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Drug Discovery in an Academic Setting: Playing to the Strengths

Donna M. Huryn*

Department of Pharmaceutical Sciences, University of Pittsburgh, 712 Salk Hall, 3501 Terrace Street, Pittsburgh, Pennsylvania 15261, United States

ABSTRACT: Drug discovery and medicinal chemistry initiatives in academia provide an opportunity to create a unique environment that is distinct from the traditional industrial model. Two characteristics of a university setting that are not usually associated with pharma are the ability to pursue high-risk projects and a depth of expertise, infrastructure, and capabilities in focused areas. Encouraging, supporting, and fostering drug discovery efforts that take advantage of these and other distinguishing characteristics of an academic setting can lead to novel and innovative therapies that might not be discovered otherwise.

Much has been written about the advent (and popularity) of drug discovery and medicinal chemistry efforts in academic settings, as well as the associated challenges.[1−3] Factors encouraging this paradigm shift include changing policy such as the Bayh−Dole Act and funding agencies' focus on translational research. The evolving environment in the pharmaceutical industry that appears to be more and more risk averse, and therefore more open to in-licensing of academic inventions and technology, is another contributor. Finally, the notable financial rewards that resulted from successful drug discovery efforts at Emory, Northwestern, University of Minnesota, and Princeton, among others, cannot be ignored.

Many of these initiatives involve attempting to recreate, in some form, a pharma model inside a university. Specific activities have included setting up sophisticated high-throughput screening capabilities and purchasing large commercial screening libraries, hiring of faculty with pharma experience, and setting up drug metabolism and pharmacokinetic (DMPK), quality assurance (QA), and current good manufacturing practices (cGMP) manufacturing facilities.[1] Academic laboratories are also adopting strategies and processes that are considered best practices in industry. The debate, described by Baell and Whitty, between academic and industrial laboratories on which types of compounds constitute viable starting points for drug discovery highlights one example of this adoption of certain industrial practices, as well as some of the barriers encountered.[4,5]

However, rather than asking how a university can mimic a drug discovery company, perhaps a better question is what unique features inherent in an academic setting can be taken advantage of, embellished, and fostered to promote drug discovery and encourage success? Rather than duplicating efforts already ongoing in commercial organizations, a university has an opportunity to offer unique, yet complementary, capabilities and an environment that fosters drug discovery that could generate innovative therapies, all the while adhering to its educational mission.

A corollary to this question is the converse—what aspects of drug discovery efforts within a university might be inconsistent with its primary goal of education and research, and can solutions be found to allow success in both? Education is one such topic for this debate: will the education and training of graduate students and postdoctoral associates, in particular organic chemistry students, change by their being embedded in a drug discovery program rather than pursuing a more traditional organic chemistry curriculum and, if so, how? Perhaps even more difficult is the question of whether a university's research mission and the widely valued expectation to freely share knowledge can be consistent with drug discovery activities that require protection of intellectual property. The academic scientific culture that values rapid and frequent publication may not be consistent with delays that can be imposed by patenting and licensing considerations. These questions are only a few of the many to be considered. A thoughtful, thorough analysis within these few pages is not possible; however, as a start, some points that address the distinguishing features in a university setting that can be brought to bear on drug discovery activities are considered here.

Without a doubt, a university has a number of unique characteristics that could contribute to making it an ideal environment where drug discovery and medicinal chemistry activities can thrive. Furthermore, some of these characteristics are quite different from a commercial drug discovery organization; highly specialized expertise in certain areas and the ability to pursue high-risk projects and approaches are just two. It would be lamentable to merely duplicate pharma-type projects and programs inside a university, rather than taking the opportunity to create a distinct environment with its own strengths and opportunities.

Practically speaking, any drug discovery effort requires a multidisciplinary coordination of activities. However, the highly specialized expertise (and associated equipment and infrastructure) in concentrated areas of biology and chemistry resident in a university setting, when combined, has the potential to lead to novel and innovative therapies in the particular areas of strength. The collective depth of expertise provides one area of distinction between academic and industrial drug discovery operations, especially when the investigators have access to the additional capabilities required for drug discovery.

