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Editorial

Neurological drug development: A guide for a start-up biotech

Editorial foreword

I started my virtual biotech venture in 2008, following an entrepreneurial seizure, after several post-ictal entrepreneurial events over a lifetime in the pharmaceutical/biotech industry.

For me, it was a game-changer, as I could see, like many others the challenges and turmoil of restructuring and diversification faced by my industry in the global economic downturn. With hindsight, perhaps 2008 was not a good time to start a business venture, but when is a good time? Starting a business is a high-risk venture in the best of economic times.

So when Dr. Erwan Bezard and I spoke earlier this year about our encounters mentoring young academic scientists and biotech start-up companies, it was clear to both of us that these young entrepreneurs, eager to spin-out of academia with their inventions and patents to form a start-up company, were desperately seeking knowledge and guidance that was not always readily available to them within academia.

So where does the young academic entrepreneur seek the knowledge and guidance to form a start-up business venture?

To address this question, we decided to produce a 'Special Edition of Neurobiology of Disease' that goes some way to answer the scientific operational and business challenges faced by an academic start-up biotech company.

We enlisted the help of leading luminaries in the various disciples associated with research and development (R&D) of pharmaceutical products. We know this Special Edition is by no means an encyclopedia of drug discovery and R&D knowledge, only an introduction and personal insight to some of the basic principles, challenges, pit-falls and decision making processes that can be applied to many other areas of R&D. In this case, the focus is on the processes involved in developing small molecular weight pharmaceutical products, but we also take a glimpse into the future and the challenges and opportunities facing innovative technologies like stem cell research.

To introduce the theme of this 'Special Edition', Professors David Nutt and Jim Attridge give an excellent 'big-picture' view of some of the geographical and global challenges facing a young start-up company in their review entitled, "CNS Drug Development in Europe — Past Progress and Future Challenges." Always strong advocates for neuroscience research and development, Professor's Nutt and Attridge passionately argue the need to build on the success of the past, not destroy decades of neuroscience innovation as seen by the recent closure of so many pharmaceutical CNS research units. It is clear to all, that neuroscience research attrition rates are no worse than many other therapeutic targets (see Fig. 1), so why have droves of senior management decided to run away from this area? One could argue 'The Lemming Mentality,' as risk adverse strategies rule the day.

Their authoritative review is thought provoking, instructive and inspiring for a start-up company, intending to develop neurological drugs in understanding the risks and rewards, market dynamics and the changing patterns of clinical practice needed to grow a successful and sustainable business model. The authors champion the need for therapeutic innovation for the debilitating effects of depression and anxiety where big pharma has closed the door. Yet, one has only to visit a primary care physician and ask which neurological disorder (or disorder) do they see a significant increase in their practice. Despite the plethora of drugs used in clinical practice to inadequately control these disorders and to listen to the physician's concerns on the need for new treatments of depression and anxiety, almost all big pharmas have 'deprioritized' neuroscience. Thankfully, new initiatives are emerging to fill the gap through EU and US NIMH biopharmaceutical technology initiatives along with policy reforms, to aid young start-up companies to open-wide the neuroscience door again for a more integrative approach for developing new innovative therapies for these and other dreadful neurological disorders.

Neuromolecular transductional research

So which area of research should the young start-up embark on? The answer is picking the right target! One such area of research and discovery that continues to be a rich source of innovative treatments for neurological disorders that has spawned numerous start-up and virtual companies is G-Protein Coupled Receptor (GPCR) research. The universe of G protein-coupled receptors (GPCRs) is largely unexplored providing promising new strategies with the potential for developing novel treatments for a variety of central nervous system (CNS) disorders. Start-ups looking for new frontiers away from the traditional drug discovery efforts targeting GPCRs, need not look further than the excellent, authoritative review by Hilary Highfield Nickols and Jeffrey Conn who takes the reader on a journey of discovery that opens the world of allosteric modulators that target a site separate from the natural ligand orthosteric site, that identifies novel ways to modulate receptor function. These allosteric agents can either potentiate (positive allosteric modulator — PAM) or inhibit (negative allosteric modulator — NAM) the receptor response and often provide much greater subtype selectivity than do orthosteric ligands for the same receptors. Experimental evidence has revealed more nuanced pharmacological modes of action of allosteric modulators, with some PAMs showing allosteric agonism in combination with positive allosteric modulation in response to endogenous ligand (ago-potentiators) as well as "bitopic" ligands that interact with both the allosteric and orthosteric sites. Novel drugs targeting the allosteric sites have the potential for increased drug selectivity and decreased adverse side effects. The authors present promising evidence demonstrating the potential utility of a number of allosteric modulators of GPCRs (e.g., mGlu1, 2/3,4,5,7,8 and M1, M4 &M5) in multiple CNS disorders, including neurodegenerative diseases such as Alzheimer's disease, Parkinson's disease, and Huntington's disease, as well as psychiatric or neurobehavioral diseases such as anxiety,

