Special Report

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CLINICAL INVESTIGATION

Anatomy and physiology of translation: the academic research imperative

The transfer of academic innovation to clinical practice and industry is taking on an increasingly important role in academic centers, but significant challenges remain. This work identifies some of the pivotal elements that are required to assemble, manage and accelerate the pace of successful translational research. These elements can be incorporated in new models of translational research facilitation that improve the process of converting academic innovations to commercial products where they can be used to benefit patient health on a large scale.

Keywords: academia industry collaboration • early translational research • facilitation team model

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Background

Translational research is one key to the future success of our biomedical research enterprise. Its promise is the realization of the benefits of basic and applied discoveries to make products that improve human health. The output of such efforts is measured by tangible metrics such as cost savings and improved patient outcomes that can be related to the financial stability of our healthcare system and the well being of our society as a whole. Successful translational research can also seed future innovation by increasing research funding diversity through research agreements and royalty payments, amplifying medical progress through a positive feedback loop.

The recognition of the importance of translational research over the past decade has led to the initiation of new journals fully dedicated to translational research and the generation of many publications on different aspects of this topic. Zerhouni [1] described the development of the NIH Roadmap for Medical Research specifically the theme titled 'Re-engineering the Clinical Research Enterprise' and dedicated to the renovation of the translational and clinical science. Wehling [2] and Wehling [3] defined pertinent terminology in translational medicine and identified key opportunities for technology transfer, such as biomarker development, efficacy and safety prediction tools for drugs and devices. Other publications have delved into the process of clinical translation and its evaluation. Feldman *et al.* [4] described the creation of centers for translational medicine in academic departments. Staff *et al.* [5] analyzed new initiatives from US regulatory and funding agencies, and highlighted barriers to accelerating translation. Lim [6], introduced the research-by-consortium model for sharing resources and tools. Valantine *et al.* [7] illustrated the elements, principles and strengths of corporate models for effective team work. Trochim *et al.* [8] examined the concept from the perspective of evaluators and introduced the model of key operational and measurable markers. The role of academia in translational medicine has also been addressed in the literature. Seker *et al.* [9] identified challenges for engineers pursuing clinically driven research. To translate a technology, engineers need to stay in the specific area of core strengths while interacting with specialists from multiple disciplines that are often very different to the ones we typically encounter in the academic world. Substantial patience is required before a long

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lasting partnership can emerge. Carpenter *et al.* [10] emphasized the 'leap of faith' many investigators need to commit to while engaging in translational research. Yousif *et al.* [11] presented a very interesting industry exploration program introducing the postdoc community to translational science careers. Alberts *et al.* [12] called on the biomedical community to 'rethink some fundamental features of the US biomedical research ecosystem' and encouraged academic researchers to take an active part in improving scientific productivity, bolstering evaluation criteria and implementing more practical research programs and policies. Edelman [13] made a strong point about the required 'new multidisciplinary thinking' and called for 'celebrating academic–industrial collaboration.'

Notwithstanding the growing awareness of the significance of translational research, the ability of academics and industry to engage in long lasting, mutually beneficial programs remains limited. Historically, there has been a gap between academic research and industry development, as the cultures and work models have typically been different and distinct skill sets are required in these environments. Research can be unguided by clinical and business reality and therefore the research push dominates over the market pull, resulting in many projects that proceed only to get stuck when real world considerations come to bear. Academic scientists have limited time and resources, making it difficult to find collaborations, conduct market assessments, write patents and even determine whether or not their ideas could have medical impact. Even once a device is transferred completely to a company, the two often go in their own directions, which does not benefit the product or its eventual adoption. As a result, translational research in academia is often stuck at different stages of the pipeline. Therefore, in the case of the biomedical research, a majority of the promising ideas are not translated clinically, and consequentially will not benefit patients and society. Better synchronization of basic research, clinical practice and industry partnerships would go a long way toward leveraging our investment in medical research to provide products that are cost effective and beneficial to more patients.

