A new model for drug discovery – meeting our societal obligation

Ross L. Stein, Laboratory for Drug Discovery in Neurodegeneration, Harvard Center for Neurodegeneration and Repair, 65 Landsdowne Street, Fourth Floor, Cambridge, MA 02139, USA; e-mail: rstein@rics.bwh.harvard.edu

Drug discovery is a complex and costly endeavor, requiring multidisciplinary know-how, interdisciplinary collaboration, tenacity and a bit of luck. For these reasons, the search for new chemical agents to treat human disease has traditionally been undertaken only within the walls of industry. In broad terms, the pharmaceutical industry has been remarkably successful at this. The success stories include antibiotics for the treatment of bacterial infections, angiotensin-converting enzyme inhibitors for hypertension, HMG-CoA reductase inhibitors to reduce serum cholesterol and heart disease, selective inhibitors of cyclo-oxygenase for inflammatory disease…and the list goes on. Although the industry might ultimately be successful where it focuses its attention, it generally focuses only on those areas that are allowed by corporate financial realities. Sadly, this means that diseases that effect only small populations of patients could go untreated. As a society, we should not be content with this situation and must make a priority of the development of new models that will enable and encourage drug discovery in disease areas that are neglected by the industry. Here, one model is described that has been established to find treatments for neurodegenerative diseases.

A community of neuroscientists

The Laboratory for Drug Discovery in Neurodegeneration (LDDN) was established in the summer of 2001 as one of the five cores of the Harvard Center for Neurodegeneration and Repair (HCNR; http://hcnr.med.harvard.edu/). Also launched in 2001, the HCNR is a response to the urgent and growing challenge that is posed by neurodegenerative disease. To meet this challenge, the HCNR was created to draw together a decentralized community of more than 500 neuroscience researchers that are associated with Harvard Medical School or its six affiliated teaching hospitals. Five core resources are at the heart of the HCNR: Translational Neurology Research, Brain Imaging, Molecular Pathology, Drug Discovery, and Bioinformatics. Each of these has state-of-the-art facilities that are available to the Harvard community. Importantly, the resources of the various cores extend beyond simple access to equipment and include a foundation of technical expertise, intellectual support and a venue for collaborative research. The HCNR gives many researchers their first exposure to advanced specialized facilities, opening up many new research opportunities.

As one of the core resources of the HCNR, the LDDN was founded on four overarching principles or objectives. First, the primary mandate of the LDDN is to discover chemical agents that can serve as lead structures in the development of therapeutics to treat neurodegenerative disease. Second, to achieve this goal, the LDDN will provide the academic community with access to the sorts of technologies and expertise in the areas of assay development, HTS and medicinal chemistry that are generally available only in the pharmaceutical industry. Third, despite similarities in technology and methodological approaches that are shared by the LDDN and the pharmaceutical industry, the LDDN was created not to compete with but to complement the drug discovery activities of industry by concentrating on disease targets to which the industry can pay little attention because of the small patient populations of these diseases. Finally, the LDDN was founded on a philosophy of dynamic and open collaboration, where drug discovery projects are advanced by members of neuroscience laboratories working closely with the scientific staff of the LDDN.

Experiments in the science, sociology and economics of drug discovery

The LDDN is an experiment in progress and this experiment is being conducted in three arenas: the scientific, the sociologic and the economic.

The scientific experiment in which we are engaged is of course not unique to the LDDN but is also being conducted by all biopharmaceutical laboratories: the search for novel agents to treat disease. At the LDDN, although our principle goal is to discover chemical agents that can serve as lead structures for the development of new therapeutics, we are also interested in finding compounds that can be used to probe the cellular and biochemical mechanisms of neurodegenerative diseases. To discover both classes of compound, we screen large collections of drug-like molecules for their ability to modulate the biological activity of

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molecular and cellular processes that are thought to have causative roles in these disorders. Optimization of these compounds to enhance therapeutically relevant properties is achieved by focused programs of medicinal chemistry.

