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Valley of death: A proposal to build a “translational bridge” for the next generation

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Abstract

There is a great need for novel drug discovery for major mental illnesses, but multiple levels of challenges exist in both academia and industry, spanning from scientific understanding and institutional infrastructure to business risk and feasibility. The “valley of death,” the large gap between basic scientific research and translation to novel therapeutics, underscores the need to restructure education and academic research to cultivate the fertile interface between academia and industry. In this opinion piece, we propose strategies to educate young trainees in the process of drug discovery and development, and prepare them for careers across this spectrum. In addition, we describe a research framework that considers the disease trajectory and underlying biology of mental disorders, which will help to address the core pathophysiology in novel treatments, and may even allow early detection and intervention. We hope that these changes will increase understanding among academia, industry, and government, which will ultimately improve the diagnosis, prognosis and treatment of mental disorders.

Keywords

Drug development; drug discovery; translational research; valley of death; psychiatric disorders; dimensional approach; education

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Introduction

Major mental illnesses remain significant medical and financial burdens on our society. For example, statistics from the National Institute of Mental Health (NIMH) highlight that there is an annual expenditure of nearly \$58 billion in the United States on mental health (National Institute of Mental Health, 2006). Since the introduction of chlorpromazine in 1952, current medications in psychiatry still stem from serendipitous findings, are limited in efficacy, and cause substantial side effects (Miyamoto et al., 2012).

While the need to invest in novel drug discovery for psychiatric disorders is clear, the pharmaceutical industry has been suffering significant business challenges (Choi et al., 2014). Often referred to as the “valley of death,” there is a large gap between basic scientific research and translation to novel therapeutics (Fig. 1). With an estimated cost of \$1–2 billion to develop a new drug, development time lines of 15 to 20 years, and a failure rate of approximately 95%, many pharmaceutical companies have been forced to downsize their operations, especially in early drug discovery (Slusher et al., 2013). This grim outlook is particularly true for neurological and psychiatric disorders, as the failure rate for experimental drugs for the central nervous system (CNS) is significantly higher than that for other disease areas (Slusher et al., 2013). Indeed, in just the past 5 years, there has been over 50% decline in the number of CNS-focused discovery and development programs in the pharmaceutical industry (Choi et al., 2014). Meanwhile, many academic laboratories do not have sufficient knowledge or infrastructure to translate their findings into commercial or clinical applications.

These problems underscore the need for increased efforts in academic translational research and drug discovery, and making stronger ties with industry. As the interface between industry and academia is potentially fertile ground for initiating discovery for new treatments, it is necessary to narrow the knowledge gap between academic research and translation of findings into novel treatments. In this article, we propose an infrastructure to educate young people in the process of drug discovery and development, encourage translational research that appreciates the underlying biology of mental disorders, and prepare them for careers across academia, industry and government.

Education: institutional level in academia

How can such training be accomplished? It is important to educate young people in the entire process of developing new drugs. This process encompasses target identification and validation, high-throughput screening, medicinal chemistry, pharmacokinetics and pharmacodynamics analyses, assessment of animal models, preclinical safety assessment and clinical trials, and regulatory approval from the Food and Drug Administration (FDA).

In addition to didactic lectures, immersion in successful cases of drug development, such as for Prozac (Wong et al., 2005) and Clozaril (Crilly, 2007), will help to provide systematic perspectives from preclinical discovery to translational, clinical and regulatory processes. In one example, the Johns Hopkins Drug Discovery Program has recently started teaching a graduate course on drug discovery case studies with lecturers from the pharmaceutical

industry (<https://drugdiscovery.jhu.edu/our-courses/drug-discovery-case-studies/>). In addition to these topics, trainees should be educated in medical statistics and the Responsible Conduct of Research (RCR) (Anderson, 2016, Bell, 2015), which will enhance their ability to perform and interpret translational research. It is important to expose young people to a wide variety of translational career options, particularly those outside academia, including government and industry positions. To help them focus their training towards their future career goals, mentors from these various sectors should help trainees to establish individual development plans (IDPs) from early stages of training. The IDP has become an important concept in academic education (NIGMS, 2011), and is particularly important when fostering young trainees at the interface of academia and industry.