The concept

The journey of a research idea from bench to bedside can be analogized to the art and science of passing a baton in a relay race between basic and translational researchers (Figure 1). As opposed to a simple handoff, however, this process can range in complexity and duration and involves navigating through different stages or 'life cycles' (Figure 2), where each stage requires specific skills and expertise (Figure 3) of interdisciplinary networks and multicultural teams within academic institutions. For successful transfer to clinical practice, not only are different expertise and skills required but academic investigators need to be able to engage with commercial partners at all stages. The distinction between academic and industry contribution along the way depends on three factors: type of topic, for example, drug, device; maturity of the idea, that is, basic research, proof of concept, development or transfer to commercial owner; and, exit strategy, that is, start-up creation or licensing to fully established industry. In order for the exchange to be clean, all elements must work in concert, like a mechanism composed of moving parts and gears.

Yet, this mechanism should also be adaptable, as maintenance of flexibility can be critical for success. While industry may have sophisticated and well-qualified preclinical, regulatory and clinical teams, the focus needs to be on linear commercialization of a given product. The fluidity of academia is one of its strengths in the translational process, as academic researchers often have the vision and relative freedom to pursue alternative biological targets or application pathways that were not conceived at the outset.

At Massachusetts General Hospital (MGH), we have a long tradition of encouraging and enhancing translational research, stemming from a culture that fully embraces the potential of research to actually improve medical care. To this end, a decade ago, MGH launched five Thematic Centers for research that are cross-departmental, interdisciplinary research entities that address certain complex biomedical research challenges of the 21st century. In order to demonstrate some elements of the hand off process (Figures 1–3), we present two specific examples of bench to bedside translation at the Wellman Center for Photomedicine, one of the five MGH Thematic Centers.

Examples

Fat removal

At its most fundamental level, translational research is a practical effort that aims to solve a healthcare problem. Sometimes, the best solution therefore turns out to be a simple and unexpected strategy that is outside one's initial research plan. A good example from Wellman Center for Photomedicine is the discovery of tissue cooling as a treatment to selectively remove unwanted fat [14].

Safe, noninvasive removal of unwanted body fat was not possible a decade ago. As much research at Wellman is conducted with light, the initial strategy was non-invasive fat removal using a novel laser that operated at a wavelength that was capable of traversing the skin without damage, with sufficient power to damage

