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The Path from Bench to Bedside: Considerations before Starting the Journey

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Our understanding of human biology has increased tremendously over the last several decades(1-5), yet the pace at which these discoveries have translated into new therapies for patients has been frustratingly stagnant(6). Universities and academic health centers, as the major recipients of public investment in biomedical science, have an obligation to translate new knowledge into applications that confer human benefit. However, translating fundamental discoveries into practical applications takes many expensive, often highly regulated steps and these activities have generally not been a major focus of academic institutions. Challenges to engaging universities and academic health centers in translational research include building the appropriate infrastructures for human investigation, training and stabilizing the careers of young scientists and physicians interested in the requisite work, educating academic investigators about the regulatory requirements inherent in successful therapeutic discovery and development, and finding more efficient ways to match good ideas with adequate funding resources.

The purpose of this article is to examine the early stage drug development process and evaluate the role academia could play. As interest in early stage drug development grows among academic investigators, the need for more integrated partnerships between academia, government and industry has become increasingly apparent.

Growing Interest in Translating Discoveries into New Therapeutics

In response to the observation that breakthroughs in basic science were not resulting in new therapies for patients, the National Institutes of Health catalyzed an effort to transform the way biomedical research is conducted and launched the NIH Roadmap for Medical Research in 2004 (7). Part of this effort was to create the Clinical and Translational Research Awards (CTSA) program. With nearly 50 of these awards distributed to date, and a goal of 60 centers to be funded by the year 2012, academic research centers in the United States are increasingly being viewed as essential players -- and potential partners -- in pharmaceutical innovation. Although the CTSA centers could potentially form a very

powerful network of clinical investigators, only a few of the centers are truly focused on creating an environment in which early therapeutics development could take place (8). At a time when the pharma and biotech communities are looking for help and are prepared to outsource work they formerly performed in-house, the mismatch between industry needs and academic resources to meet those needs is glaring. The desirability of academia participating in this work, from a scientific and medical perspective, seems obvious, but there are cultural and political barriers that must be addressed if meaningful, ethical, and productive partnerships are to be formed.

Roots of Today's Technology Transfer at Universities

To understand the needs and limitations of early stage drug development in academic settings, one must understand the history of such drug development efforts. In the 1970s, as scientific discovery based on federally funded research blossomed, there was a feeling that tax-payer funded research was not being leveraged efficiently to create new medicines/technologies. As a result, Senators Birch Bayh of Indiana and Bob Dole of Kansas in 1980 sponsored the University and Small Business Patent Procedures Act, commonly known as the Bayh-Dole act. It allowed academic entities and non-profit/small businesses to retain the rights to inventions made during the course of research supported by federal research funds at these institutions. Previous to this legislation, those discoveries were considered in the public domain, free for anyone to use. Without ownership rights, biomedical discoveries that had commercial potential were frequently not pursued by either academe or industry because the investments needed to bring those discoveries to the clinic were viewed as unrecoverable in the absence of intellectual property rights protection. In addition, universities and academic health centers were unlikely to make such investments, as they lacked capital to do so and had no way to manufacture, market or distribute products arising from the inventions of their faculty. After passage of the Bayh-Dole Act, patents based on federally funded research were controlled by the originating academic institutions and the discoveries covered by these patents could then be licensed to industry partners possessing the capital and expertise to transform them into commercially valuable products.

The securing of patent rights for academic institutions came with several very important strings attached. If universities were to take advantage of this new privilege, they had to enable others to use the discovery in non-commercial ways, which meant granting the federal government a non-exclusive license to the invention. The bill also codified the right of the inventor(s) to share in the financial benefits that accrue from the invention, even though it was the university that would file and hold the patent. The specific benefit faculty inventors would receive was not mandated in the bill, so different universities created different royalty sharing schemes. On average, universities have given 40% of the royalties to the inventor(s) themselves, another 16% to the inventor's lab, and 26% to the hospital or university. Remaining royalties went to the technology transfer offices and other administrative bodies in the university system (9). At our institution, the Massachusetts General Hospital at Harvard Medical School, there is a four-way split: a quarter of the royalty will go to the hospital, a quarter will go to the department in which the work was conducted, a quarter will go to the lab in which the work was conducted, and a quarter will go to the inventors (as listed on the patent) collectively.