It is also critical to support young investigators during the initial steps of turning academic findings into commercial partnerships or new companies. For example, at what stage can an idea be patented, and how does one determine the market opportunity for a particular product? Many academic and business “incubators” and “accelerators” have emerged over the past decade to guide young researchers and entrepreneurs in the early stages of commercialization (Soetanto, 2016). The trainees are provided with the skills and knowledge of intellectual property management, considerations of whether to form a company or license the intellectual property to a larger company, logistics of incorporation, hiring management talent, obtaining the appropriate type of funding at each stage, and writing a business plan, including assessment of the potential market.

Education: communication skills and networking

This concept differs from traditional M.D./Ph.D. programs, in which medical and research training are simultaneously but separately administered. Instead, we emphasize the continuum from research to drug development. Early efforts in this endeavor include workshops that bring together research and clinical trainees to discuss a topic together from each of their perspectives, such as the “Mind the Gap” workshops at Johns Hopkins University (Posporelis et al., 2014, Sawa, 2014). The goal of such training is to send young people into all sectors involved in translational research and drug discovery and development. The strategy of this approach infrastructure is to build ties among academic, industry and government experts by helping to understand their complementary roles, and facilitate productive collaborations to ultimately improve the diagnosis, prognosis and treatment of mental disorders.

In attempt to build community amongst the growing number of academic drug discovery centers, in 2012, leaders from several centers formed the Academic Drug Discovery Consortium (ADDC) (<http://addconsortium.org/>) (Slusher et al., 2013). Since then, this community has greatly expanded to include over 140 centers and 1,500 members worldwide. In addition to an interactive network, this consortium provides opportunities for collaborations with pharmaceutical companies and other service providers relevant to translational research, as well as events, including an annual conference, educational materials and job postings to foster translational research and drug discovery in academia. Another effort being implemented is a neurotherapeutics course administered by the National Institute of Neurological Disease and Stroke (NINDS) (<http://>

www.neurotherapeuticscourse.org/). This course is taught by experts from industry, government and academia (with backgrounds in industry) to individuals with drug discovery ideas in order to educate them in every aspect of the drug development process.

Education: international level

Other developed countries have also initiated broad translational efforts. For example, in Japan, the Department of Drug Discovery Medicine has just been launched at the Medical Innovation Center at Kyoto University (<http://www.mic.med.kyoto-u.ac.jp/dddm/>). Like the above examples, this program aims to cultivate young academic researchers who will enhance all aspects of drug discovery and development. Starting with a medical science education similar to that in a medical school, trainees perform translational research, learn every aspect of drug development, and experience internships at pharmaceutical companies and regulatory agencies. This program is funded by an alliance of pharmaceutical companies, and represents a true collaboration between academia and industry. In future, such arrangements may involve fund-matching from academic institutions, providing additional incentives.

Another approach in which industry and academia are collaborating to foster the next generation of translational researchers has been developed in Denmark. In this country, Industrial Ph.D. programs, managed by the Innovation Fund Denmark and supported by the Danish government, allow young trainees to conduct translational research in the pharmaceutical industry guided by both academic and industry mentors. Industrial Ph.D. students are contracted into a three-year research collaboration between a private industrial partner and an academic institution, after which students receive a Ph.D. from the university. The Ph.D. students push the frontier of academic knowledge while solving industrially relevant research problems. In addition to the Industrial Ph.D. programs in Denmark, an educational Master's program in Medicine with Industrial Specialization allow young researchers to kick start a career within drug discovery and development at the early stages of their career path. The Master's program is composed of three health-related profiles covering the different stages of pharmaceutical drug development: Biomedicine, Translational Medicine and Medical Market Access. Linking medical knowledge with clinical and industrial skills provide students with a strong research profile, which is highly essential for the future progress in translational research.

