Rescuing the Lost in Translation

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The translation of medically relevant academic inventions that could transform public health has been notoriously difficult, stemming largely from cultural differences between academia and industry. New initiatives to kindle academic entrepreneurship and establish stronger public/private partnerships are helping to align these differences and accelerating the translation of promising new therapies.

Academic medicine is experiencing a revolution that is poised to transform public health, growing largely out of a culture of innovation and a deep knowledge of human disease mechanisms. This has led to groundbreaking advances in the fields of oncology, cardiology, hematology, and neurology, among others. Translation of these innovations is key to meeting global health care demands; however, <5% of all life science discoveries made in academia are translated into use in clinical practice, new medications, diagnostics, or devices. What is the root of this disappointingly low rate of translation? Is it because the initial ideas were poorly conceived, immature, or misaligned with the interests of potential industry partners?

The answer is complex (Butler, 2008; Duda et al., 2014). However, one factor is that, in order to reach the market, efforts in academia must pass through industry. Unfortunately, industry’s market-oriented structure places a highly selective filter on which discoveries are taken and developed, in part based on restricted portfolios and a need to embrace projects with low risk and high return on investment. This filter is particular tight for new drug-based therapeutics, due to the extremely high costs of development (> $100 million) and the long development time (~ 15 yrs) that consumes most of a patent’s life (20–25 years), thereby further reducing a company’s return on investment. To compensate for these costs, pharmaceutical companies not only charge high prices for their drugs, but also have often reduced or eliminated their expensive in-house research and development (R&D) efforts, looking instead for growth by acquiring new technologies through mergers and acquisitions and me-too-drugs, policies that have greatly slowed the development of new drugs.

Academia’s response to these translational roadblocks has been to capitalize on their own entrepreneurial spirit and “do it themselves.” This has led to an expansion of university-based, technology-transfer offices, attempts to commercialize academic inventions by forming startup companies, and the creation of incubators to support fledgling startups. However, pursuing these opportunities can be a daunting task for academics, as know-how on nearly all levels and strategic funds are often lacking for such risky ventures.

How can this critical gap be bridged (Figure 1)? Cultural change in both academia and industry is needed so that each can learn and profit from one other’s strengths and compensate for weaknesses (Duda et al., 2014). This will require not only a better understanding of what motivates each group, but also the creation of cross-cultural education programs that teach the fundamentals of drug development, as well as strategies for engagement and establishment of meaningful partnerships. Here, we highlight programs facilitating a cultural change in academia to overcome these obstacles (for more on cultural changes in industry, please see Ehrißmann and Patel, [2015]). We also discuss the importance of academic inventions and knowledge as a vital university currency that needs to be protected and developed to further accelerate translation.

Fostering Translation in Academia
Over the last few decades, the culture within academic institutions has been changing from one focused largely on acquiring basic knowledge to one that is ever more applied (Fang and Casadevall, 2010). Of particular note are the changes within the life sciences, where an increasing proportion of research is becoming oriented toward medically relevant problems. This change is motivated by patient advocacy groups and foundations and by policy changes within government programs. These organizations seek to create a stronger translational atmosphere wherein clinicians and basic scientists work across disciplines to solve medically relevant problems. Academic institutions are responding in turn by creating programs that reduce the barriers associated with the inefficient translation of new technologies. These include institutional structures that facilitate the design and execution of clinical trials, educational programs for faculty, students, and post-doctoral fellows on the fundamentals of translation and entrepreneurship, and the establishment of savvy technology-transfer (TT) offices that not only streamline the consolidation, patenting, and licensing of innovative projects/concepts, but also make possible partnering agreements and project management to facilitate the acceptance and development of high-impact programs by industry.