A final, and most notable, codicil in the Act is the provision that the academic institution will lose its rights to a patent if it does not “actively” attempt to commercialize it. Senators Bayh and Dole wanted to make sure that research discoveries were actually being turned into economically viable products that benefited societyⁱ. So in today’s environment, where academic-industry relations are strained by high profile, if rare, incidents of misconduct (10), many believe the idea of the hospitals or universities devoting effort to commercializing research discoveries runs counter to the values of the academy. It is therefore important to remember that the federal government expects and demands that academia commercialize its scientific discoveries if the latter’s intellectual property rights are to be retained. The issue is, therefore, not whether to commercialize, but rather how to do it. The key to managing that process is to recognize the inherent conflicts between academic discovery and product development and ensure that those conflicts are dealt with in as transparent a manner as possible (10).

It is worth noting that some of the most esteemed universities in the United States are the most prolific patent filers (see table below) (11) These universities and hospitals take seriously the business of patenting the inventions of their faculty in an effort to further their research missions and to provide society the benefits of their work.

Although the chief benefit to an academic institution of the commercialization of its inventions is almost certainly the enhancement of the institution’s reputation as a major contributor to the well-being of society, some discoveries do generate very substantial revenues. Although rare, several institutions have earned half a billion dollars or more from one invention. For example, Northwestern University sold its royalty rights to the anti-convulsant/pain reliever Lyrica (pregabalin) for \$700 million and New York University’s Remicade (infliximab) generated over \$650 million. Massachusetts General Hospital’s fusion protein technology that led to the development of the anti-inflammatory medication, Enbrel (etanercept), earned the hospital more than \$630 million and Emory University’s Emtriva (emtricitabine), a reverse transcriptase inhibitor used against HIV, returned \$525 million(12). None of these universities or hospitals actually sold the products themselves, but rather their discoveries led pharmaceutical companies to develop commercial products whose sales generated the royalties just mentioned. It is notable that these innovations span the gamut of medicinal therapeutics. The above list includes a small molecule, a recombinant DNA protein and a monoclonal antibody, all of which differ in the processes needed to take them from laboratory discovery through to the clinic. In addition to therapeutic molecules, universities also generate medical devices or enabling technologies (e.g., Baylor developed an antimicrobial coating for medical devices that makes them less susceptible to infection). Two of the biggest patents ever rewarded to universities were actually for methods that enable commercially important processes. One such patent was for the method of calcium phosphate transfection of mammalian cells, developed at Columbia University, which allows scientists to engineer cell lines that can produce substantial quantities of a recombinant DNA molecule in a cell culture system. The recombinant DNA

ⁱTo date, this right has not, to our knowledge, ever been acted upon by the government

revolution itself was the result of ground-breaking work by Boyer and Cohen that was patented by the University of California, San Francisco and Stanford University.

Though these discoveries provide dramatic examples of the financial rewards of patenting faculty inventions, they are by no means typical. Only 0.6% of almost 21,000 active licenses in the year 2000 generated royalties in excess of \$1 million (13). In a report quoted by Thursby (14), the average income per license was \$66,645, and 43% of licenses earned no royalties at all. However, it is the perception, or perhaps more accurately, the hope that any given patent could be worth millions that has frequently slowed collaborative efforts between universities and industry partners, as each side tirelessly negotiates to ensure their organization is best served by the licensing agreement.

What Type of Drug Development Happens in Universities Today?

What often happens with innovation in research laboratories is an investigator makes a discovery, that discovery is deemed to have market value by the university, and a provisional patent is filed on the inventor's behalf before the discovery is made public (usually a 30-60 day delay for writing the patent). That patent is converted to a full patent within 12 months by submitting a formal application, and if granted by the US Government, can then be licensed either exclusively to a partner to further develop the technology or licensed non-exclusively to many partners to all use. Sometimes the inventor becomes involved as a key scientific member of the team that further develops the ideas in the patent, other times not. Importantly, investigators should be aware that the US patent system (in contrast to the rest of the world) uses a first to invent standard, rather than a first to file (the paperwork) standard. The moral is thus to keep good laboratory notebooks and records of your thinking and work so if someone else files a patent on work you think is yours, you can show documentation of your priority.

For many investigators the process often ends with the filing of the patent. Occasionally however, the investigator will pursue the development of the invention in the small start-up company that has licensed his or her invention from the university. Alternatively, the investigator may simply continue to do research at her or his home institution that is related to the original discovery but not focused on its actual commercialization. The latter approach makes sense for most investigators because the process of drug development is long, expensive, highly regulated and requires specialized expertise not typically found in academia. Too often, glib discussions about the ease with which academic institutions might become dominant contributors to the therapeutic pipeline do not take into account how expensive and time consuming this process really is.