Sociologically, we are asking if these scientific goals can be achieved in an academic atmosphere. Can we successfully marry the directed focus and goal orientation of the industrial culture with the academic culture that stresses no-holds-barred creativity? One unique aspect of the LDDN that will help to ensure a positive outcome to this experiment is its staffing, which comprises a group of permanent specialists in assay development, HTS, informatics and medicinal chemistry, and a group of post-doctoral fellows that originate from within the Harvard neuroscience community. This whole operation is led by a management team of 'hired guns' brought in from the biotech and pharmaceutical industries. It is this staffing that enables us to sustain the strong collaborations with the various laboratories of Harvard Medical School that is the key to our success.

The diseases on which the LDDN is focusing include amyotrophic lateral sclerosis (ALS or Lou Gehrig's disease), Huntington's disease, Parkinson's disease and multiple sclerosis (MS). Because of their relatively small patient populations, all pose economic challenges in the near term, effecting our ability to raise funds to sustain our research activities and, in the long term, effecting our future ability to develop and, ultimately, market drugs for their treatment. Of course, these are the same challenges that any drug discovery organization will encounter if they work on less common diseases. These challenges must be met by innovative partnerships and funding arrangements with big pharma and the financial community (see below).

Drug discovery at the LDDN

Drug discovery programs at the LDDN proceed down a path that starts with the initiation of a collaboration with a Harvard neuroscience laboratory. This collaboration generally centers around a post-doctoral student's recent discoveries that hold promise for being the foundation on which to build a discovery project. The staff of the LDDN works closely with the student to transform their discovery into a robust assay that can stand up to the rigors and demands of HTS. As the project progresses from the stage of assay development to miniaturization, automation and validation, responsibility gradually migrates from the student to the Leads Discovery group of the LDDN and, finally, the screen is launched in fully automated form. Any 'hits' that emerge from the screen, providing they pass various secondary criteria centering around potency, selectivity and mechanism-of-action, become the focus of LDDN's Medicinal Chemistry group, which optimizes these compounds for a variety of biological and pharmaceutical properties.

The discoveries of any group that uses screening as its principle tool are only as good as its chemical library. At the LDDN, we are sceptical of the need to engage in ultra-HTS, where many hundreds of thousands of compounds are tested. The redundancy of chemical motifs in these massive libraries suggests that their use might not be required to discover chemically and biologically interesting 'hits' [1]. Instead, we have adopted the strategy of testing a small but highly diverse collection. Our goal is to never test more than about 100,000 compounds that comprise drug-like synthetics adhering to Lipinski's 'rule-of-five' [2], natural products, tetrapeptides, compounds from university synthetic chemistry laboratories and FDA-approved drugs.

These compounds are tested in numerous assays. At any given time, the LDDN has a steady-state of about 10 on-going projects in five disease areas: ALS, Huntington's disease, MS, Parkinson's disease and Alzheimer's disease. Because the molecular causes of none of these diseases is known in as much detail as we would like, it is our goal to screen as many targets as possible. We are currently running assays to discover a variety of molecular types: inhibitors and activators of various enzymes, agonists and antagonists of receptors, modulators of protein polymerization and aggregation, and compounds that effect the expression of key proteins in neuronal cells. Specific examples of these include: activators of ubiquitin C-terminal hydrolase L-1 for Parkinson's disease [3]; activators of insulin degrading enzyme for Alzheimer's disease [4]; antagonists of the specific major histocompatibility complex (MHC) class II molecule HLA-DR2 (human leukocyte antigen DR2) for MS [5]; and inhibition of huntingtin polymerization for Huntington's disease [6].

Once discoveries are made, it is our intellectual property philosophy to patent and publish them aggressively. The former is clearly needed to protect our discoveries for future licensing and development activities, while the latter is required by our commitment to the training and career goals of the post-doctoral students with whom we collaborate.