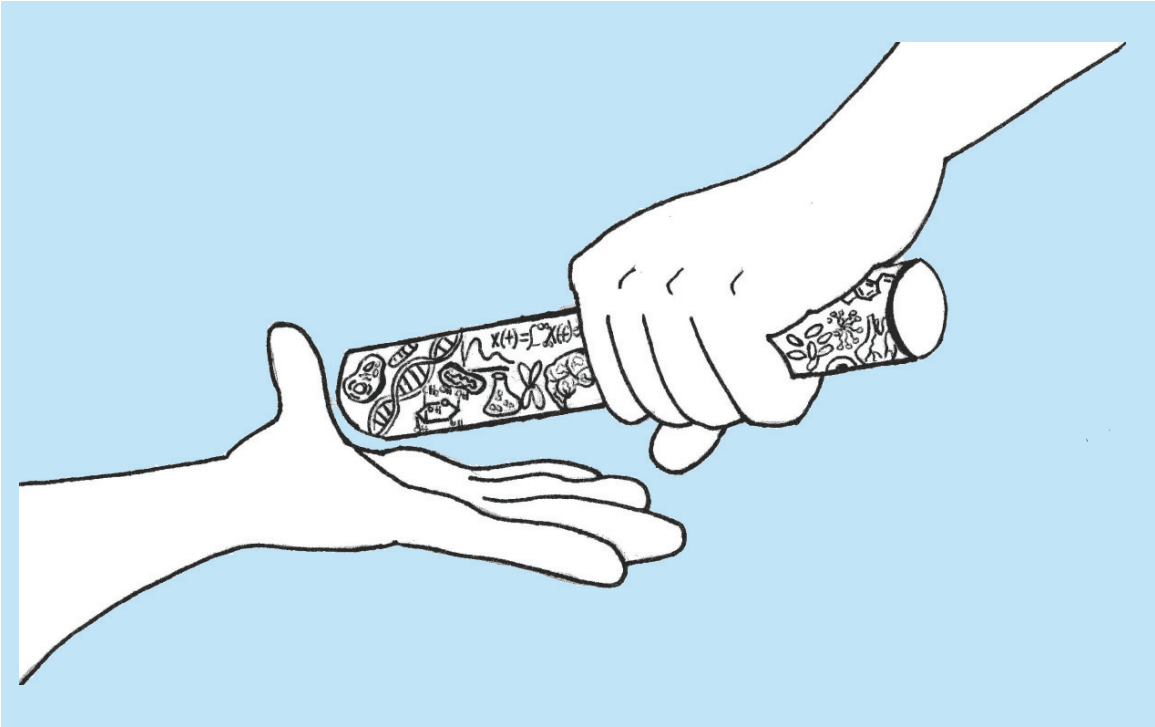

Figure 1. Translational research relay race. Passing the baton from exploratory to proof-of-concept research then to development is a science *per se*, a full continuum of scientific research.

the underlying fat. In a series of experiments culminating in a clinical trial, this strategy was shown to be feasible, safe and effective. However, it was also painful, tedious and required an expensive new laser – a technical solution that was impractical medically and financially.

Rather than abandoning the problem, the research team looked at other, easier strategies. Dermatologists are familiar with a rare condition in which young children who come into contact with ice develop local inflammation followed by selective loss of fat. Could this be become a well-controlled treatment to remove fat in adults? By studying the mechanisms involved, optimizing tissue cooling with mathematical models, building new cooling devices and then conducting preclinical animal and finally clinical trials, a novel treatment for local fat removal was created. Like the previously described laser approach, tissue cooling selectively removed fat while sparing the overlying skin and other tissues. But unlike the laser approach, tissue cooling was painless, used much more straightforward technology, was easy to perform over large areas and had a wide safety margin. A start-up company was formed that licensed the technology, grew quickly and has since brought a successful new treatment to millions of people.

This example illustrates that practicality and a willingness to change one's research strategy are central to translational research. Unlike research driven by scientific curiosity or technology development, translational research is driven by the need for practical, affordable and adoptable solutions to an important problem. Very often, proposed technologies are too complex, and, as a result, there is a high 'infant mortality rate' for many translational research projects and new companies. Fortunately, the failure of one translational approach does not mean that the problem is unsolvable. More often than not, the initial failure often outlines a roadmap for subsequent success.

Age related macular degeneration treatment

The synergy between basic science and clinical needs can also be at the origin of translational research provided the right alchemy happens at the right time. The research strategy at the exploratory and proof-of-concept stages can be extremely straightforward while development and commercialization steps remain complex, require long-term interdisciplinary efforts, multiple academia–industry collaborations and significant investments. A good example from the WCP is the discovery of a new treatment for age-related macular degeneration (AMD) [15].

Two decades ago there was a large unmet clinical need in ophthalmology since there was no accepted treatment for million of patients with AMD, a major cause of severe vision loss in people older than 65 years resulting from choroidal neovascularization. The challenge was to selectively destroy the neovascular