Specific Requirements in Early Stage Drug Development – A Long, Complicated Path

	Preclinical		Phase I	Phase II	Phase III
Years	3.5-6.5	File IND with FDA	1-1.5	2	3-3.5
Test Population	Laboratory and Animal Studies		20-80 healthy volunteers	100-300 patient volunteers	1,000-3,3,000 patient volunteers

Purpose	Assess safety and biological activity	Determine safety and dosage	Evaluate effectiveness, look for side effects	Confirm effectiveness, monitor adverse reactions for long term use
Success Rate	5,000 compounds evaluated		5 enter clinical trials	

As shown in the chart above, taken from the Food and Drug Administration web site, the drug development process is complicated and time-consuming. And if you are a young investigator with a new faculty position, spending the 11-16 years it takes to develop one medicine from bench to clinic may not be a wise career decision, because you will probably be off the faculty for lack of research productivity before the new medicine reaches its first patient. Yet while support for full-scale drug development is difficult to envision in academia, there are aspects of drug development that academia can do and do very well (8).

Discovery and Target Selection

Drug discovery begins with first identifying the target for the intended drug. A good target is one where the mechanism of action in human biology is well defined and for which one hypothesizes that engaging the target by activation or inhibition (e.g., through the addition of your drug) will have a desired effect on that system (and will not have undesirable effects on other systems in the body). Then, one sets up an assay (model system) in the lab to manipulate that target and to measure the biological effect. Academic investigators do this regularly. However, making this testing of potential drug compounds more efficient and high throughput is the forte of industry. Industry also has large libraries of molecules that can be tested in these assays. With recent efforts of groups like the NIH (with Pubchem), academic researchers have gained more access to large libraries of potential compounds, though even these libraries are typically not as sophisticated or large as those available in industry.

In continuing the development, what often is misunderstood by many academics is that once a compound that acts on a given target is found, that is only a starting point. The initial screening process commonly identifies compounds whose affinities for the target are low (i.e., requiring micromolar concentration ranges for the desired effect). But for safety and specificity in humans, one seeks compounds with 1000 times that affinity (nanomolar range concentrations for effect). Industry's approach to solving this problem is to employ teams of 15 or 20 medicinal chemists who make hundreds or thousands of modifications to the original compound to find ones that have the desired profile with higher affinity. Academia has enormous chemistry expertise, but is focused on cutting edge concepts in chemical synthesis rather than on this type of applied high throughput chemical modification and screening. The latter chemistry is often being outsourced by industry to contract chemistry labs in China or India because of the lower labor costs there (which, however, are rising rapidly). In some cases, the candidate compound is not a small molecule but rather a protein. For these biologics, proteins can typically be made in a cell culture system. However, it can take \$10-15 million to get a master cell line system to produce the grams or kilograms of protein needed for large scale testing. All told, the medicinal chemistry and manufacturing challenges of drug discovery are thus formidable obstacles to drug development in academia. Most NIH grants are not budgeted to cover this type of work as they are intended instead for the biological discovery work that has led to the target identification concept. So

partnering with industry, both for financing and manufacturing expertise, can be critical at this stage of drug development.

Safety

Another aspect often not fully appreciated in the academic community is that to test a drug in humans, one needs to have substantial compound characterization and animal-based safety data. Before safety studies can be done in animals, it is critical to show that the compound (drug) being tested: 1) can be made in a reliable and consistent way; 2) that the drug has few impurities and that those impurities it does have aren't biologically important; and 3) that the drug has a long shelf life. None of this work plays to the usual strengths of university labs. Thus to efficiently accomplish these tasks it makes sense to outsource this work to contract research firms who do this all the time. These processes cost \$350,000-\$600,000, a large sum for any single investigator. To then also show that the compound doesn't cause chromosomal defects in cells, an additional study costing approximately \$100,000 is needed. Other safety work that is generally required before going into a human trial involves *in vivo* toxicology studies, conducted in two different animal species for a relatively brief period (two to four weeks). These studies give insights into the dose-toxicity relationships and point investigators toward the tissues most likely to bear a toxic insult in humans. In an effort to assure the FDA that the first patient who gets the drug will not die of a cardiac arrhythmia (due to activation or inhibition of a critical cardiac ion channel), ion channel studies are also typically done and these can cost up to \$200,000. And depending on the target human population, additional safety studies may be required, such as respiratory or kidney safety studies. Finally, longer *in vivo* toxicology studies may be required, since the animal exposure to the drug must last at least as long as the planned length of exposure that people will be subjected to in the first-in-human trial. If the only appropriate model for the toxicology work is a primate (e.g., if the biological therapeutic only cross-reacts with primate proteins or the small molecule drug only inhibits primate enzymes), the toxicology studies' costs can quickly escalate to over \$1 million for a 4 week study. All told, the safety studies for a new drug can cost \$1-\$2 million, a sum out of reach for most NIH-sponsored investigators, and are all just a prelude to putting the drug into a human for the first time.