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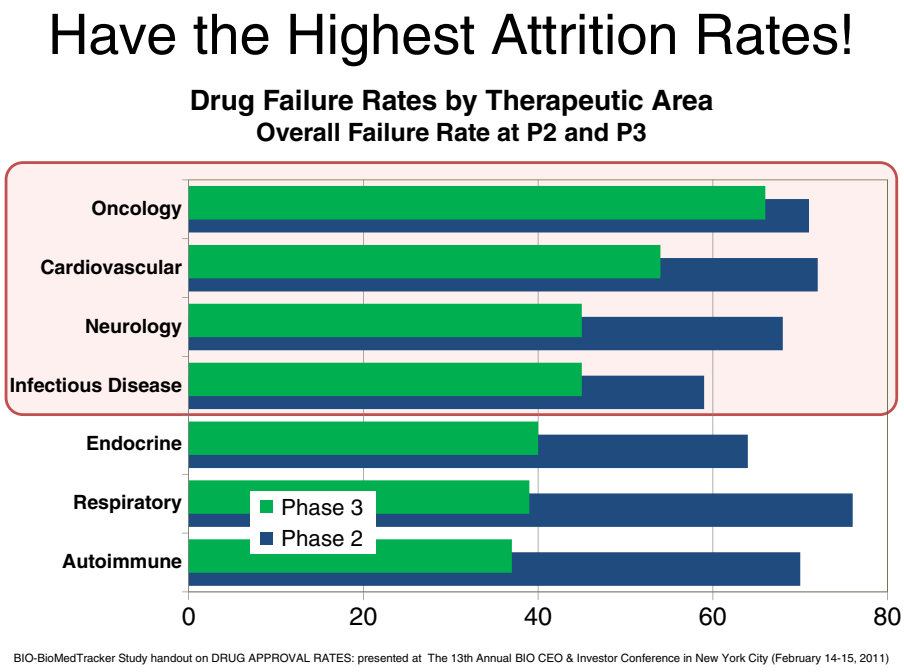

Fig. 1.

schizophrenia, and addiction. In their review the authors lead the reader through an allosteric galaxy within the neuromolecular transductional universe of GPCR research, which we are only now beginning to explore.

Neurological in vivo studies

Start-ups based on molecular/genetic innovations, are more than likely at some stage to perform in vivo studies. One has to only attend a major CNS scientific meeting, like the ACNP, Society of Neuroscience and British Neuroscience Association meetings to hear how molecular biology researchers have gone full circle from genotypes to phenotype knock-out and knock-in animals of neurological disorders and evaluating them in animal "CNS" models that have stood the test of time, which some have argued bear no relationship to the neuropathological disease under investigation. It goes without saying, that most CNS compound testing is performed on naïve, non-pathologically anxious/stressed, male animals, which is a potential limitation to current strategies since these animals may not reflect the neurological disorder. Yet we continue to use in vivo tests to discover and develop new treatments for various neurological diseases?

In their review, Andrews, Papakosta and Barnes focus on anxiety disorders and critique the relevance of the many behavior models used to model anxiety disorders and discuss the many strategies now employed to choose the "right" rodent animal models to evaluate novel compounds.

The authors conclude with a short perspective on where the field is moving to improve our understanding and successful translation of novel targets into new therapies in the clinic and give useful links to various guides on experimental necessities, reporting standards, animal husbandry and experimental design. They strongly recommend the reader to consult the ARRIVE guidelines published by Kilkenny et al. (2010). The ARRIVE guidelines represent the current experimental standards that young start-up companies embarking on in vivo work to advance their scientific innovation need to fully embrace. The guidelines make excellent recommendations on how to improve reporting standards for in vivo experimental work and when implemented facilitate the design of a comprehensive and well-controlled experiment. It is this area of experimental design and execution that will be subject to due diligence in reviewing the relevance of the discovery to a disease pathology and valuation of the innovation to the start-up company.

Translational neurological imaging research

In their comprehensive review on Positron Emission Tomography (PET) drug imaging, Hargreaves and Rabiner discuss the application of new technology biomarkers to aid the progress of drug development and regulatory approval. This is of critical importance today, where it is estimated that over 30% of drug failures in late stage clinical trials are due to lack of efficacy. Regulatory and funding agencies see this key technology in testing the mechanism of action and optimizing target engagement and it is rapidly becoming standard practice in neuroscience research. The authors discuss the challenges to mitigate risk of early clinical efficacy failure for CNS drugs and the need to differentiate new drug candidates from currently available drugs. They argue that novel mechanisms carry greater inherent risk of failure as they generally lack clinical validation and they present strategies for early decision-making and cost effective drug development. They argue that deferring proof-of-concept on poorly validated targets to late stage clinical trials is financially unsustainable. However, the cost of such studies early on in a clinical program are high and as such academic partnerships with University PET centers may be the answer to building this technology to a research/business plan. The FDA provides draft guidance on Investigational New Drug applications for Positron Emission Tomography (PET) Drugs Imaging and is one of a number of regulatory guidelines that emphasize the increasing importance regulatory authorities attach to early detection and confirmation of whether drugs reach their targets. Thus, using translational PET imaging markers for target engagement is fast becoming central to successful clinical proof-of-concept testing and has become an important feature of most neuropsychiatric drug development programs. The authors also suggest that CNS PET imaging can also play an important role in the clinical investigation of the neuropharmacological basis of psychiatric disease and the optimization of drug therapy and present case studies. This notion was further supported in a recent publication by C. L. McGrath and colleagues in JAMA Psychiatry 2013, (June 13th,Vol: 498, pp 2013). In this study, using PET scans to measure metabolic activity in various brain regions of people with untreated depression the authors showed a clear-cut below