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TRANSLATIONAL RESEARCH IN ACADEMIA – MOVING TOWARDS THE D SIDE OF R&D

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INTRODUCTION: AN INTEGRATED APPROACH TO BASIC AND TRANSLATIONAL RESEARCH

Historically, academic scientists have sought to understand fundamental biological processes, without considering whether or not their discoveries may be inventive or have therapeutic value. The freedom to pursue intellectual interests has led to numerous discoveries such as the structure of DNA, reverse transcriptase, the intron structure of genes, RNA interference, and Clustered Regularly Interspaced Short Palindromic Repeat (CRISPR) that have transformed the way we understand the world around us. By contrast, translating and commercializing academic discoveries has been left to biotechnology and pharmaceutical companies.

In the past two decades, technological and bioinformatic advances have transformed scientists' ability to study complex

biological processes, often in complex tissues or patient samples. At the same time, granting agencies and companies have invested in the use of these technological and bioinformatic tools to facilitate drug development. During this time, federal research funds have remained relatively constant while the number of grant applications has increased. As a result, it has become more difficult to obtain funding for traditional basic research. The challenges and opportunities for academics and their home institutions have never been greater.

I am a scientist at the Dana-Farber Cancer Institute (DFCI) and my laboratory has historically focused on basic research. In response to recent challenges, I have reorganized my laboratory to incorporate translational research and commercialization perspectives. This re-organization has accelerated – not limited – basic scientific discovery and has enabled new and alternative sources of funding to support my research programs. I also find this way of working personally rewarding. I became a physician and scientist to help people. This new approach has allowed me to more closely connect with the clinicians treating the patients who may be helped by my work.

This chapter is written in three parts:

- Part One describes how incorporating translational perspectives presents opportunities for basic research programs.
- Part Two describes steps for integrating translational and commercial thinking into basic research.
- Part Three suggests how institutions can support scientists in this endeavor for mutual benefit.

There are many ways to define translational research (see Text Box 1). This chapter focuses on the translation of technologies and mechanistic insights discovered in academia by beginning technology and drug development within academic walls.

Text Box 1 The spectrum of translational research activities

At one end of the spectrum, mouse modeling of a human disease can be considered translational research. While frequently an important component of an Investigational New Drug (IND) application to the Food and Drug Administration (FDA), mouse modeling is far removed from clinical adoption and is not a consistent predictor of drug responses in humans. At the other end of the spectrum, translational research is testing whether a drug approved for one indication can work for another indication or testing whether a combination of two different drugs for an indication works better than either drug alone. Studies that attempt to expand labels or repurpose drugs are clearly close to human use and can be an excellent predictor of drug responses in humans. However, these studies may not provide mechanistic insights into drug function and may not be a major source for new discoveries that can become future drugs. Translational research can also be defined as anything in between these extremes.

This chapter is written to help individuals in the biotechnology and pharmaceutical industries better understand the academic's perspective which may facilitate partnerships that improve the likelihood that laboratory discoveries are developed for human benefit.

However, this chapter is written primarily for academics: physicians, scientists, students and even their home institutions. For physicians and scientists, this chapter describes methods to actively participate in the translation of laboratory discoveries, become entrepreneurs themselves, or simply better position their academic research to increase their chances for funding. A recent study found a bias in academic textbooks against industry and commercially-focused research (Simon et al., 2018) and yet a majority of students end up in such jobs, outside academia. For students, I hope this chapter will illuminate ways to integrate basic and translational research and the benefits of performing due diligence on the topic of their graduate work. For academic institutions, this chapter describes how building supportive structures and creating incentives to foster translational research with an eye towards commercialization can benefit academic physicians and scientists, academic institutions, and ultimately the progress of medicine and science.

WHY PARTICIPATE IN TRANSLATIONAL RESEARCH?

Setting the stage: drugs and the practice of medicine

Biological products as drugs

Prior to the recombinant DNA revolution in the 1970s, "drugs" were almost exclusively small molecules. The pharmaceutical industry was best equipped to perform, and thereby establish, the traditional drug development process: first identify "druggable targets", then identify small molecules that can "drug" these targets, perform structure-activity relationship (SAR) analyses and subsequent lead optimization studies and, finally, formulate these compounds into pills for packaging and distribution through pharmacies. The scientists who participated in these processes were chemists, pharmacologists, and others who derived these new chemical entities (NCEs) and tested the biological activities of lead NCEs, optimizing their activity for both safety and efficacy. This well-established process of drug development resulted in a significant separation between the underlying basic research and the final deliverable pill.

Biological products, such as blood transfusion (1795) (Rivera et al., 2005), small pox vaccine (1796) (Ridel, 2005), and insulin (1921) (Rosenfeld, 2002), have been an essential part of medicine for hundreds of years. Since the FDA approval of recombinant insulin in 1982 (Junod, 2007), there has been an exponential increase in the development of "biologics" as drugs (Kinch and Griesenauer, 2018; Kinch, 2015). Examples include recombinant DNA, RNAs, and proteins (especially antibodies; see Text Box 2). In addition, there has been a parallel research area focused on the delivery of these biologically-based drugs. Understanding the mechanism of action, defining the use, and determining the optimal delivery of biologics is the expertise of basic research. For scientists, this means their work is not as many steps away from the drug that is administered to patients, as it was for traditional drugs. This makes translation an easier and more natural expansion of one's basic laboratory research and brings the scientist that much closer to realizing one possible outcome of his or her work: helping people.

Text Box 2 Biologics are becoming more prevalent in the practice of medicine

The past 30 years have seen a significant increase in the number of biologics applications to the FDA (Kinch and Griesenauer, 2018; Kinch, 2015). One of the most common forms of biologics are monoclonal antibodies. Antibodies that activate or inhibit biological processes can be drugs. Humira (Adalimumab, anti-TNFα), Keytruda (Pembrolizumab, anti-PD1), Herceptin (Trastuzumab, anti-Her2), Avastin (Bevacizumab, anti-VEGF), Rituxan (Rituximab, MabThera, anti-CD20), Opdivo (Nivolumab, anti-PD1), and Stelara (Ustekinumab, anti-IL12 and anti-IL23) are all antibodies within the top 10 best selling drugs in 2018 (Urquhart, 2019). The success of antibody-based drugs demonstrates the promise of biologics as therapy. In addition, it may be easier and quicker to identify and develop antibodies or other biologics against a novel target compared to finding and developing a small molecule against the same target.

Precision, personalized, and living medicines

Recent years have seen an increase in the practices of precision medicines (analyzing genomic data, stratifying patients into cohorts, and rationally administering impersonal medicines to selected cohorts of patients), personalized medicines (designing medicines specific to individuals, e.g. neoantigen vaccines), and "living medicines" (administering living organisms or patients' cells with or without molecular engineering into patients, e.g., fecal transplants, engineered bacteria, allogeneic or autologous cells for therapy). All of these practices involve working with human biological material, sometimes harvested from patients themselves. Personalized and living medicines are frequently administered by physicians and the development of these treatments can be improved by close collaboration between physicians and academic researchers. Engineered living medicines are often generated by applying biological tools and altering endogenous pathways in bacteria and patient cells. In many cases, the steps of engineering living medicines are within the basic scientist's expertise.