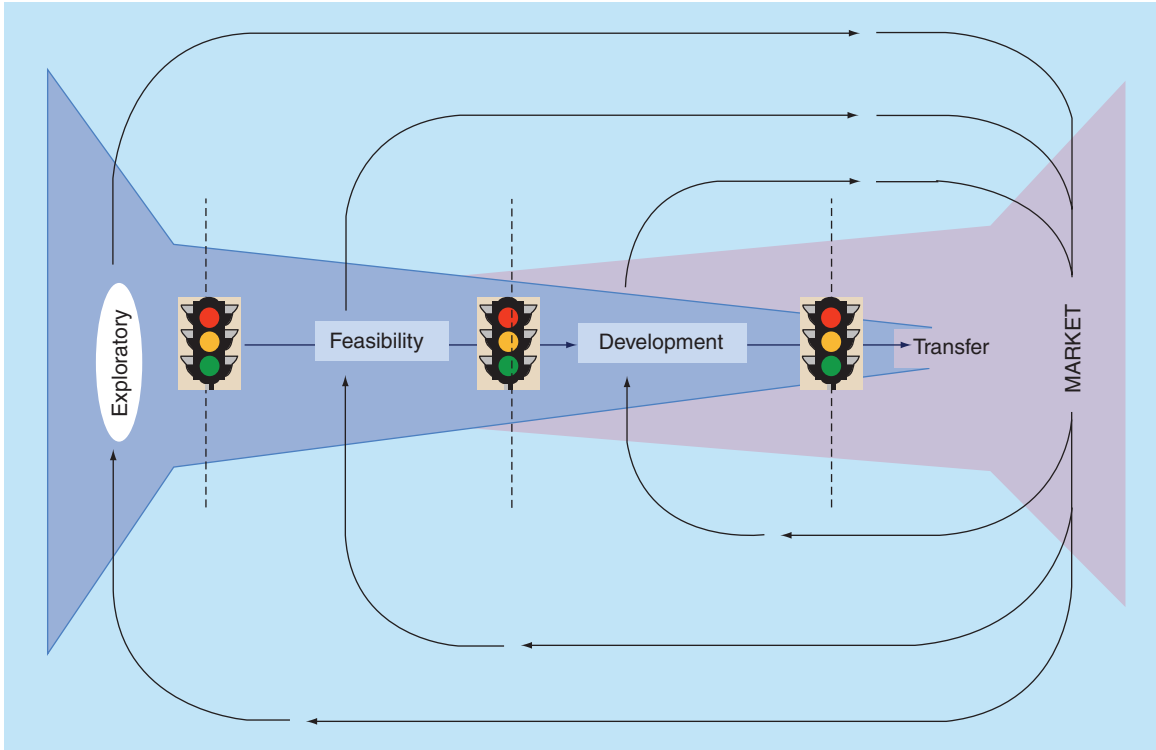

Figure 2. Stages of academic translational research. Typically, the path starts at the exploratory stage where the reservoir of know-how and skills is developed, moves to the feasibility stage where the objective is identified but many scientific uncertainties remain, then onto the development stage where clinical feasibility is established and the final product is identified and ultimately to the transfer stage where it is handed off for commercialization. The figure captures multiple steps where feedback from the real world is required to guide each stage. The diagram also indicates typical points where 'go/no-go' decisions should be made and highlights the early input that is needed from the market perspective (business development, regulatory and clinical).

structure of the choroidal neovascularization without damaging the surrounding intact retinal and choroidal vasculature. At the same time, advances in basic photodynamic therapy (PDT) cancer research became key for improving selectivity by linking special carrier molecules to the photosensitizer in order to target specific tissue components.

Two basic research groups at WCP came together, bringing complementary expertise one in photochemical targeting and PDT, the other in biophysics and ophthalmology. The two groups decided to join forces to develop and test specific carrier-photosensitizer complexes for PDT in AMD.

In vitro and preclinical experiments clearly showed the potential of covalently bound benzoporphyrin derivative with low-density lipoprotein complex to target ocular vasculature and selectively treat endothelial cells inducing intravascular thrombosis and vessel closure preferentially in the pathologic neovasculature. The temporal control inherent in PDT added to the selectivity. These results were crucial and lead to the development of multiple partnerships with industry. The first major collaboration was with one small biotechnology company developing and manufacturing photochemical drugs for cancer treatments. This company had the vision and internal expertise to understand the potential of a proof-of-concept stage academic technology. Recognizing the need in AMD they rapidly changed their market strategy and shifted the application to ophthalmology applications and gave access to the technology to a large pharmaceutical company to allow mass production of the photosensitizer. The second collaboration was with a medical device company for the development of photoactivation laser instruments. The international, multicentral clinical trials were very successful and led to regulatory approval of PDT for the proliferative form of AMD. Starting in 2000 and within a period of 5 years, more than 5 million procedures in 2 million AMD patients were performed. After that, the procedure using VEGF drugs replaced PDT as the standard treatment of proliferative AMD.