A survey of programs across the most successful translational institutions worldwide reveals no one path for successful translation but a myriad of strategies tailored to perceived and evolving needs. These operate on many levels, addressing different steps in the translational cycle of discovery, development, clinical assessment, and commercialization (Table 1). Early efforts to facilitate
clinical translation within academia included the establishment of a national network of medical research institutions in the US by the NIH. These centers, managed by the National Center for Advancing Translational Sciences (NCATS) and supported by Clinical and Translational Science Awards (CTSA; http://ncats.nih.gov/ctsa/about), are designed to improve and streamline the translational research process and to catalyze innovation in the training of translational scientists and the development of new research tools.

At present, there are ~50 medical research institutions in the US receiving CTSA program funding. In general, CTSA funds are used to organize resources within each hub. For example, in Boston, the Harvard Catalyst works to enhance translation between 10 schools and 17 affiliated academic healthcare centers (https://catalyst.harvard.edu/). This program offers clinical and translational investigators the necessary resources to design, analyze, and conduct clinical trials, including consulting in areas such as biostatistics and biomedical imaging. At present, there are more than 1,800 open clinical trials supported by this program (http://www.harvardtrials.org/home). In addition, the Harvard Catalyst provides courses and training programs on translational and clinical research, which include a practitioner’s teaching program called KL2 (https://catalyst.harvard.edu/services/kl2/). Importantly, this program is designed to streamline the process of translation by removing barriers and creating a culture of collaboration and acquisition of third-party funding.

Such features are similarly highlighted at other highly successful translational programs, including those at Duke (Duke Translational Medicine Institute) and Johns Hopkins (Institute for Clinical and Translational Research), both supported by the CTSA program. Moreover, the concept of government support of clinical translational programs is not unique to the United States. Indeed, similar initiatives can be found in Canada (CQDM, Quebec Consortium for Drug Discovery), Japan (TRI, Translational Research Initiative), the United Kingdom (MRC, Medical Research Council), and Germany (Helmholtz Gemeinschaft).

Educational Initiatives
While the augmentation of clinical translational programs is a key step in the efficient assessment of potential therapies, the creation of innovative therapies requires a series of iterative steps that begin with a basic science discovery or clinical observation that can be causally linked to disease. Though many of these outstanding discoveries appear in high-profile journals, few (<5%) enter the clinic, are licensed for further development, or become the new standard of care. There are several reasons for these low

Figure 1. Building Translational Bridges
The culture of unbridled creativity in academic institutions is poised to transform public health with a vast array of new potential therapies. Unfortunately, 95% are never developed due to their immaturity and/or misalignment with the interest of potential industry partners. In response to these translational roadblocks, governments, academic institutions, and the biotech industry have begun to lay the ground work to accelerate the development of academic innovations by creating new programs to educate the next generation of entrepreneurs as well as infrastructural changes to support fledgling startups and finance these risky ventures.
numbers. One is the failure of academic inventors to protect their ideas through patenting, a tool that is crucial for industry to conduct business. Other factors include the absence of proof of concept data demonstrating that the potential therapy has clinical relevance; the poor characterization of new chemical entities or diagnostics; and the selection of diseases/indications for which there are existing therapies or that pharmaceutical/biotech companies (pharma) have already invested billions into without success (e.g., stroke and Alzheimer’s disease). These issues point to a larger problem, namely that scientists and clinicians do not fully understand how industry works or what is needed to make their inventions attractive for further development and/or commercialization.

From a 10,000-ft perspective, the answer seems obvious: education. Yet oddly enough, academic programs designed to address this unmet need only began to emerge during the last decade. Many of these have been driven by early academic entrepreneurs who faced daunting challenges in de-risking and promoting their programs and who brought the knowledge they gained...
through such experiences back to their host institutions. Daria Mochly-Rosen, a Professor at Stanford University, is one such person, who has worked passionately to influence the conversation of how academia can enhance drug development in industry. She labored for years to translate discoveries from her laboratory into clinically viable therapies, including the founding of a company to develop drugs to treat cardiovascular and kidney diseases (www.kaipharmaceuticals.com). After a year’s leave of absence from Stanford, she realized that much of what she learned was not part of the academic culture or organizational knowledge held within academia. This drove her to establish one of the first educational programs for academics, called SPARK, which teaches the fundamentals of drug development from discovery to market access (med.stanford.edu/sparkmed). Importantly, programs like SPARK empower scientists and clinicians to gain control over the licensing and marketability of their inventions, a prerequisite for successful academic translations. This new power is helping to shape the landscape of academic/industry partnerships.