Biologics, precision and personalized medicines, and now living medicines, are revolutionizing the present and future practice of medicine; basic scientists working in academic

institutions can participate in biotechnology and drug development in ways that were not possible 20 years ago (see Text Boxes 3 and 4). Academic institutions and their affiliated hospitals are ideally suited to identify, develop, and translate these discoveries for therapy. Armed with these tools and with access to advanced technologies available at major medical institutions, many more scientists are well positioned to participate in translational research and drug discovery. To leverage these intrinsic advantages, it is important to understand the key factors that are essential for commercializing a technology or drug candidate.

Text Box 3 FDA may need to create a new model to evaluate personalized and living medicines

Personalized and living medicines may force the FDA to create new paradigms for evaluating drug candidates (Hamburg, 2013). Personalized medicines may use a consistent pipeline, however, the composition of each "drug" will be unique and may have distinct toxicity profiles. Both personalized and living medicines require access to patient samples and clinicians who administer the drugs; this is especially true for engineered patient-specific microbiomes and autologous immune cells.

Text Box 4 Personalized and living medicines will require new business models

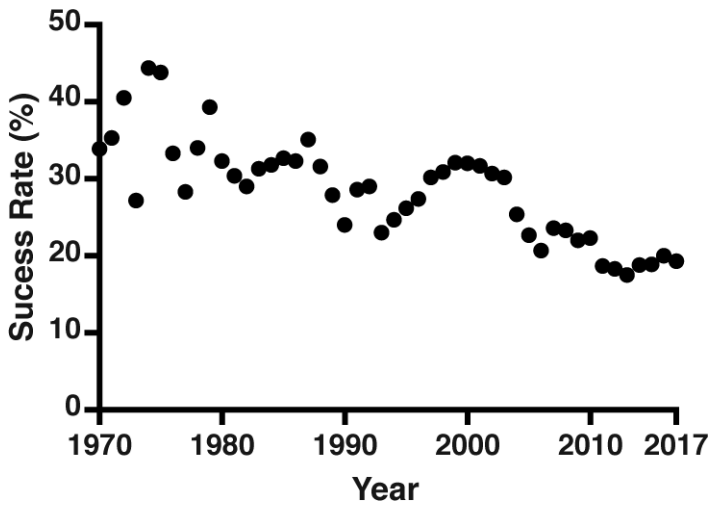
Personalized and living medicines do not easily fit into the traditional drug development business model. Instead, the generation of successful personalized and living medicines requires new business models in which (1) the production of a drug might start with patient biopsy or sample acquisition and proceed to tissue or cell isolation in the hospital; then (2) harvested tissues or cells might need to be shipped to a Good Manufacturing Practice (GMP) facility which manufactures peptide vaccines or engineers receptors or other payloads into autologous cells; then (3) patient-specific biologics or engineered cells might need to be shipped back to the hospital for the physician to re-administer personalized or living medicines to the patient. It is precisely because this development process is different than traditional drug development, that issues such as defining the regulatory path, standardizing methods for engineering, guaranteeing chain of custody of the medicines, and billing for this procedure are not standardized and are still being negotiated. As a result, new business models are evolving.

Setting the stage: funding for basic versus translational research

The National Institutes of Health (NIH)

Over the past two decades, it has grown increasingly difficult for academics to obtain federal funding to support their research. The NIH is a major source of biomedical research funding in the US with an annual budget of ~$34B (NIH, 2013; 2018). During this time, the number of R01 and other grant applications has increased (Research Project and R01-Equivalent Grants, 2018). Thus, the success rate or "payline" has decreased from approximately 30% in the early 2000s to approximately 20% in 2017 (Figure 1) (Research Project and R01-Equivalent Grants, 2018).

Figure 1 The success rate of R01-equivalent grants is decreasing



The sucess rates of R01-equivalent grants were determined using data produced by the statistical analysis and reporting branch using the NIH success rate definition (Research Project and R01-Equivalent Grants: Competing Applications,Awards and Success Rates, 1970 to present (Table #218)). R0l-equivalent awards include DP2, R01, R23, R29, R37, and RF1 activity codes. The DP2 activity code was added in FY 2017. Not all of these activities may be in use by NIH every year. A similar trend was also observed for NIH research project grants.

To obtain NIH funding, it has become more important for applicants to show a connection between their work and human health. Research that might impact our understanding of a disease or result in improved detection or treatment of a disease increases the chances of obtaining a fundable score (see Text Box 5). It has always been a challenge to win a grant to fund basic research that has no discernable health application. In recent years, it has gotten even harder as taxpayers – who support the NIH – increasingly demand drugs that prevent or cure diseases and place ever more pressure on NIH to fund translationally-oriented research.

Text Box 5 Positioning basic research in a translational context improves the likelihood of R01 funding

The institutes within NIH are generally organized by organ systems, disease areas, or medical disciplines. Grants submitted to the NIH are reviewed by study sections within these institutes and are often organized by disease interests, pathology mechanisms, tool development, and other translational issues. There are relatively few study sections dedicated to truly basic and mechanism-driven research. NIH grants are reviewed by five criteria (Significance, Innovation, Approach, Investigator, Environment) each scored independently on a scale of 1 to 9. The overall score for an NIH grant is a combination of scores for each of these categories; the lower the score (the better), the more likely the grant will be funded. The guidelines for evaluating the "Significance" of an R01 is described below *https://grants.nih.gov/grants/peer/guidelines_general/impact_significance.pdf*

"Does the project address an important problem or critical barrier to progress in the field? Is there a strong scientific premise for the project? If the aims of the project are achieved, how will scientific knowledge, technical ability, and/or clinical practice be improved? How will successful completion of the aims change the concepts, methods, technologies, treatments, services, or preventative interventions that drive the field?"

Though it is contained in the description above, it has been my experience that most reviewers have re-interpreted "Significance" to mean the importance to human disease and the likelihood to have clinical impact (e.g., lead to insights into disease mechanisms, improve detection, or lead to a cure for a disease).

The NIH uses an "Impact Score" which is not necessarily an arithmetic mean of the five elements listed above. "Reviewers will provide an overall impact score to reflect their assessment of the likelihood for the project to exert a sustained, powerful influence on the research field(s) involved, in consideration of the following five core criteria, and additional review criteria (as applicable for the project proposed)."

One of the best methods to increase the likelihood that the project will exert a powerful influence on a field is to position your grant so that it is a step on the path to overcoming a critical barrier or developing a technology that addresses a key unmet medical need. Addressing an unmet medical need is one of the three pre-eminent considerations in the due diligence process that determines the likelihood of investment in a project, as described in Chapter 1.