This example illustrates that the willingness of basic scientists from different fields to share knowhow and expertise and to integrate clinical experts as full members of their team are fundamental to translational research. Research driven by scientific curiosity and clinical motivation for solving important healthcare

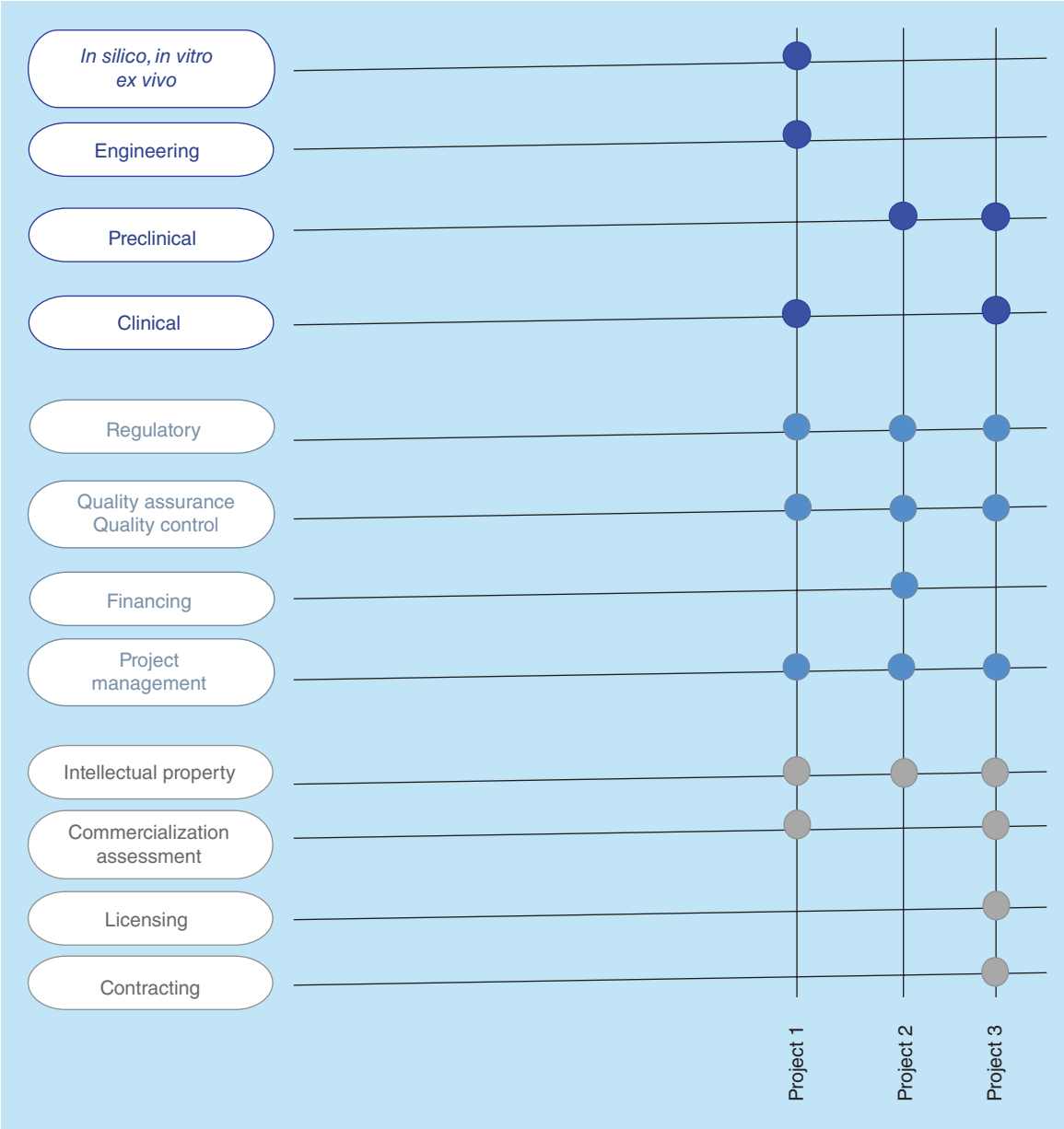

Figure 3. Academic translational research needs. Some are naturally embedded into the research environment – dark blue colored – and are related to in silico, *in vitro* and *ex vivo* work; engineering design and prototyping; preclinical experiments and, first in human tests. Others need to be provided by the institution or by external sources and can be classified in two groups: operations – light blue colored (regulatory compliance, quality assurance and control, finance administration, project management) and technology transfer – gray colored (intellectual property development, basic commercialization assessment, licensing and contracting). Different projects (e.g., Project 1, Project 2 and Project 3) may have different translational research needs, as shown by the dots in the right on the project matrix.

problems led to a strong and relevant research strategy. It permitted the research scientists to consistently engage the clinical community as well as the commercial partners. This example also illustrates the flexibility of the first company involved that allowed them to shift product strategies and adapt to the market.