The concepts embedded in SPARK are not unique and are emerging with different flavors at institutions around the globe. These include project-oriented educational programs designed to foster entrepreneurship in academia, an understanding of drug development in industry, and project-management skills. Most are small grass-roots initiatives with a strong entrepreneurial focus. Some examples of these programs include Duke University’s Innovation and Entrepreneurship Initiative, Stanford’s Bodesign Innovation Fellowship, the Entrepreneurial Workshops at the University of Vermont, and the Biomedical Innovation and Entrepreneurship program at the University of Technology, Sidney, among others.

A common thread in these programs is that they combine inquiring minds with sound management skills in a hip Silicon Valley style. Academic initiators of these different programs obviously agree that clinicians and scientists of life sciences lack an entrepreneurial self-image as well as solid knowledge of business culture. Many of these initiatives follow a very thoughtful attempt to guide scientists step-by-step until their projects are ready for licensing, clinical development, and/or startups. For example, within SPARK, innovative projects thrive under the guidance of experienced and dedicated local teachers, mentors, and advisors who volunteer their time, knowledge, and networks (Mochly-Rosen and Grimes, 2014) and who help define and guide nascent entrepreneurs along the path of drug, diagnostic, or device development. A typical Stanford-SPARK project can be oriented toward any indication, yet must address an unmet need, represent a novel strategy, and hold the potential to advance to commercialization and/or clinical testing within 2–3 years (med.stanford.edu/sparkmed). Additionally, teams are actively encouraged to embrace the Biotech and Venture Capital community, establishing partnerships, funding, and paths to commodification (www.bio.org).

A key feature of these educational programs is a crash course in drug, device, and product development, intellectual property management, and introduction to venture capital, as well as opportunities to establish startup companies. The success rate of SPARK-Stanford is amazingly high, with >55% of projects/yr being licensed, entering the clinic, or becoming commercialized (med.stanford.edu/sparkmed), compared to ~5% before the program began. Moreover, since its inception in 2006, 24 universities in 8 countries have created SPARK-like programs. This global initiative is designed to build a strong network of academic institutions and industry partners that foster innovation, entrepreneurship, and translation in human health care, as well as share resources, educational programs, advisors, and strategies for efficient project management. These programs are beautifully complemented by educational programs such as I-Corps, OneStart, and Startup-Class. Programs such as these teach business skills to budding entrepreneurs, helping them determine the best path to commercialization and a successful startup (Ledford, 2015).

Commercialization of Academic Inventions

To complement these educational programs, academic institutions are increasing their emphasis on technology transfer and commercialization of their academic inventions. This is clearly a rocky path that requires experienced technology transfer offices (TTO) to provide firm legal and business knowledge and extensive networks to achieve successful translation. Most institutions create their own offices that work closely with faculty to craft, file, and license patents, such as Unitecrap in Switzerland (Basel, Bern, and Zurich), the Office of Cooperative Research at Yale University in the US, or Technology Ventures at Columbia University, also in the US. These classical TTOs offer the university patent protection, funding, and support in commercialization by licensing or starting new companies.