Other sources of funding

In this seemingly bleak picture for many academic laboratories, there is good news. In my experience, a move towards translational research not only increases the chances of obtaining funding from the NIH but from other sources as well. Foundations are typically organized to support research that provides a critical insight into or improved therapy for a disease or condition. Historically, foundations have supported more forward-thinking, intellectually risk-taking research proposals. More recently, it has been my experience that peer-review at foundations have become closer to the style of peer-review at the NIH and thus fewer truly high-risk, high-reward proposals are funded; favoring instead proposals with a solid foundation of preliminary data and a clear path towards translation. Nonetheless, foundations remain a potential source for additional funding worth pursuing. Grateful donors are another source of funding for forward-thinking translational work. High net-worth individuals who were treated or cured may give money to their treating physician who, in turn, sometimes provides these funds to scientists who contributed to the area of medicine that helped the patient.

During the past two decades, there have been other trends in the pharmaceutical industry that also favor translational research in academic settings. As the cost to bring a drug to market increases, larger pharmaceutical companies continue to look towards academia for new ideas and drug candidates (Schuhmacher et al., 2016). To fill their drug discovery pipelines, large pharmaceutical companies have outsourced their research to smaller biotechnology

companies through partnerships and to academia through sponsored research agreements (Palmer and Chaguturu, 2017). Indeed, it is often cheaper to partner with or simply buy a smaller biotechnology company or to license technology from an academic institution than to invest in expanding their internal research programs into a new area of research.

This trend creates opportunities for academic physicians and scientists (see Text Box 6). Pharmaceutical companies continue to turn to academia for their research, which can lead to additional forms of support through a sponsored research agreement. However, sponsored research agreements can also provide challenges for academic scientists. Certain trainees may not be eligible to work under sponsored research agreements. Some agreements have restrictions over publication rights. Because publication is frequently a criterion for graduation, students may not be able to participate in research sponsored by a company. Additionally, sponsored research in an academic setting may limit an academic scientist from continuing this research at the end of the agreement. Moreover, sponsored research agreements may also prevent a scientist from getting access to his or her own intellectual property and becoming an entrepreneur for this technology.

Still, the pharmaceutical industry can be a strategic partner for academic institutions. An excellent example of this is the partnership is between Dr. Adrian Krainer (Cold Spring Harbor Laboratory (CSHL)) and Ionis Pharmaceuticals, which sponsored work on RNA splicing and led to a drug for spinal muscular atrophy called Nusinersen (Hua et al., 2007; Rigo et al., 2012). Pharmaceutical companies that embrace this vision will likely be ahead of the curve compared to companies that are unable to leverage partnerships with academic institutions.

Conducting translational research can also provide resources to continue basic research efforts when support for basic research is scant. The decision to embrace translational research does not mean that you will have to abandon or even deprioritize truly basic

Text Box 6 Translational research with commercial potential can support early stage work in your laboratory and could lead to new company formation

Translational research with commercial potential can also qualify your research program for support by additional sources of federal and non-federal funding. If you are interested in becoming an entrepreneur and starting a new company, one option may be to fund your company through non-dilutive mechanisms using support from the federal government through the Small Business Administration (SBA) (*https://www.sba.gov/*). The Small Business Technology Transfer (STTR) funding mechanism is designed to support collaborations between research institutions and small businesses by funding both entities under one grant, which facilitates the transition of a program from academia to the commercial entity (*https://www.sbir.gov/about/about-sttr*). Once a small business is started, the federal government has programs to support development of competitive technologies that have the potential for commercialization including the Small Business Innovation Research (SBIR; *https://www.sbir.gov/about/about-sbir*) and the Federal And State Technology (FAST; *https://www.sbir.gov/about-fast*) programs. The TIBBETTS award, named after Roland Tibbetts, recognizes individuals, projects, organizations, and firms that made a technological impact on the socioeconomic front (*https://www.sbir.gov/about-tibbetts-awards*). TIBBETTS awards are intended to stimulate and encourage diverse participation in technological innovation and increase commercialization of federal research.

A major benefit of all these mechanisms is that the federal government supports commercialization of research. While some of these granting mechanisms do not provide large sums of money, the peer-review process provides a robust vetting system for the technology being considered for commercialization. The value of these grants to early round investors are often a multiple of the actual dollar amount awarded. These grants support research and are non-dilutive to early investors. The commitment to supporting research through these mechanisms may take patience but with fortitude, there are opportunities for greater dollar amounts. For example, Phase I SBIR are usually $150K for less than one year but a Phase II SBIR may be up to $1M over two years (*https://www.sbir.gov/about/about-sttr*).

Additionally, companies can apply for Defense Advanced Research Projects Agency (DARPA) grants (*https://www.darpa.mil/work-with-us/opportunities*). These grants are meant to support research that can lead to "transformational change rather than incremental advances". These grants support "multidisciplinary approaches to advance knowledge through basic research and create innovative technologies that address current and predicted practical problems through applied research". These awards can be quite substantial and would go a long way towards translating and commercializing technologies for therapy. Obtaining one or more of these grants could demonstrate to early investors the commitment of the investigator to the research program and his or her willingness to grow the company organically minimize the number of rounds of dilutive funding.

research. Translational and basic research are often complementary. Financially, participating in translational research can provide additional opportunities and resources for basic research which, as described above, is becoming increasingly difficult to fund solely from traditional governmental sources.

HOW TO INTEGRATE BASIC AND TRANSLATIONAL RESEARCH

Step One: Align bottom-up and top-down thinking

Academic scientists are typically trained to think in a "bottom-up" manner, using the simplest and most efficient system to study a biological phenomenon or to demonstrate a proof-of-concept irrespective of how the concept might be developed or whom it might help if applied. In this approach, individual cells and organisms are engineered to mimic human diseases. In a broad sense, this can be defined as translational research; the earliest and most upstream step in translation. Demonstration of a principle in a model system might be an important first step on a critical path towards translation but, typically, these activities are not designed to address the requirements necessary for clinical adoption.

By contrast, industrial scientists often think in a "top-down" manner, starting at the end of the drug development process and working backwards from there. A first question might be, how would one treat a particular disease or condition or "how might a potential drug be used to address an unmet medical need?" More specifically, "what is the intended product label (see Chapter 1)?" Based on the intended product label, "how should a clinical trial for this drug be designed to support the *intended product label*?" followed by, "what preclinical data is needed to support that clinical trial?" and then "what is the best proof-of-concept experiment to demonstrate a principle that could be used as a basis for pre-clinical testing?". This ends-oriented approach to experimentation can help focus early efforts on the key experiments that would put a drug candidate on the critical path towards translation. In comparison to

small molecules, biologics used in research are generally closer to the ultimate drug product and thus are more amenable to "top-down" thinking for scientists.

"Bottom-up" research predominately addresses open-ended questions where outcome is informative regardless of the results. In contrast, "top-down" research is inherently designed to be dependent on outcomes that have translational potential. While this approach can be risky for the basic scientist, there is commercial and therapeutic value in understanding translational potential when "top-down" thinking is considered at an early stage. Until recently, I have found that many academic scientists have been reluctant to approach experimentation from a "top-down" perspective because it is essential to do research devoid of any application or profit motive, which are principal goals of commercialization. Indeed, one of the greatest strengths of academia is the ability to pursue purely intellectual interests, where freedom of thought is a necessary driver for discovery. However, while "bottom-up" research is essential for discovery, adding a "top-down" perspective may lead to more innovation and translation. Translational research is an additional step towards the goal of helping people. Commercialization helps assure that academics' discoveries reach the maximum number of people. I believe that scientists would be well served to integrate "top-down" and "bottom-up" perspectives.