Dosing, Pharmacokinetics and Pharmacodynamics

If the molecule is deemed safe in the studies described above, one must now choose a dose. The dose chosen for the human study is capped at the highest (scaled to body surface area) safe dose tested in the long-term animal toxicology studies. Often that dose is then reduced by a factor of 10 to create a margin of safety. With healthy volunteers, you start with that dose, given once, in a controlled environment, and measure several physiologic parameters, such as liver enzymes, white blood cell counts, vital signs and cardiac rhythm (as global markers of how the body is reacting to the drug). If there are no serious events, you can give a slightly higher dose to the next set of healthy volunteers, leading to giving multiple doses for several days. This early dose escalation work is most often done in healthy normals, but in some circumstances the FDA will permit patients with the disorder of interest to be the first human recipients of the drug. During the initial study period, other parameters related to the drug are measured, such as drug Absorption (how it gets into the body), Distribution

(where it goes), Metabolism (how it gets modified and if those metabolites have biological activity), and Excretion (how it gets cleared by the kidney or liver) in humans. This group of studies, lumped under the rubric of ADME, is critical to the future use and dosing of any experimental agent. Academic investigators rarely have experience in the ADME disciplines. So while it's exciting to find a molecule or protein that targets a biological system, the safety and toxicology studies are pre-requisites for moving it into the clinic. The common translational medicine catchphrase, "from bench to bedside," glosses over the reality of the ramp that must be climbed to move something from that bench to anyone's bedside. Only with an extensive body of pre-clinical information in hand, can you apply for an investigational new drug (IND) approval at the FDA and actually do the human studies that test whether a drug works on the patients for whom it is intended (i.e. a phase IIa proof of concept study to show the drug leads to a desirable clinical outcome with an acceptable safety profile).

There are a few exceptions to this drug development process that are worth mentioning. A drug that has been approved for clinical trials for another indication can much more easily be re-purposed for a new disorder, since the qualifying background work has already all been done. In addition, the FDA does recognize that investigator-initiated IND's, targeted for high-risk or orphan populations, can be very valuable. In these circumstances, some abbreviation of the package needed for human studies can be permitted, but the overall path and requirements remain very similar.

Finally, we have been focusing on the academic research contributions in the earlier stages of drug discovery and development. Later stage clinical trials often are carried out by clinical research organizations (CROs), but Academic Health Centers (AHCs) also contribute in these later stages of the drug development process. The AHCs have well-characterized patient populations, electronic health records with rich patient histories, substantial funding from the CTSA awards to train translational researchers, and, most importantly, the systems biology expertise and core medical/scientific platforms that enable physician-scientists to elucidate the molecular underpinnings of human biology. With an industry or contract partner to help with the medicinal chemistry, toxicology, regulatory compliance and financing, academic centers could add greatly to the number of medicines that enter clinical practice every year. For the most part, these two types of organizations, academic and pharma/biotech have extraordinarily complementarity, but forming effective partnerships to exploit these synergies has proven remarkably difficult due to differences in goals, cultures, incentives, timelines, and perceived (and real) conflicts of interest.

The Need for Novel Academic-Industry Partnerships

As outlined in this article, taking a molecule even through just the early safety and clinical testing is laborious and expensive, and most academic centers do not have the money (nor do its investigators have the patience or expertise) to do this. Many flavors of academia-Industry relationships have been tried in the past, but most have been stymied by the differing goals, cultures and timelines of the partners(15).

On the academic side, licensing agreements can be complicated and very time consuming to negotiate, as academic institutions are wary of not receiving adequate compensation for the value of their ideas. As a result, some partnerships are never consummated due to negotiation impasses, despite the rarity of the truly lucrative academic discovery. The academy is also engaged currently in a heated discussion about how much of its effort can be legitimately focused on developing commercial products. The right to publish its results, the openness with which academic research needs to be discussed, and the role that students should or should not be playing in applied research projects are all major sticking points in academic/industry partnership discussions. Many institutional leaders also fear that some faculty will transgress on their ethical obligations to their students and patients and put the academy in an embarrassing or legally compromised position. When these issues are added to the differing cultures of academia and industry, it is perhaps more surprising that any agreements are negotiated than that so few good ones are.