Other institutions have created regional consortium agreements, with a centralized office that provides technology transfer to local networks of academic organizations. For example, the Boston Biomedical Innovation Center, supported by the National Centers for Accelerated Innovation (NCAI), is a consortium of universities, non-profits, government organizations, pharma companies, and venture capital firms. It is designed to accelerate translation of early stage biomedical innovations into commercially viable products by providing pilot grants, project management, and coaching, as well as connections to industry and investors. Similar strategies are used by the Max Planck Society in Germany, the Medical Research Council in the UK, and the MaRS Innovation program in Toronto, Canada. While most of these are homegrown TTOs and feed revenues back into their own network to support further research, others are privately held for-profit enterprises (e.g., 360, Ascension).

Increasingly, academic institutions and governments are recognizing the need to do more in the area of drug development, where risks are high and failure frequent. Thus, to complement efforts in TT and commercialization, the last decade has seen the appearance of numerous centers for drug development. For example, Canada has set up a national Centre for Drug Research and Development (CDRD), providing expertise and infrastructure to enable researchers to advance early stage drug candidates (http://www.cdrd.ca). Similarly, MaRS Innovation and Max Planck
Innovation have created spinoffs, the Quebec consortium for Drug Discovery (CQDM; http://www.cqdm.org/en) and the Lead Discovery Center (LDC; www.lead-discovery.de), respectively, which work to transform promising projects into innovative pharmaceutical leads that reach proof of concept in animal models. A particularly interesting enterprise for facilitating drug development is the Structural Genomics Consortium (SGC; http://www.thesgc.org/about), a not-for-profit public-private partnership between 6 major universities and 13 separate organizations that include 9 pharma companies, government institutions, and foundations. The goal of this effort is to determine the 3D structures of biomedically important human proteins, representing potential drug targets. This open-source program deposits each solved structure into the PDB, providing global access to less well-studied areas of the human genome, simplifying target identification and increasing the chances for drug discovery.

There are obvious pros and cons to each of these programs. In general, all sow the seeds for a translational surge that helps otherwise-trapped medically relevant innovations to reach the public. They also provide critical knowledge from business and industry experts. The advantage of programs with educational components is that knowhow is more systematically transferred into universities and institutions, a process that also helps create a new generation of true translators and entrepreneurs. A further incentive for the acquisition of this knowledge is the increasing recognition by universities that their creativity and inventive ness are valuable currencies that need to be both managed and exploited. Ultimately, these features will make them stronger and more valuable to industry as they forge partnerships to more efficiently translate new potential therapies. Yet, the challenges for these programs are numerous. Resources and quality management for such programs are often limited, a situation that is best solved by tapping into government programs or entering into a regional network of universities. These programs may also force unwanted changes in institutional culture, currently dominated by the “publish or perish” attitude, with little or no recognition or incentives for faculty who invest time in the business side of translation.

**Academia/Industry Relationships**

As we have already noted, academia and industry possess complementary knowledge and skills, so it makes sense for them to find strategies for working together effectively. Clearly, this requires an understanding of what motivates each party, defining what each does best and how to work in a mutually beneficial arrangement. While breaking down these barriers has been challenging, new emerging business models are beginning to make a difference. These include proactive policies to engage academic institutions and inventors, through incubators and partnerships.

Most incubator programs function to help startup companies get established by providing space, infrastructure, project management, business assistance service, and access to venture capital. They are often associated with research and technology parks placed in close proximity to vibrant academic and biotech communities and can be operated privately by pharmaceutical companies or by governments (Kirkpatrick, 2015). In Europe, these programs also offer mentoring, consulting, and prototype creation services. For example, Bayer’s Collaborator provides incubator space for rent (labs, offices, and meetings spots) next door to their R&D facilities in Berlin and San Francisco (http://www.colaborator.bayer.com). In addition to space, they provide infrastructure and equipment as well as an environment that offers young entrepreneurs, with a focus on drug targets and candidates, opportunities to exchange ideas and obtain expertise from Bayer’s research network. Similar programs have been created by Pfizer (Centers for Therapeutic Innovation in Boston), Novartis (Novartis Institutes for Biomedical Research in Singapore), Celgene (Celgene Institute for Translational Research Europe in Spain) and Johnson & Johnson (Johnson & Johnson Innovation’s JLABS), to mention but a few.