Seek clinicians' perspectives to define unmet medical needs and refine research programs

Defining the unmet medical need is the essential first step in translational research because that is how an investigator knows what research is most needed and is most likely to be translated for therapy. Physicians, nurse practitioners, pharmacists or others closely tied to clinical practice best understand the current standard of care and can describe the unmet medical needs in one's area of investigation (see Text Box 7). Treating physicians are usually happy to talk with scientists who focus their attention on clinical problems and a dialogue with clinicians can transform a basic research

Text Box 7 My experience of working with clinicians

I am privileged to work at DFCI, which has numerous talented physicians who have deep knowledge in their areas of clinical expertise and a willingness to explore fundamental biological questions in collaboration with scientists. My laboratory has been developing autologous cell approaches, epigenetic editing technologies, and a long non-coding RNA platform technology. I work closely with clinicians who have expressed interest in helping me translate these technologies for immunotherapy for diffuse intrinsic pontine glioma with Drs. Mimi Bandopadhayay, Daphne Haas-Kogan, and Mark Kieran; gliobastoma multiforme with Dr. David Reardon; melanoma with Dr. Steven Hodi; multiple myeloma with Dr. Nikhil Munshi; and ovarian cancer with Dr. Ursula Matulonis. All technologies in my laboratory are being developed for these indications, which builds synergies into my research program. All members of my laboratory are thinking about common indications from different angles.

Regular discussions with these thought leaders have broadened the thinking in my laboratory to include consideration of specific patient populations, treatment strategies, and specific modifications of these technologies for these indications. Our clinical collaborators are committed to helping my laboratory develop technologies for these indications. In most cases, these clinicians are willing to write physician-initiated clinical trials to test these technologies in patients. Our clinical collaborators have described to me what types of preclinical data are needed to convince an internal review board that the potential benefit is worth the risk of trying a new technology in a small number of patients. Thus, we have begun to develop a translational research program (several projects) around a theme that integrates bottom-up and top-down approaches.

program. In my experience, the identification of an unmet medical need leads to increased reading in specific areas and the reading becomes a hunt for information that better defines the unmet need. This process has allowed me to better understand what has and has not worked and which patients would ideally benefit from a particular technology or drug candidate. Frequently these questions are very basic in nature and a research program thus begins examining basic processes in a clinically-relevant context. Moreover, I have found that clinicians are often knowledgeable about recent advances in molecular pathophysiology and can assist in identifying molecular and cellular targets that when "drugged" can address unmet medical needs and advance clinical care. Also, I propose that

scientists and physicians engage in an active and ongoing dialogue and not merely a one-off conversation. For example, this continuous dialogue has allowed me to define the intent-to-treat population earlier in the process of developing certain technologies. Clinicians are a great source of this ongoing information and their deep expertise can thus affect the experimental plan.

Another possible benefit to dialogue with physicians is access to patient samples. Not only can physicians provide scientists with patient samples to examine a biological process in a disease setting, they can also help inform which samples are most representative for analyzing performance drugs or technologies in a particular disease setting.

Seek perspectives from drug development experts; the case for an entrepreneur-in-residence

Perhaps the most important aspect in broadening my perspective has been talking with drug development experts. There are several key considerations beyond unmet medical need that determine whether a technology or drug candidate should be commercialized, which are not necessarily obvious to academic scientists. These considerations are highlighted in First Principles (Chapter 1) and directly influence how to position a technology so that drug developers would want to spend the time and capital to advance that technology for patient benefit. Therefore, increasing academic scientists' access to entrepreneurs, venture capitalists, and successful industry executives who have successfully developed and commercialized drugs is an important second step toward translating their discoveries.

However, merely increasing academics' access to drug development experts is not sufficient. Academics and drug developers often focus on different issues and often speak different languages, as noted in the "bottom-up" and "top-down" discussion above. Academics generally focus on funding their research programs through federal and foundation grants and publishing the results of their research in journals through the peer-review

process. Drug developers tend to begin with an unmet medical need then focus their attention on intellectual property (IP) considerations, intended product label and clinical trial design, manufacturing, reimbursement, and pricing strategies, and many other issues covered in this book. I have had to learn how to communicate more effectively with drug development experts. However, it is my perspective that there also needs to be a mutual commitment by academics and drug development experts in the private sector to learn each other's languages to support an integrated approach to basic and translational research.

Some academic institutions support an entrepreneur-in-residence, someone experienced in drug development who can help scientists and their home institution to understand key perspectives in the drug development and approval processes that determine whether or how to develop a technology at the institution, while it is being developed. While many considerations are common to drug development, it is likely that there will also be unique considerations for each drug candidate. In my experience, there is no substitute for having someone with drug development expertise think about the specifics of translating a technology being developed in my laboratory (see Text Box 8).

Text Box 8 My experience with an entrepreneur-in-residence

Dr. Fred Mermelstein is an Entrepreneur-In-Residence at DFCI, who successfully initiated and participated in the development, approval, and commercialization of two drugs, including Trisenox, now the frontline treatment for acute promyelocytic leukemia and Dyloject, an analgesic for the treatment of post-operative pain. Dr. Mermelstein has a keen ability to integrate scientific and clinical knowledge with IP, business development, clinical/regulatory pathways, strategic partnerships, reimbursement strategies to the early considerations of how to translate the technologies being developed in my laboratory. Many of these are key considerations for commercializing academic discoveries. Dr. Mermelstein introduced me to "top-down" thinking and he influences my research with his perspectives on how best to position the technologies being developed in my laboratory. He has also introduced me to other individuals with expertise across the drug development spectrum who have further influenced the direction of my research program with their insights.

Moreover, once a plan is in place, the entrepreneur-in-residence can bring significant resources to address critical issues. He or she can introduce academics to a wider range of people outside their institution who they might not otherwise meet, including industrial scientists, clinical and regulatory experts, formulation chemists, and other key individuals who can offer advice. One common theme in translational research is that no single individual has expertise in all the disciplines that lead to a new drug. More heads thinking about a problem typically leads to better solutions for the end-users.

Finally, academics have access to scientific talks often from local or visiting physicians and scientists with expertise in clinical and basic biology, technology, statistical and computational biology who can help define and model human disease. I have found it helpful to attend talks outside my areas of expertise. These talks have affected my decision whether to develop a technology.

Step Two: Plan your program

It is important to integrate the information collected above into a plan that drives research. Defining an unmet medical need and the likely intent-to-treat population that would benefit from the intended product can inform the design of proof-of-concept experiments. Incorporating clinical considerations in the design of these early experiments can (1) generate preclinical data that are required to support the planned trial, (2) refine patent claims (e.g., intent-to-treat population, dosing, formulation, and route of administration), and (3) build a robust IP portfolio that will be more attractive to potential licensees or acquirers of the technology (see Step Four below and Chapter 19).

