Incubator, and the Virginia Bio-technology Research Park. These mentors work to ensure that there are physical resources available such as laboratory space and reagents, help develop their business plans, and introduce innovators to regional venture funding and potential collaborators. This category of knowledge brokers typically work with innovators that have technologies at post-inception stages and have demonstrated feasibility, but need additional resources for further validation to attract licensing or partnerships. For example, many of their clients have established the requirements for a small business with enough justification to obtain a Small Business Innovation Research (SBIR) award from a federal Government agency. These are considered as post-tech transfer because their technology is developed past the pilot stage in which market potential has already been assessed as part of the SBIR application, and intellectual property rights most likely have been secured.

B. Supporting the development of a novel application

Successful passage of the bottlenecks described above requires the establishment of a team that contains basic scientific expertise in the problem (the lack of a marker of a disease) and proposed solution (use of proteins X and Y to indicate the disease), and expertise in the physical development of the solution (diagnostic test or drug). The next hurdle occurs before the project pursues its first milestone, as the team immediately faces the need for financial support and resources to pursue the project. The type of project described in this scenario exemplifies many innovative and interdisciplinary ideas in that they lie in an undefined overlap of traditional disciplines, but do not reside with the boundaries of any single one. Thus, these projects rarely have pre-allocated resources because many are unanticipated. Unfortunately, this bottleneck is relatively narrow because many large capital financiers, such as venture capital, would deem this stage of development as that of the highest risk; the project may show high scientific promise but there is the lack of data demonstrating its actual application and market potential. In addition, the majority of scientists do not have the knowledge and experience to "market" their idea to attract these sources of private financing. Some universities have addressed this problem by introducing elective courses as part of their basic science graduate school curriculum. For example, MIT offers a course called "i-Teams" and UCSF similarly offers a course called "Idea to IPO" in which its graduate students, fellows, and faculty learn from venture capital and business development experts about commercialization strategies, the focus of both are on a mentored project where student-teams develop either imaginary or early-stage life-science companies. The Kauffman Foundation, a private organization focused on advancing innovation in the US, also directly supports the education of early- and latter-stage scientists in business development strategies through their Entrepreneur Fellows and Entrepreneur Postdoctoral Fellows Programs.

This bottleneck to innovation can be minimized with a dedicated business mentor and a robust leadership plan to guide the scientific team. The leader should have the time and resources to coordinate the development and submission of a grant or business plan to the appropriate Government agency or financier. This includes designing the experimental and technical plan, as well as delegating the essential parts of the grant to the different team members. This leader also needs to work with a business mentor to communicate the potential of the technology to the venture capital community through a targeted roadshow effort, or if the goal is a federal grant, to work with the program directors at the agency to ensure that it is the appropriate funding mechanism, and follow its progress through the study section review. All of these efforts, from both the leader, business mentor, and team members, are done in the midst of little to no funding for this unanticipated project, limited funding and time available for existing projects, and an increasingly competitive grant and private finance environment.

Under a stronger economic climate, private financing had an "Idea-to-IPO" investment model. A venture capitalist following this model would invest in the early-stage inception of a business, support its growth, and withdraw their support and partake of the return on its investment when a company has attracted larger financing and has become self-sustainable (such as through an IPO). With the recent downturn of the global and domestic economies, venture funding for early-stage companies has all but dried up as these financiers are looking for investments with a lower risk. Many of these venture financiers have now moved upstream and only consider investing in relatively mature companies (post-Clinical Stage II trial), with a goal of withdrawing support once a partnership with a larger company has been secured. The end goal of recent venture financing no longer encourages waiting for an IPO and many have begun to focus their resources on already publicly-traded entities. The results from this conservative shift are evident, as the number of biotechnology-focused IPO's has witnessed a steady reduction annually since the early 2000's [1]. For those innovators who have successfully secured venture financing, many are denied requests for additional resources to conduct research aimed at expanding the utility of their platform by their financiers who have partial control over their company. In other words, even when a company has successfully disseminated their technology to the commercial market with support from a private funding source, their innovation is limited to its initial use as pilot research and development studies that could potentially expand their platform technology for other applications are considered too risky.

This puts a heavy burden on the Government to seed and continue to support innovation, as the Government has the capability to absorb the high-level risks associated with these types of early-stage efforts. This brings up a common theme that will be addressed throughout the roundtable discussion at the Atlanta Conference on Science and Innovation Policy: Is the grant mechanism to directly support innovation at the investigator level the best use of taxpayer resources? Are there alternative mechanisms available through partnerships that maximize taxpayer dollars by combining and leveraging resources?

III. CAN IMAT FURTHER SUPPORT INNOVATION BEYOND A STANDING GRANT MECHANISM?

The goal of this manuscript and the ensuing discussions at the Atlanta Conference on Innovation and Science Policy is to propose and evaluate different strategies that could be leveraged by a program such as IMAT to reduce the non-fiscal bottlenecks inhibiting the development of innovative technologies.