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In fact, many successful academic drug and probe discovery programs benefited from the colocalization of investigators with complementary, yet highly specific, expertise. The partnership between Dennis Liotta and Raymond Schinazi that resulted in the AIDS drugs 3TC and FTC is representative of such an opportunity.[6] At the time of that work, only a handful of sites worldwide had the capabilities and infrastructure necessary to run HIV assays. One could argue that the colocalization of expertise in synthetic organic chemistry and nucleoside chemistry, the ready access to HIV assays, and the willingness of the individuals to collaborate were essential to the success of this drug discovery effort and would have been difficult to reproduce outside of Emory at that time. Another example is that of Chet Matthis and Bill Klunk at the University of Pittsburgh who developed the widely utilized β-amyloid imaging agent, PiB. Matthis's expertise in positron emission topography (PET) imaging and Klunk's in Alzheimer's disease (AD) and β-amyloid, along with their access to AD brain slices and importantly a PET imaging facility at the University of Pittsburgh, all conspired to make this project successful.[7]

This combination of specific expertise in chemistry and biology is not often found in commercial drug discovery organizations where flexibility is valued over high degrees of specialization and access to experts occurs through consulting agreements. Stopping a project due to business reasons and eliminating (or outsourcing) entire departments focusing on a particular therapeutic areas (anti-infectives come to mind) or technologies (e.g., natural products isolation and chemistry) are so common in pharma that it is no longer a surprise when it happens. In fact, the frequent changes in focus of pharma organizations that many working in industry have experienced argue against specialization and suggest that breadth of knowledge and flexibility are more important for continued employment than a depth of knowledge in a focused area.

Practically speaking though, collaborations are hard. In a commercial organization, attempts to mitigate these well-known challenges include requiring teamwork of the individual scientists working on the same project and insisting that the entire team and their management be accountable for any collective successes or failures. In addition, entire departments devoted to project management facilitate the difficult decisions about prioritization, resource allocation, and timelines, and there is a clear hierarchy for conflict resolution. Despite these efforts, conflicts still occur.

Collaborating within an academic institution can be even more challenging due to the culture that encourages and rewards individual accomplishments and where conflicting views of goals, priorities, and credit may be difficult to amicably resolve. Furthermore, a strong focus on collaborative research by a professor early in his or her career, when tenure decisions rely on the individual accomplishments of the candidate, is often considered disadvantageous. In addition, perceptions of joint projects between new faculty and those with more established laboratories might give disproportionate credit for any success to the senior collaborator, further discouraging such a relationship.

While it seems that a university should have the tools to make significant contributions to drug discovery by taking advantage of the resident expertise, a cultural change might be required to foster an environment that values the teamwork required to make these efforts successful. Certainly funding agencies are moving in this direction with the establishment of multi-Principal Investigator designations that are designed to "maximize the potential of team science efforts".[8] Additionally, internal grants offered by academic institutions often insist that the proposed research involve multiple disciplines, departments, or even schools within the University. However, it seems that a concerted effort to "match-make" scientists with complementary expertise and an interest in drug discovery, finding ways to reward collaborative research efforts, and even, perhaps, establishing a project management-type infrastructure would facilitate a university-based drug discovery program.

Another characteristic of an academic setting that distinguishes it from a commercial one is the ability to pursue high-risk projects. In this case, high-risk can refer to biological or pharmacological approaches that are not well enough validated to ensure that a molecule targeting a particular protein or pathway will be effective in a disease. Alternatively, it can refer to novel structures or chemotypes that have no precedence as drugs and do not fit the conventional "druglike" characteristic mold. Probe molecules containing nonconventional atoms and strategies targeting protein−protein interactions are a few such examples that are well suited for pursuit in academia but too risky for industry. These projects are most likely to result in innovative approaches and, therefore, should be an important component of a university's drug discovery portfolio. Because an academic environment does not require a project to be commercially successful, these high-risk projects are a perfect opportunity for academia to complement the activities ongoing in pharma. However, by necessity, high-risk projects require longer time frames than typically adhered to in commercial settings. The academic culture and environment along with the nature of these projects makes pharma timelines unrealistic for those high-risk projects.

There is no doubt that academia can play an important role in drug discovery. However, instead of establishing a small pharmaceutical company inside a university, a better model might be to develop an environment that supports, enables, and encourages drug discovery and medicinal chemistry projects that take advantage of the unique characteristics of academia. By valuing and fostering collaborative research projects between experts with complementary skills and providing the necessary infrastructure, an academic drug discovery effort could make significant impact in focused disease areas. Furthermore, by encouraging and supporting high-risk projects and allowing realistic timeframes for their execution, universities and funding agencies can play an important role in bringing innovative therapies to patients that would not be available otherwise.

AUTHOR INFORMATION

Corresponding Author

*E-mail: Huryn@pitt.edu.

Notes

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(8) For a description of multi-PI leadership, see National Institutes of Health. Office of Extramural Research: Grants and Funding (http://grants.nih.gov/grants/multi_PI/faq.htm#2952) (accessed January 4, 2013).