Paths to the development and commercialization of discoveries

The discovery and characterization of a screening hit and its optimization by medicinal chemistry are, of course, only the first steps along the long and arduous road that runs from these early stage activities through clinical trials to a new therapeutic product. A crucial component of this process is the pharmacological characterization of our lead compounds. At the LDDN, we made the strategic decision not to do the pharmacology in-house, but rather through a combination of outsourcing

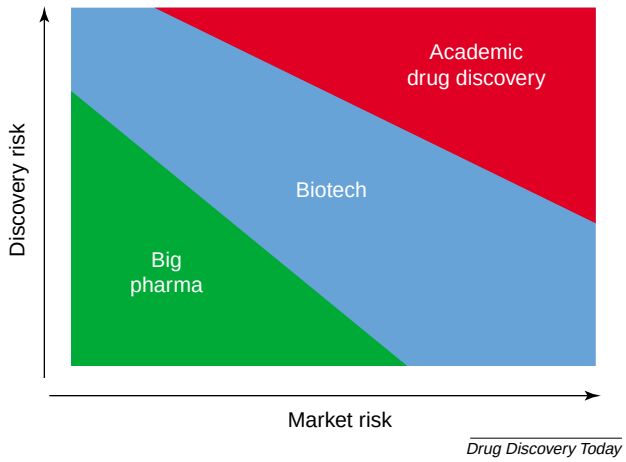

Figure 1. Coverage of the discovery and market risk-space by drug discovery organizations. Although big pharma rightfully must occupy low risk territory, the onus is on biotech and academia to ensure complete coverage of this space.

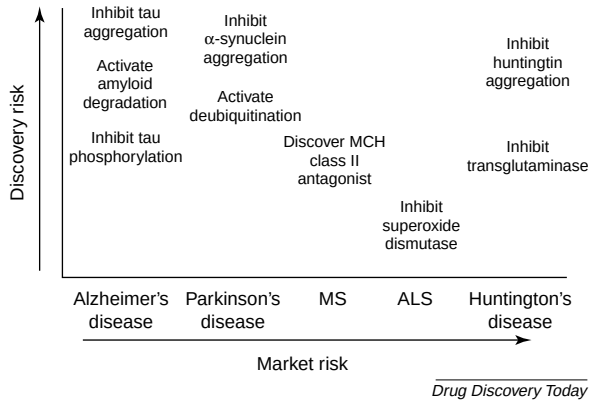

Figure 2. Coverage of the discovery and market risk-space in neurodegenerative disease discovery by the Laboratory for Drug Discovery in Neurodegeneration (LDDN). The LDDN has chosen to principally work in high-risk disease areas and on high-risk targets. Some of the molecular targets that are worked on are indicated, as well as their position in the discovery/market risk-space. Abbreviation: MHC; major histocompatibility complex.

and collaborations with colleagues within the neuroscience community.

To advance a chemical series still further, after it has achieved status as active in appropriate animal models of disease, we will seek collaborations, partnerships and licensing arrangements with biotech and major pharmaceutical companies. Although there are, of course, many ways to do this, some creativity might be needed given our status as a non-profit organization. Clearly, the option will remain to spin-out a company if an LDDN discovery warrants it and the venture capital climate allows it. In the end, the success of the LDDN will be its ability to add significant value to its early stage discoveries to attract industrial partners and investors that can help develop and commercialize its discoveries.

Unique aspects set the LDDN apart

From the preceding discussion it is clear that the LDDN resembles a small bio-pharmaceutical company in both its organization and the methods and technologies it employs. However, it does differ in several significant ways:

- The LDDN focuses on disease areas that are typically neglected by industry because of their small patient populations.
- The LDDN often works on molecular targets and discovery strategies that are considered high-risk and unattractive. For example, several of our current projects involve searching for activators of enzymes that might have a causative role in neurodegenerative diseases, as well as compounds that can interfere with the aggregation of proteins whose polymerization is disease modulating.
- Biology comes into the LDDN via post-doctoral fellows.
- The crucial infrastructure of basic biological and medical research expertise (e.g. cell-based assays and animal models) is provided for the projects from the 'home' laboratories of the post-doctoral students and the Harvard Medical School community at large.