To further enhance collaborations with academics, many pharma companies engage in partnering agreements to explore promising drugs, diagnostics, and devices (Luijten et al., 2012). In addition to providing resources, these programs offer industry-style project management with clear sets of milestones that focus projects toward proof of concept. As with the incubator programs, they provide advice from industry experts and access to sophisticated screening, testing, and manufacturing facilities. From our experience, the trickiest and most time-consuming aspect of partnership with industry is the establishment of fair contracts, as language about shared intellectual property hugely impacts future success during commercialization. As “the devil is in the details,” we highly recommend creating a frame contract with every industry partner that tackles intellectual property topics and allows the addition of contracts for further projects without having to renegotiate the heart of the collaboration.

Importantly, academics should not enter such programs with rose-colored glasses and the illusion that access is a guaranteed path to commercialization. There are still very strong market and portfolio barriers that dictate whether promising programs are continued or killed, irrespective of how brilliant they seem. In this regard, educational programs such as those mentioned above should help to balance the expectations of academic scientists with reality.

In the coming years, the dialog between academia and industry will need to be further expanded. This conversation should include how each can best contribute to a more fruitful translational atmosphere. At present, academia brings two extremely useful components to the discussion. First, the academic culture of unbridled creativity is the genesis of many future medically relevant therapies, diagnostics, and devices. Second, the large clinical establishments and well-characterized cohorts of patients at academic medical centers will be of vital importance to the evaluation of emerging therapies. On the other hand, industry offers unparalleled expertise in drug development and regulatory issues. It also has the capacity, through incubators, investments, mentorships, and partnerships, to take on and de-risk early academic discoveries, facilitating their further development.

In considering partnerships, there are advantages to engaging both large and small pharma companies, depending on
the product. For example, big pharma, with its aversion to risk and its desire for blockbuster drugs (> $1 billion; Fischer and Breitenbach, 2015), to cover the high cost of R&D, tends to favor new therapeutic targets/drugs for unmet medical indications, where they can gain market exclusivity. Conversely, smaller biotech companies are more easily inspired by innovation. They are generally less risk averse and more entrepreneurial in their approach and thus willing to embrace new early stage technologies. This flexible ideology likely arises in part because these companies have a recent academic/entrepreneurial origin. One of the hardest groups of drugs to develop through industry is off-patent drugs. However, many of these fall into the repurposing class, which are already approved for other indications and can be rapidly evaluated and introduced for use in a clinical setting.

Change Management and the Evolving Culture of Translation
Based on the growing number of translational grassroots programs, it is clear that academia is seeking to do more to move basic scientific findings to the clinic, a path complemented by government programs to validate new drugs and targets and to test them in humans. Importantly, the success of these exciting programs will require a cultural change within universities as well as new project-management skills. Each project requires a thoughtful process of change management (http://www.kotterinternational.com), adapted for each institution. In this respect, we advocate a policy wherein universities continue to recognize that their intellectual property is a currency that needs to be protected, properly managed, and expanded. Projects with commercial potential need to be identified early, protected with patents, managed, de-risked, and validated and have value added by investment until they are attractive for licensing, startup, or commercialization. This strategy should be viewed as a team sport and should occur at nearly all levels of university management, including basic and clinical scientists and university administration. It is also critical to recognize that patenting is the currency required by businesses to commercialize all concepts and products. Thus, in order for academics to become true translators, they need to understand the culture of industry and to engage in all aspects of the translational process.

Finally, it is important that the burden of translation not fall solely on the shoulders of academia. Industry must do much more than simply wait for academic inventions to fill their dwindling pipelines. They must be more proactive in creating mechanisms to fund early stage projects, establishing attractive partnership agreements that incentivize academic collaborations, and sponsoring educational and mentorship programs. Let us share the burden for the benefit of patients.

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