Research framework

Academic institutions are increasingly undertaking translational research. In the field of psychiatry, these efforts have been challenged by a lack of understanding of the pathophysiology underlying many mental disorders. A contributing factor to this problem may be, at least in part, the traditional, categorical approach to diagnosing mental disorders, such as the Diagnostic and Statistical Manual of Mental Disorders (DSM) (American Psychiatric Association, 2013). The DSM largely describes mental disorders as cross-sectional clusters of symptoms, prioritizing clinical reliability over biological validity (American Psychiatric Association, 2013). Thus, there is insufficient attention to the disease trajectory and underlying biology. This approach has posed a challenge to the

neurobiological understanding of mental illnesses, leading to treatments that tend to target symptoms rather than the core pathophysiology.

To address this challenge, the NIMH has proposed the Research Domain Criteria (RDoC) (Insel et al., 2010). This initiative dissects mental disorders according to a matrix of dimensions or phenotypes with defined biological etiology, and provides a scaffold for research to understand disease from genetic and molecular to behavioral levels (Casey et al., 2014). It is particularly useful when translating comparable phenotypes between animal models and humans during research as well as clinical trials. In addition, paying attention to the developmental trajectory may allow early detection and intervention in patients, as with other physical disorders such as cancer and hypertension. While RDoC provides a helpful, biology-based clinical framework, its validity and utility are actively under debate (Cuthbert, 2014). Some criticisms are that the selection of dimensions is arbitrary, and that the domain constructs and sub-constructs for each dimension are too detailed.

The FDA will play a key role in undertaking the challenges specific to drug development for brain disorders. While the FDA primarily focuses on indications according to the DSM, it is beginning to recognize indications like cognitive impairment for schizophrenia (Yum et al., 2016), which are not included in the DSM-5, and is moving towards dimensional approaches as in other disease areas (Cuthbert and Insel, 2013). Furthermore, collaborations between academia and industry can contribute to drug development at the regulatory level, not just to identify potential drug targets. For example, the Dominantly Inherited Alzheimer Network (DIAN) and Alzheimer's Disease Neuroimaging Initiative (ADNI) are performing brain imaging studies and identifying biomarkers to eventually test in clinical trials. These initiatives are being conducted international academic sites, and are sponsored by pharmaceutical companies, foundations, and the NIH. Such collaborations will be key to successful drug development for brain disorders.

Future perspectives

This article proposes an innovative infrastructure for education and research in an academic setting to bridge the gap between research and clinical applications. Another challenge to the development of novel treatments is the very high failure rate in CNS-related drug development (Arrowsmith and Miller, 2013), which has led the pharmaceutical industry to take their focus away from mental disorders. To minimize such risks, drug companies are starting to collaborate with each other and with academic institutions by forming consortia for translational research. For example, companies are collaborating with leading academic institutions that have clinical resources, such as brain collections and data analysis capabilities to study molecular signatures associated with disease in autopsied brains, which may provide key information for drug discovery (Schubert CR, 2015). A similar consortium exists to share postmortem brains among multiple industrial partners and the University of Pennsylvania, University of Pittsburgh, Mount Sinai Hospital and NIMH (CommonMind Consortium). In Europe, the Novel Methods leading to New Medications in Depression and Schizophrenia (NEWMEDS) Consortium is a public-private partnership among several academic institutions and industrial partners to develop novel animal models to discover improved drugs (<http://www.newmeds-europe.com/>). Finally, there are numerous “pre-

competitive” collaborations between pharmaceutical companies – that is, competitors sharing and working together at early stages of research (Gastfriend and Lee, 2015).

In summary, providing a supportive and resourceful environment to prepare trainees for the full range of careers outside the purely academic track is paramount for the future success of translational medicine. In addition to exposing trainees to these options, deliberate training in necessary skills, such as project management and communication with a variety of audiences (Janero, 2013), will prepare them to succeed in such positions. Early immersion in the increasing trend of collaborations among various sectors of drug development and patient care will hopefully bridge these different cultures, and inspire career choices for the next generation.

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Highlights

- There is a dire need to invest in novel drug discovery for psychiatric disorders.
- “Valley of death” between academia and industry is exacerbated for brain disorders.
- We propose an academic infrastructure to teach drug discovery and development.
- We propose a framework for academic institutions to perform translational research.

Figure 1.

We propose a novel infrastructure for education and research to overcome the “valley of death,” the large gap between basic scientific research and translation to novel therapeutics, and cultivate fertile ground between academia and industry