In my experience, the next important consideration in planning a research program is its commercialization potential. Drug development is a capital-intensive process. The average cost of bringing an asset to the market is ~$2.168B (Deloitte, 2018). Returns for pharmaceutical companies have reduced from ~10% in 2010 to ~1.9% in 2018 (Deloitte, 2018). Consequently, performing a due

diligence process early during development is essential to determine whether a technology should be commercialized. The three critical elements of due diligence that affect early investment are unmet medical need, IP position, and reimbursement (introduced in Chapter 1). There are helpful resources for due diligence at many academic institutions although they can also be limited. For example, technology transfer offices can advise on IP issues (discussed in detail in Chapter 19), and hospital billing departments can assist with reimbursement considerations (discussed in detail in Chapter 20). However, the specific considerations of your technology may require a more thorough examination than these offices and departments can offer. Moreover, identifying the right questions to ask, meeting with the key people, and then integrating these considerations into a cogent plan that will focus laboratory research to support translation may be difficult and time-consuming.

Fortunately, academia is uniquely suited to collective learning. Many members of a typical academic community are interested in learning how technologies and drugs are developed and approved for therapy. I have found that many graduate, business, and medical students, postdoctoral fellows and physicians are willing to perform due diligence to determine which technologies should be translated and commercialized. This process evaluates the data iteratively in the context of unmet medical need, competitive landscape, IP exclusivity and freedom to operate analyses, market size, reimbursement, and available resources. Text Box 9 describes an example of a program at Harvard Medical School (HMS) demonstrating how due diligence for drug commercialization can be taught in an academic setting to the benefit of all who participate, including the scientist whose work is brought through the due diligence process. The SPARK program at Stanford is another example (*https://med.stanford.edu/sparkmed/about.html)*.

Step Three: Initiate and maintain your program

Once the information from due diligence is integrated into a plan to address an unmet medical need, resources will be needed to

Text Box 9 Mentoring trainees in the academic community to identify commercial opportunities can focus translational research efforts

In 2014, Dr. Mermelstein and I started mentoring the GSAS Harvard Biotechnology Club (HBC), a student run organization at HMS (*http://thebiotechclub.org/*). HBC's mission is to bridge the gap between industry and academia by providing education, skillsets, and networks for students to succeed in life science innovation and commercialization. Whereas HBC supports courses, lectures, panel discussions, networking events with people involved with commercializing technologies and drugs, Dr. Mermelstein and I worked with HBC student leaders to form the GSAS Harvard Biotechnology Incubator (HBI; *http://the biotechclub.org/hbi*), for experience-based learning.

HBI started organically. A Harvard Medical School Neuroscience graduate student and leader of HBC, Alex Simon, wanted more practical experience in conducting the types of analyses that determine whether a drug is commercialized. For the past five years, HBI has done due diligence exercises on the technologies being developed in my laboratory. HBI is an HMS student-led group but is composed of HMS physicians, postdoctoral fellows, and graduate students and has expanded to include graduate students from the Faculty of Arts and Sciences (the undergraduate campus) and Harvard Business School. The first semester of HBI is composed of a technology lecture and a due diligence overview lecture. Then HBI members split up into groups and perform due diligence on the technology under consideration. In the first semester, the group meets every other week to review due diligence and get feedback from the HBI mentors (Dr. Robert Distel (introduced below), Dr. Mermelstein, and myself). By the end of the first semester, each HBI group produces a target product profile sheet. In the second semester, HBI members break into different groups and produce the different sections of a business plan, generate a pitch deck, and present their work to KOLs, venture groups, or strategic partners. HBI leadership petitioned the Dean of HMS and this work is now a part of a Certificate in Life Sciences Entrepreneurship (for students who complete HBI and the Harvard Innovation and Commercialization (HIC) course at Harvard Medical School).

As a result of this work, HBI members have gained invaluable experience, something to put on their resumes, and also something to discuss during job interviews. Over the last three years, my laboratory has received due diligence evaluations for each of the three major programs being developed in my laboratory (epigenetic editing, autologous cell therapy, and long non-coding RNA (lncRNA) platform technologies). The result of these due diligence processes has resulted in better definitions of the commercial opportunities for these technologies and how these might best be developed for therapy. In many cases, these due diligence processes have led to new collaborations that affected the work being done in my laboratory.

support the new, translationally-oriented program. When resources are limited, "bottom-up" and "top-down" approaches to academic research can be at odds with each other. The resources to support translational research are not identical to the resources used by a laboratory historically focused on basic research. Though there are a few programs under the NIH's High-Risk, High-Reward Research Program (*https://commonfund.nih.gov/highrisk)*, which are specifically designed to help investigators shift research directions, only a few investigators receive these flexible grants. Additionally, integrating "bottom-up" and "top-down" approaches raises unique personnel, management, and financial considerations. As a result, many investigators may need to slowly incorporate "top-down" approaches into their research program.

Clinical collaborators

If addressing an unmet medical need requires skills outside of your expertise, then some creativity may be required to support this new trajectory in your laboratory. In my experience, establishing collaborations and co-authoring grants with clinicians has given my grants more credibility and more of my grants have been awarded. Though the award is split with the clinical collaborator, collaborations are more robust because both grantees are invested in the success of the project. If a research project is not conducive to support from the NIH, foundations dedicated to curing a disease are excellent alternative sources of funding. I have found that many foundations appreciate close collaboration between clinicians and scientists with complementary expertise in a disease area, which increases the likelihood of earning the foundation's support.

Another potential benefit of collaborating with expert clinicians is that they sometimes have high net-worth patients who become grateful donors to the treating clinician. Donor funds often include discretionary funds which the treating physician can allocate to support the generation of proof-of-concept data. These data can lead to peer-reviewed publications and can support federal grant

applications which require a significant body of direct evidence that the proposed experiments will yield results in the anticipated research area.

Clinicians have made critical contributions to the work of my laboratory. They have informed the translational potential of early stage experiments and have identified cell lines, animal models, or patient samples to use in preclinical experiments. They also have provided key insights into the genetic background or subtypes of patient populations most likely to benefit from a given technology. Moreover, a clinician's interest in translating a discovery may embolden scientists to pursue new lines of investigation. Conversely, if a clinician does not think a particular line of investigation is likely to help patients, it may be unwise to develop this technology for translation. Finally, clinicians can help drive regulatory approval by government-run agencies such as the FDA and can facilitate adoption of products into clinical practice. I have found that actively maintaining a dynamic collaboration with clinicians can improve the therapeutic relevance of a research program and increase its likelihood of funding, translation, and commercialization.

Characteristics of successful individuals in a translational research laboratory

Another important, though less apparent, aspect of translational research is who is hired to conduct the research. The specific skillsets to conduct the work will depend, in part, on the project but, generally speaking, will require a combination of traditional model-based, hypothesis-driven basic research skills using validated experimental models *in vitro* and *in vivo* and discovery-driven research using high-throughput screening, high-content imaging, and "omic" approaches on normal donor samples and patient biopsies. Hypothesis-driven research is needed to drill deep into a specific biological or technical problem. Discovery-driven research using human model systems is critical for identifying translationally-relevant problems and plausible actions that could benefit patients (see Text Box 10).