In the two cases presented, the levels of complexity required for translation were quite different. The AMD case required not only that basic research and clinical expertise come together but also strong collaboration between three commercial partners for the development phase: one biotechnology company, one pharmaceutical company and one device company. The exit strategy model was license-to-industry. In contrast, the noninvasive fat removal product idea came from a failed attempt that resulted in an alternate but much

more straightforward solution. Most of the development of the tissue cooling device was conducted in house by the research team and the exit strategy model was the creation of a start-up.

One significant challenge for the translation of the AMD research work was to find a commercial partner that was willing to take the risk for this highly expensive development. The scientists had been very successful by largely disseminating their scientific results in the biomedical community and emphasizing the exceptional potential of this unique therapeutic alternative. For the noninvasive fat removal research work, a major obstacle to translation was the successful, but not clinically realistic, first solution. With this feedback from the industry partner, the scientists were able to overcome this situation by persisting and creatively thinking of simpler ways to solve the same problem.

Discussion

These two examples were successful because the ingredients for translation for each project were present and the timing was just right – these products could not have come to fruition without a substantial degree luck. There is a need to set up systems and models that reduce the reliance of perfect timing and luck in order to achieve successful translation. These systems must fill in gaps for academic scientists who currently face too many constraints on their time and resources to be able to consistently reach out to clinical partners and coordinate with industry in a manner that ensures successful translation of their ideas and research.

Inefficiencies in academic translational research have led to the development of new models. One decade ago, the NIH created the Clinical and Translational Science Awards (CTSAs) program as integrative part of the National Center for Advancing Translational Sciences [1]. The CTSAs role is to fund transformative efforts in academic institutions across the country, to encourage the conduct of relevant translational research work. The CTSA model for external support of translational research within academic centers has been highlighted, discussed and evaluated in multiple publications. Lim [6] suggested the research-by-consortium model as an option to consider in order to overcome common challenges in translational research such as scientific, regulatory, adoption and reimbursement. Valantine *et al.* [7] described the model of transdisciplinary science to be performed by research and development corporate-type teams from different disciplines but focusing on solving a specific problem. Trochim *et al.* [8] introduced the process marker model to help assess whether translational research efforts such as the CTSAs can increase the rate and volume of translation.

Several institutions around the country created their own translational research centers to speed the transfer of research results and train the future translational researchers. The John Hopkins Institute for Clinical and Translational Research (ICTR) [16] has been established in 2007 to address obstacles in translating basic discoveries into research in humans with a focus on three subject areas: drugs, biologics, vaccines and devices; biomarkers and diagnostic tests; and, behavioral, social and systems interventions. As an example, ICTR provides to any translational researcher across John Hopkins University consultive programs organized in five cores: translational laboratories; human subjects research; quantitative methodologies; clinical research informatics and research participants and community partnerships. ICTR also provides several degree and nondegree training programs such as predoctoral clinical research training and study coordinator apprenticeship. The Harvard Clinical and Translational Science Center (Harvard Catalyst) [17] has been established in 2008 to enable collaboration and providing tools, training and technologies to clinical and translational investigators to all Harvard faculty and trainees across Harvard schools and academic healthcare centers. The main goal is to provide investigators from different disciplines and institutions with a systematic way to form multidisciplinary teams, share tools and technologies through multiple cores available in the participating institutions, provide advanced training and education and obtain seed funding for new areas of investigation.