Translational Medicine Group at MGH as One New Model for Academic/Industry Partnership

Despite the barriers, there is a growing opportunity for academic centers to get involved in drug development in specific ways that are suited to an academic center's strengths. Janet Woodcock, the director for the Center for Drug Evaluation and Research at the FDA recently spoke at an NIH forum on best practices for academia, government and industry relationships, and urged academic institutions to remain committed to the development of enabling technologies like animal models, new biomarkers, new ways of assessing the activity of a molecule saying, "I think industry needs to provide academia with support to get that type of work done"(16).

Groups like our own Translational Medicine Group at MGH have begun to forge some new partnerships with industry that we think can serve as models for a path forward. Unlike some of the partnership models that have come before(15), we have hired a group of former industry-based scientists with knowledge and experience of the drug development process to manage the complicated drug discovery tasks outlined above and oversee work within and outside of the academic scientific community. This managerial role helps alleviate many of the competing tensions between industry and academia's goals and expectations. For example, we have created templates for negotiating many of the most challenging obstacles that have hindered prior industry/academic collaborations, and we are hoping this will expedite future partnership discussions. Our academic project managers understand the time pressures that industry drug developers labor under because they work under those same time constraints for both our internal and external projects. In a new initiative that will be launched in coming months, we expect to work closely with a team of pharma scientists to select targets identified by our institutional scientists and then jointly create molecules that can interrogate those targets for potential therapeutic benefit. This relationship will entail scientists sharing information freely between the academy and pharma, with pre-negotiated intellectual property rights and royalties agreed from the outset to further facilitate the free flow of information. Molecules that emerge from this collaboration can be more easily channeled into the clinic in a timely manner, if appropriate, because the partnership outlines

in advance the roles and responsibilities of the academic and industry partner in advancing drugs into the clinic. At the same time that we are experimenting with new forms of partnership, we are also trying to facilitate the dialog by becoming an institutional interface for biotech/pharma discussions about a multitude of projects. The goal is to try to ensure that the accumulated experience and wisdom gained from prior interactions is not lost in future partnership negotiations.

The MGH Translational Medicine group has also created some financial incentives for industry to work with us and industry, in turn, has accepted that some return from commercially successful endeavors rightly should be returned to the academy for its contributions. While agreements of this kind are complicated to negotiate, it appears that industry has come to recognize that academia's freedom to publish is a principle that must be honored and academia has learned that an idea's practical value is frequently only realized when commercial resources and know-how are intelligently combined with a novel concept. In initiating collaborative relationships of this kind, we have worked closely within our academic community to build programs where patients can feel their safety is protected as much as possible, while still enabling discovery of novel treatments for diseases we cannot adequately treat today. This entails careful selection of clinical investigators who are free of financial conflicts and the creation of oversight boards that can monitor pharma/academy relationships. In the coming years, we expect that core technologies (constantly and rapidly changing in the academic health centers), such as whole genome sequencing, proteomics and metabolomics, will be integrated with new imaging modalities to enable better monitoring of disease prevalence and response during early stage clinical trials.

In this process, we are also trying to change cultural attitudes, convincing industry that academia can and will make a meaningful commitment to efficient, timely execution of its contracted work and convincing our academic colleagues that working with industry to make new medicines is not, in fact, making a pact with the devil, but is an important and valuable way for us to help the patients who place their trust in our care. A recent survey suggests that the attitude of academic investigators may indeed be changing. Many investigators now perceive that working with companies is a source of both valuable ideas and collaborations as well as an enabler of productivity, and 40% of researchers have initiated industry relationships that have had important non-financial scientific contributions to their work(17). It is our hypothesis that by improving academic/industry partnerships on terms that preserve the integrity and independence of the academic investigative community, we will also improve the lives of those who suffer from diseases we now cannot effectively treat.

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Table 1

Patenting ranking of US Universities (Data from <http://www.uspto.gov/go/taf/top05univ.htm> (U.S. PATENT AND TRADEMARK OFFICE, Electronic Information Products Division, Patent Technology Monitoring Branch (PTMB))).

Preliminary rank 2005	Preliminary number of patents 2005	University	Final rank in 2004	Final number of patents in 2004
1	390	Unv. of California	1	424
2	136	MIT	3	132
3	101	Cal-Tech	2	135
4	90	Stanford	6	75
4	90	Univ. of Texas	4	101
6	77	Unv. of Wisconsin	8	64
7	71	Johns Hopkins	5	94
7	71	Univ. of Michigan	7	67

This numbers concern patents from all fields, not only MedDev-related. Univ of California is always at the top because it includes all its 10 campuses (Berkeley, Davis, Irvine, Los Angeles, Merced, Riverside, San Diego, San Francisco, Santa Barbara and Santa Cruz)