Text Box 10 Having many investigators with complementary skill sets is an important source of innovation

My laboratory has traditionally been populated by reductionists who excelled at hypothesis-driven research, especially in the areas of RNA and protein biochemistry. As my laboratory developed an integrated approach to basic and translational research, many more scientists with expertise in human genetics, virology, immunology, computational biology, and protein engineering have joined my laboratory. Additionally, technology specialists and clinicians have joined my laboratory, specifically residents and fellows interested in translating technologies. In some cases, the residents and fellows described their interests in becoming a "clinical trialist". This, in turn, has resulted in the development of CAR T cell and lncRNA-based platform technologies. Translationally-oriented thinking has helped us to narrow the candidate list of cell surface targets for CAR T cell-based therapies and to prioritize lncRNA candidates for specific disease indications.

For me, it has also been important to hire people with an adventurous spirit. Translational research increasingly involves a willingness to adopt advanced tools and technologies to interrogate human biology. Unlike research done exclusively in cell culture or model organisms, experiments done in human systems are often less-controlled and the resulting data are often less "cut-and-dry". There can be great variation between normal donors (control) and patient (test) samples. Occasionally, normal donor or patient samples are not available at precise times or in sufficient numbers to derive statistically-meaningful results. Translational research projects sometimes require greater levels of intuition and belief to make forward progress. I have found that people with higher risk tolerance are able to better deal with the higher levels of ambiguity in experimental design and result in interpretation that can come with translational research. In my experience, an adventurous spirit is also required to accept and manage the goals of translational research, which include publication but also could include technology development for clinical implementation, submission of patents, licensing of technologies, and starting new companies.

I have also found that these complex goals require that individuals have a collaborative spirit. The goals of translational research require scientists to efficiently manage relationships and

communicate clearly with clinicians, computational biologists, technology specialists, entrepreneurs, patent attorneys, and business development and licensing professionals. Additionally, it is relatively common that these translational projects require skillsets that extend beyond the scope of a single individual. Therefore, scientists in the laboratory may need to collaborate and leverage each other's skillsets to efficiently move a project towards clinical implementation and commercialization. This is counter to the traditional academic mindset in which scientists are hired and promoted because they have the key skills to initiate and complete a project. However, adding and maintaining a team-based approach to a research program can promote a culture where both individuals and the group can thrive. In my laboratory, I have tried to create a culture of "enlightened self-interest" in which individuals can succeed by contributing to their collaborators' successes.

Adopt advanced technologies

Deep interrogation of human biology is a natural step towards translation. Advanced technologies enable scientists to identify and manipulate pathogenic processes in human primary samples more rapidly. The use of advanced technologies to interrogate biological processes and the development of biologics to modulate these processes present opportunities for academics to actively participate in the early steps of drug and druggable target discovery. There has been an explosion of technologies that allow sensitive analysis of individual cells or interacting molecules (e.g., RNA-seq, ATAC-seq, Perturb-seq, SLAM-seq, etc.) and human samples (organoids, organ on-a-chip, humanized mice) (Wang and Navin, 2015; Reuter et al., 2015; Rossi et al., 2018; Walsh et al., 2017). Adopting advanced technologies to interrogate human biology is risky and takes courage. For one, human biology may be less predictable, less well controlled, and samples may not be readily available, or signals may be more obscured by noise requiring further technological development and thus more innovation. Sometimes technologies are not fully worked out before they are shared. Other times, technologies need to be adapted to a specific research problem.

Thus, the effort to try something new comes with a time and financial cost and there are no guarantees of success, publication, or reimbursement through a granting strategy. And yet, I feel this risk is worth taking. Being an early adoptor of advanced technologies creates opportunities for biological discovery and innovation (see Text Box 11).

Text Box 11 Bringing advanced technologies into an institution

Another advantage of working at DFCI is the opportunity to interact with the Belfer Office of Dana-Farber Innovation (BODFI), which has an enlightened approach to technology transfer in many ways. Whereas most technology transfer offices have an outward focus, to license out technologies developed within the walls of their institutions, BODFI added an inward focus, to bring outside technologies into the institution. BODFI hired a Special Advisor on Technology Development, Dr. Robert Distel, who identifies recently-developed technologies and presents these to DFCI physicians and scientists whose research programs might benefit from these technologies. Frequently, these technologies are focused on sensitive and accurate measurement of low abundance molecules and cells in clinical samples. In one specific example, Dr. Distel connected my laboratory with Signosis, a company that produces a luminescence-based transcription factor activation profiling plate. We leveraged this technology to identify interactions between lncRNAs and transcription factors. The success of this technology provided the foundation for the lncRNA platform technology currently being developed in my laboratory.

Step Four: Manage your data with an eye towards intellectual property considerations

The goal of academia is to share your ideas and discoveries with the world. Traditionally, this is done mainly through publication, which is critical to sustaining funding for the laboratory and gives rise to the academic's axiom: "publish or perish." Patents are another means of sharing one's work with the world but patents have generally been of secondary concern to the scientist and left mostly to the institution that owns the IP rights to the academic's work. Traditionally, the technology transfer office of each institution not

only files patents but also facilitates translation of the technology by finding a biotechnology or pharmaceutical company or a venture capital firm to license the technology for development and commercialization.

However, incorporating translational work with an eye towards commercialization into my research program has required strategic planning for patents. The translation-oriented scientist can participate in positioning the IP to increase the likelihood of investment. Specifically, biotechnology investors will not invest in a technology unless it has a strong IP position which means (1) novelty, (2) early priority date, and (3) strong data to support the claims on the patents. In my opinion, inventors should participate in these steps.

An invention must be useful, non-obvious, and novel to be patentable (see Chapter 19 for more information). Academics must be especially careful about novelty. My colleagues and I generally consider novelty with respect to publishing; however, novelty with respect to patents has a strict definition. Any public release of information can be considered a disclosure of prior art and can prevent an invention from being patentable. Presenting data at an inter-institutional seminar, sharing data with a collaborator, or presenting research during a job talk all fall under the broad definition of public disclosures. As a result, I am conscientious about what and when data are presented. I have found that it is helpful to discuss inventions with technology transfer offices early and often during the research process to help manage and avoid last minute deadlines. Technology transfer offices can also assist with confidentiality agreements to allow for open discussions that minimize risks of sharing confidential information.

Early priority dates refer to US patent law which holds that, among similar, competing inventions, the patent is awarded to the first to file a patent claim with the United States Patent and Trademark Office (USPTO), giving it priority over all other claims. This is important because patents are awarded by the USPTO on the

first to file and not the first to invent. It would seem that patents should be filed immediately upon making a discovery, to always be first to file and increase the chances of being granted a patent. The USPTO allows for the submission of a provisional patent, which allows for an early priority data, but starts a one-year clock to update the specification and claims of the patent before conversion into a regular non-provisional patent application.