These differences reflect a commitment by the LDDN to develop a discovery strategy and a product portfolio that will compliment, but not compete with, the activities of the industry. As described in more detail below, this strategy serves to spread the scientific and market risk of the drug discovery process, and help to ensure full coverage of even rare diseases.

Balancing risk in drug discovery – a new paradigm that incorporates academic laboratories

By its very nature, drug discovery is a risky business. These risks exist for a drug discovery organization in two principle arenas: (1) the market place, where risk increases with the rarity of the disease that is being attacked, and (2) the laboratory, where discovery risk increases in proportion to the difficulty and the uniqueness of the molecular target or discovery approach. Despite these formidable risks, we – as biopharmaceutical professionals – have a societal obligation to ensure complete coverage of the entire discovery/market risk-space. How are we to meet this challenge?

First, we must recognize and build on the fact that certain organizations are better suited to assume greater risk. This concept is illustrated in Fig. 1 where we see that large pharmaceutical companies, with their urgent financial imperative to pursue the next block-buster, are in no real position to take much risk, either in the choice of disease or molecular target. Therefore, big pharma must occupy low risk territory.

As risk increases, with greater attention being paid to rare diseases and difficult and uncertain molecular targets and strategies, so must the involvement of biotech and academic laboratories, which are less risk-adverse by their natures. This seems especially true for NIH-funded academic laboratories whose mandate must be to provide the taxpayer some measure of return on their tax dollars in the form of drug discovery research in diseases areas that are neglected by large and small pharmaceutical companies.

In the specific case of neurodegenerative disease, market risk increases from Alzheimer's disease to Parkinson's disease to Huntington's disease, while discovery risk increases from tried-and-true enzyme inhibition programs, such as those exemplified here by β- and γ-secretase inhibition, to inhibition of the protein–protein interactions that control the polymerization of proteins such as α-synuclein, tau and huntingtin. At the LDDN, we have chosen to aim at high-risk targets when we are focusing on a low-risk disease and, likewise, to aim at lower risk targets when we focus on a high risk disease (Fig. 2). With such a strategy, it is our hope to complement the discovery activities of industry in the arena of neurodegenerative disease.

To ensure the success of this new strategy, the pharmaceutical industry, financial community and government must work together with academics to develop innovative ways to fund organizations that are involved in high-risk drug discovery efforts. Only in this way will our society be able to meet the urgent needs of patients suffering from rare diseases.

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Letting biology do the work ▼

Cancer drug development is in transition. We are moving out of an empirical era of blunderbuss cytotoxics used at their most tolerable toxic dose to a far more sophisticated molecular-mechanism-based approach to cancer. The drugs are already there in the laboratory – over a 1000 such projects are recorded as being in the preclinical phase. They target cell-cycle control proteins, apoptosis systems, cell invasion and metastasis, angiogenesis, signal transduction, inflammation and differentiation. But there is a missing link – how best to measure their effect, which was the subject of a recent review [1].

Biomarkers that reliably quantify the effect of a drug on its molecular target are now becoming essential. The high cost of clinical development has made the cost of identifying a relevant marker before going on to clinical testing seem like peanuts. Translational research – bridging the gap between discovery and clinical operations – is here to stay. Furthermore, such biomarkers might also act as surrogate endpoints of successful treatment for cancer, which is ultimately judged by the effect of a therapy on long-term survival. Two other tools are also being intensively investigated. Functional imaging using magnetic resonance (MRI) and positron emission tomography (PET) allow us to follow in real time the subtle effects of a drug on cellular biochemistry whilst gleaning detailed anatomical information to search for differential effects between normal tissues and tumour. The fourth tool is the molecular subclassification of disease, which divides apparently homogenous groups of patients into new categories with different natural histories and likely responses to therapy.

Personalised medicine for cancer is the final goal. Currently the technologies used are holistic, searching for needles in

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