The three bottlenecks for the pre-tech transfer development of innovative cancer technologies - identified and summarized through conversations with IMAT grantees, private financiers, and business development experts - are the following:

- Recognition that an initial discovery can be used to develop a technology –or- recognition that a technology can be developed for broader applicability
- Formation of a team of collaborators
- Dedicated mentors and leaders to help an innovator advance an idea

Proposed below is an idea aimed at using federal Government resources to address the described bottlenecks, for consideration in IMAT's strategic plan. It is believed that the US Government is uniquely positioned as the only entity with the resources capable of establishing a national knowledge broker network. This network has the potential to advance the global standing of the US in innovative technology development by leveraging and harmonizing existing resources, with the end goal of increasing the numbers of solutions to the problems, such as cancer, that continue to plague society.

A virtual forum for collaboration and mentorship

IMAT is an investigator-initiated program that supports innovators regardless of institutional affiliation. Many of its grantees are not associated with the larger universities described previously in this manuscript, such as QB3 or MIT, and thus do not have access to the resources available to innovators at these larger centers. Nor can it be expected that the smaller institutions create these types of resources for its investigator community.

As shown with the limited case studies at MIT, QB3 and other pre-tech transfer innovation centers, the "knowledge broker" approach appears to be effective addressing some of the pre-tech transfer hurdles by fishing out potential technologies and guiding their development to the commercial market. These centers are vital catalysts for the innovative atmosphere of their respective institutions and the federal Government is at a unique position where it has the resources to establish a similar nation-wide knowledge broker network. Such a network would strengthen the beginning and continuation of the pipeline for innovative cancer technologies, ensuring their dissemination and broader use at the end through directed mentorship and access to resources.

The purpose of a national knowledge broker network would be to establish and follow harmonized protocols for identifying potential applications at its inception and by providing the infrastructure to bring them to market. This network addresses the first two bottlenecks described earlier by acting as middlemen between the "needs" community and those that can develop the technologies to address those needs. For equal access to all innovators, it is envisioned that the network would be regionally dispersed with physical centers of innovation that are connected to each other virtually. One level of access to the network would be restricted to confidential communications between a knowledge broker and an innovator. The second level of access would be inter-innovator communication through a technology showcase to encourage collaboration and possible multiplexing/combination of technologies. The third level of access would for the public, detailing the executive summaries of the individual projects to potential financiers.

The development of this knowledge broker network could occur in two stages, which should allow for stepwise evaluation of its effectiveness and feasibility. The initial pilot study would address the third roadblock by focusing on the commercialization aspects of a post-inception technology, involving the latter-stage IMAT grantees (R33 awardees) as the innovators. These innovators already benefit from the fact that an external panel of experts, as part of the grant application process, has vetted their technologies so the supporting science should be sound. The knowledge brokers would come from pre-existing innovation centers and their involvement would be supported financially, in addition to regular workshops that address harmonization of the methods used to mentor their innovators. Again, their focus in this pilot study is not on translating a discovery to an application, but the direct mentorship of the innovators through the stages of pre-commercialization. Combined with the knowledge brokers, this group of innovators is expected to be attractive to

larger sources of financing because they have a combination of appropriate business mentorship and the scientific vetting of a government grants program.

The second stage for the development of this national network is more work-intensive that the initial pilot study and the focus would be the translation of a discovery or undirected technology to an application. This would involve partnerships with groups such as the Biomarkers Consortium, who are addressing a scientific issue but lack the technology to accomplish some of their aims. It is envisioned that through such partnerships, such groups could utilize the knowledge broker network to provide "technology wish lists", communicating the specific needs for technologies to the innovator community. Additionally, this network could also be a forum for those scientists who have made a breakthrough discovery but are searching for collaborators who can help build a technology.

The need for innovative technologies is not limited to cancer research, nor is it isolated to the US. Recognizing that innovators and needs communities may exist outside of our national boundaries, it is envisioned that international partners can also link into the knowledge broker network to leverage the resources of other science and technology initiatives such as the European Commission's Framework Program.

IV. CONCLUSION

The advancement of an innovative idea to the dissemination of an application has always been a difficult trek for most academic scientists. This has been made more difficult in light of the increasingly risk-adverse atmosphere for financing innovation. Unlike other government programs which purchase the technologies that were developed through their funding mechanism, the goal of the IMAT program is to disseminate the technologies to the broader laboratory and clinical communities. Proposed here is a virtual infrastructure that can help reduce the hurdles for advancing innovation. The proposed network has a mechanism for identifying potentially high-payoff technologies, providing application development expertise to innovative scientists, and showcasing of the developed technologies to the public.

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