Once a patent converts, no data or changes to the specification can be made. Therefore, filing too early has its risks. While additional data may be used in the examination of the patent, specific claims may be rejected or require revision because the data contained within the patent are not sufficient to support the claims. Importantly, the full patent is now considered prior art which means your subsequent work and data, even if building on that patent, is not new or novel as required to obtain a patent. You will have essentially blocked yourself from patenting the subsequent developments of your own work. While this has always been the case, traditionally, academic scientists were less concerned about priority dates because the institution owns the IP. Thinking commercially, however, an inventor and the institution have to consider the value of the IP and its likelihood to be licensed and make a strategic decision about what is the best chance of obtaining a patent, whether filing early or waiting if more supporting data and potential additional patents are expected. Examining the strength of an IP position is part of the due diligence process. Inventors are not trained in it but I believe inventors should be familiar with these key IP issues.

Even those academics who participate in commercializing their technology generally do so in the context of a venture firm that has done the job of evaluating IP position and licensing the technology from their home institution. In this case, the academic does not directly participate in the key steps of due diligence that determine whether or how a technology is viable for future commercialization.

Thinking commercially, it is important to consider the value proposition of your patent. A patent can generate alternative sources of funding for projects in the laboratory. If a patent is strategically positioned relative to an outside company's commercial interests, a patent can help secure a Sponsored Research Agreement from a corporate partner. A patent can also generate funding through a licensing agreement or through direct purchase from a venture firm that starts new biotechnology companies or from a pharmaceutical company. Finally, patents can be critical for academic scientists who wish to directly license their own technology to start a new company. It is also important to note that many foundations that provide research grants include provisions in their research agreements that either give them rights to IP or seek a share of licensing payments and royalties generated by the research.

ACADEMIC INSTITUTIONAL SUPPORT FOR TRANSLATIONAL RESEARCH PROGRAMS

Basic research is the life-blood of ideas that can be translated into future medicines. Because academic institutions are traditionally structured to support basic research, changes may be needed for them to support translational research as well. There is an assumption or fear that bringing translational research into academia will diminish basic research; however, integrating the two can support more basic research, not less. For one, translational research accelerates innovation, which enhances basic research. Moreover, an integrated strategy can enable basic research to impact more patients at an earlier time. Also, in my experience, scientists and their home institutions can benefit financially as more sources of funding become available and technologies become more developed, more valuable, and more likely to be licensed. These increased financial benefits can, in turn, support more basic research so that basic research can remain the mainstay of research in academic institutions, and less dependent on government funding.

Many academic research institutions and their affiliated hospitals have built-in advantages that enable integration of basic and translational research to the benefit both the scientists and their institutions: (1) treating physicians can help position technologies to address unmet medical needs; (2) talented scientists can thoughtfully develop technologies for maximum patient benefit; (3) patient samples can be used for tools development for specific disease indications; (4) research cores are often well-equipped with advanced technologies and analytical tools. With these resources at the ready, more translation and development can be done within academic institutions and integrated with basic research. The following are a few simple changes they can make to support this integration.

Institutional support for technology development

Because academia has *not* been guided by translation or commercialization considerations, many potentially transformative technologies are delayed, never developed or lost to prior art (disclosures of innovation in the public domain). For example, many academic scientists don't realize that their discoveries are patentable or appreciate that publication can invalidate the ability to file new IP. In some cases, programs fail in academia without ever being seriously considered by groups with expertise in drug development. Moreover, until recently, the growth of the biomedical industry was largely driven by venture capital and private equity firms investing in new companies, and, therefore, academic institutions and their scientists have not fully participated in or benefited from this growth.

However, over the past two decades, pharmaceutical companies have been increasingly turning to smaller biotechnology companies and academia for their research to feed into their product development pipeline (Harrison, 2016; Bansal et al., 2018). This interest from industry creates an enormous opportunity for institutions to receive more funding for their scientists' work, to see more of their work developed and put out into the world and for the scientist and institution to reap greater benefit from this development.

Improve communication between technology transfer offices and scientists

Typically, venture capital groups have identified key technologies in academia for development. This presents an excellent opportunity for technology transfer offices within universities to work more actively with academic physicians and scientists to better position a technology for licensing by investors. Technology transfer offices can assist scientists by (1) increasing the value of their IP, (2) establishing sponsored research, (3) connecting scientists with advanced technologies, (4) providing insight into market opportunities and commercialization potential, (5) identifying partners, and (6) licensing IP. In my experience, effective technology transfer offices proactively communicate with scientists to increase the value of discoveries or technologies. However, academic institutions must also commit resources to staff these offices with people who have expertise in these areas. Additionally, educating academic scientists in the licensing process often reduces the work of technology transfer offices and maximizes the value of the technology for licensing deals. Historically, deals with universities are quite lucrative mostly for the licensee. An integrated approach in which the scientist and technology transfer officers work together to better position a technology for development would result in a greater share of the financial benefit for the licensing institution and the inventing scientists.

Integrate bottom-up and top-down thinking

In my opinion, academia needs to support "bottom-up" and "top-down" thinking. The technology that scientists develop for specific applications is more likely to become commercially viable when the scientist actively participates in the technology transfer process. Academic institutions can create a culture of innovation and entrepreneurship. Similar to the way venture capitalists approach new company formation, institutions can encourage technology transfer officers and scientists to scour the universe of technologies for ideas that complement analysis of human samples using application of

home-grown technologies for specific indications. Institutions can also support an entrepreneur-in-residence, who can advise scientists and help inform important decisions that affect whether a technology or drug should be translated and commercialized. An entrepreneur-in-residence could also identify high net-worth individuals interested in developing a particular technology. Such high net-worth individuals typically have a higher risk tolerance and an expanded timeline for obtaining a return on their investment. The willingness to invest in earlier stage technologies, sometimes even before company formation is more consistent with the stage of technology development and experimental timelines in academia (see Text Box 12). An entrepreneur-in-residence can help investigators and technology transfer offices strengthen patents, determine which technologies to invest in, and find licensing partners thereby improving the value of the technology and reducing the work of the technology transfer office.

Text Box 12 DFCI is initiating a National Cancer Angels program

Mr. Richard Anders (Founder, Executive Director of Mass Medical Angels) and Dr. Mermelstein are expanding the model initiated at DFCI to a national level. Working with leaders at DFCI, Mr. Anders and Dr. Mermelstein initiated a National Cancer Angels group initially composed of approximately 70 high net-worth individuals interested in investing in cancer-relevant technologies and therapies. Each of these individuals could become an entrepreneur-in-residence for developing a particular technology and therapy in a major cancer center. This pilot program could effectively pair particular academics with interested and like-minded entrepreneurs.

An additional mechanism to help academic scientists integrate "bottom-up" and "top-down" thinking is to perform a sabbatical in drug development and commercialization. Instead of taking a sabbatical in another academic laboratory, academic scientists might take a sabbatical in a venture capital or private equity firm, early-stage biotechnology or established pharmaceutical company. Each of these experiences can provide unique perspectives on developing and commercializing discoveries. There are a few risks

in taking a sabbatical in drug development and commercialization. This experience may not directly relate to the technology or research being performed in the academic's laboratory and may influence academic promotion. Additionally, the ability to participate in an commercially-oriented sabbatical depends on stable laboratory funding during and after the sabbatical and on independent laboratory personnel to maintain research activities. It is my impression that incentives to mitigate these risks would benefit both academics and their home institutions.