The models we pilot at WCP are strategically similar since dedicated to facilitate the translational research process. However, our main target is early in the translational path, at the transition between exploratory and early feasibility/proof-of-concept stages. The implementation concept is different because our models are functionally and physically embedded at the level of the research center, working very closely with the researchers to identify discoveries eligible for translation and prepare for this type of track. These models have the potential to accelerate the pace of similar cases to the WCP ones described above, to capture and develop new ideas. Such translational facilitation teams maintain an active inventory of research projects and help prioritize them for translational push. The many internal, institutional and external interactions foster and stimulate intellectual property management, support market and regulatory assessments, assist the development of commercial partnerships, encourage funding efforts and promote the construction of collaborative agreements. Education is also an integral part of our approach, the goal being to provide young scientists with the perspective, knowledge and skills to capture

and develop clinically relevant promising ideas in the context of both the real medical environment and the business world. At MGH, several clinical departments and thematic research centers are in process of establishing and experiencing this translational research facilitation paradigm. Other models in the field facilitate the engagement of academic scientists in understanding the substance of specific research portfolios managed by industry. The aim is to help potential commercial partners to continue to innovate by identifying new clinical indications for already discovered targets, existing products or services.

Choosing the appropriate exit strategy and the right time remains a critical, challenging multifactorial decision for academic investigators and their institutions. Handing off a technology to a large industry partner or to a start-up company are very different scenarios in terms of resources allocation between the parties and the decision-making process along the development pathway. Larger companies may have the resources to pursue product development with more independence, whereas a new company may need to leverage more time and resources from acadamia initially. Time to market can also be different between large and small companies, owing to business strategies, degree of focus and different financial pressures. These considerations are important when choosing the most appropriate academic–commercial partnership.

Conclusion

The changing landscape in biomedical research requires that translational research development efforts be operationalized, comprehensive and dynamic. The challenges ahead are significant and new models of translational research facilitation are moving the lines and overall inducing a cultural change. In these models, the principal investigator becomes part of a team that combines not only different research backgrounds but also regulatory, business development, market and management expertise. Research remains the foundation of this teamwork but not the exclusive driver. The work focuses on feasibility (instrumentation prototyping, preclinical tests and first in human studies) and funding sources come through application driven governmental mechanisms or industry. This type of approach requires strategic planning and basic business assessment. Project prioritization for translational push needs a strong and creative effort at the research center level, high transparency and solid commitment to the success of the center as a whole. Training at all levels has to encompass two different worlds, that is, academia and industry. These two worlds need to listen to each other, understand each other, be committed and be responsible together. At the institutional and senior management levels, a long-term, strong leadership commitment is absolutely necessary in order for these concepts to make a significant and sustained impact.

Future perspective

Over the next 10 years, translational research will become a central tool to seed future innovation, to diversify and sustain resources for academic research and overall to leverage our investment in biomedical science by providing new treatments and diagnostics that are cost effective and beneficial for more patients. To this effect, promoting and developing collaborations with industry at all stages of research will be exceedingly important. The reliance of industry on academia to innovate and translate science into commercial products will only grow because of increasing regulatory and reimbursement complexities that industry is facing as it brings new ideas to the market. We believe that academic institutions will morph to pick-up these new roles, will engage in solid collaborations spanning academic, clinical and commercial partners, and will establish translational research as a new discipline and research field of expertise.

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Executive summary

- Translational research is one key to realize the benefits of basic research and applied discovery to improve human health and a central tool to diversify and sustain income for academic research.
- The ability of academics and industry to engage in long lasting, mutually beneficial programs is important for bringing new products to the market that are cost effective and beneficial for more patients.
- The journey of a research idea from bench to bedside involves navigating through different stages of development, specific expertise and skills from interdisciplinary networks and multicultural teams.
- Translational research should be driven by the need for practical, affordable and adoptable solutions to an important healthcare problem.
- The translational research models we pilot at the Wellman Center for Photomedicine are focusing on early stage translation, and are functionally and physically embedded in the research ecosystem.

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The authors have no relevant affiliations or financial involvement with any organization or entity with a financial interest in or financial conflict with the subject matter or materials discussed in the manuscript. This includes employment, consultancies, honoraria, stock ownership or options, expert testimony, grants or patents received or pending, or royalties.

No writing assistance was utilized in the production of this manuscript.

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