Incentivize translationally- and commercially-oriented scientists

The central goal of translating discoveries into therapies is to help people. The central goals of commercializing therapies are to (1) increase the benefit of drugs for the greatest number of people and (2) maximize profit. The value of this latter goal is important to recognize. Commercializing discoveries (especially drugs) is capital intensive. In my experience, academia tries to draw a clear line separating research and commercialization. There is a legitimate concern that research should not be unduly influenced by a profit motive.

However, there are ways to build bridges that connect research and commercialization activities and simultaneously help maintain the integrity of research. One bridge is a licensing agreement for a technology from academia to investors who will commercialize the technology. A second bridge that connects the two sides is a Sponsored Research Agreement in which corporate sponsors can subsidize the development of a technology in an academic setting. These bridges and other structures described in the "Managing Conflicts of Interest" section below can help mitigate the concerns that ulterior motives could affect the integrity of research.

Institutions can provide scientists with direct access to drug development experts; however, providing access alone is not

sufficient. There is a greater chance of failure than success in attempting to commercialize a technology or drug candidate. Therefore, I suggest salary and research support for those individuals who are willing to commit the significant time and effort to participate in the key aspects of translating discoveries. While many institutions provide financial compensation to the individuals, laboratories, and departments that generate licensed IP, increasing the incentives and mitigating the risks independent of the outcome will encourage more researchers to purse high-risk high-reward translational projects. Institutions can support scientists' participation in translational and commercial activities through internal grants or partnerships with investment firms. Institutions that incentivize translation and commercialization will enhance the value of their home-grown technologies.

Institutions should also encourage investigators to start new companies. Most institutions allow faculty to consult with companies, but few institutions allow faculty members to also have positions in a company. However, in some circumstances, it may be best to allow the discovering scientist begin translating and commercializing a technology with established entrepreneurs. The discovering scientists are often the ones who best understand the potential and limitations of a developing technology. Indeed, the desire to translate and commercialize discoveries could figure prominently in the hiring process. I anticipate these institutions will also have an advantage in recruiting entrepreneurial students, postdoctoral fellows, and faculty interested in translating research and commercializing discoveries. Once the company is funded, it may be advantageous for the discovering scientist to let people with the appropriate expertise run the day-to-day operations.

Manage conflicts of interest without limiting funding opportunities

The integrity of research requires the academic scientist not to be biased in his/her interpretation of the data. This is especially true for physicians and scientists working in hospitals that perform

clinical trials. Many institutions, therefore, will simply not allow an investigator to receive support from a group in which the scientist or his/her laboratory has an interest in the outcome of the research.

However, structures can be put in place so that physicians, scientists, and their home institution can receive funds without violating the integrity of research and biasing the results of a study. First and foremost, scientists need to disclose any ties to their funders to an Office for Research Integrity. If there are any ties with the funding agency, academic scientists should meet with a Conflict of Interest Officer. A scientist's financial conflicts should also be disclosed in publications and presentations. If a scientist is allowed to participate in research funded by a company in whose outcome the scientist has financial interests, additional mechanisms to mitigate risks will be necessary. A Conflict of Interest Officer will likely need to play an active role in approving funding for research performed by an associated company. If the funds are accepted, it may be possible to structure blind and double-blind experiments to assure the research and resulting data are performed and analyzed in an unbiased way. While this is common for clinical trials, these same principles could be applied to pre-clinical experiments.

Another conflict of interest concern for many academic institutions and their affiliated hospitals is their not-for-profit status. This requires structures to assure patients, funding agencies, and the public at large that the results of the research are not motivated by profit and are genuinely in the best interests of patients. One structure is a license for the development and commercialization of their technologies to venture firms, small biotechnology and large pharmaceutical companies. Licensing agreements entitle institutions to a share of the profits in the form of royalties from the sale of the resulting products. However, as discussed earlier in this chapter, institutions that develop a technology and demonstrate its value increase the attractiveness of the technology for licensing. The institution can thereby enjoy a greater share of the profit without engaging in for-profit activities. The increased proceeds from these activities can and should be reinvested in basic research.

CONCLUSION

Even if academic physicians and scientists do not form a new company or license a technology, I have found that adding a translational focus to your research program advances basic research in the same laboratory. Some institutions make this process more tangible for basic scientists. However, many academic institutions currently do not have the resources to integrate translation and commercialization perspectives into basic research. Basic scientists therefore may not have access to (1) sufficient funding, (2) key opinion leaders, (3) entrepreneurs-in-residence, (4) robust technology transfer offices, or (5) sufficient IP resources. I anticipate that success in translating and commercializing research will encourage institutions to provide more of these resources to basic scientists. By adding structures to support academic scientist's participation in translation, institutions will increase their control of commercialization and accelerate translation of home-grown technologies to benefit a larger number of people. In the meantime, I recommend that scientists utilize available resources to begin performing due diligence processes and making small changes in their program to incrementally participate in more translationally-relevant research.

Translationally- and commercially-focused research is a risky endeavor. However, it potentially holds greater rewards. This process requires significant intellectual, financial, and time commitments. Scientists may need to perform more expensive experiments that are more relevant for translation but may turn out to be negative. Translational programs tend to be more expensive and competitive as a whole and often have limited windows of time in which they are profitable (or publishable in high-impact journals). Scientists engaging in this process may need to hire a collaborative and ambitious staff that "buys in" to this type of research program. I have found that maintaining a staff that supports this type of research is not trivial; success often results in staff moving into more advanced positions. Everyone involved in translationally- and commercially-focused programs needs to be

willing to invest the time and energy to make the laboratory work most productively. This starts with the due diligence process and continues with numerous hours communicating with clinicians, conflict of interest officers, technology transfer officers, legal teams, entrepreneurs, investors, and many others. Slowly transitioning a laboratory towards an integrated approach to basic and translational research will help minimize these risks.

I have personally adapted my laboratory to incorporate the principles discussed throughout this chapter. I am very fortunate to work at DFCI where I have access to talented scientists, clinicians and entrepreneurs, and have the support of my home institution. Despite this incredible support, my research program remains a work in progress. Ultimately, I believe that refocusing the research in my laboratory will be worth the risk. The approach to integrating basic and translational research increases the likelihood that the work of my laboratory will positively impact patients' lives.

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Dr. Novina's laboratory has made several important discoveries about the biology of noncoding RNAs, their dysregulation in cancers, and their development as biomedical tools to address unmet medical needs. His laboratory has developed platform technologies to discover and drug noncoding RNA functions and has engineered tools for epigenetic and cellular therapies. Dr. Novina has established numerous collaborations with clinicians and industry partners to accelerate the translation of these tools to the clinic.

Dr. Novina is the recipient of numerous awards and honors including the Doris Duke Clinical Scientist Development Award, American Cancer Society Research Scholar Award, W.M. Keck Distinguished Young Scholars Award, Department of Defense Idea Award, The NCI Director's Provocative Questions Award, and the National Science Foundation Collaborative Research Project Award. He is also the recipient of the prestigious NIH Director's Pioneer Award, which funds high-risk research with transformative potential.