Neuropsychopharmacology REVIEWS (2012) 37, 278–280

COMMENTARY

Drug Discovery and Development

New Era for Novel CNS Drug Development

William Z Potter*[1]

[1]*Philadelphia, PA, USA.*

Neuropsychopharmacology Reviews (2012) **37,** 278–280; doi:10.1038/npp.2011.186

Novel CNS drug development will become a societal priority given continued advances in the treatment and prevention of infections, cardiovascular disease, and cancers. Physical health in one's 90s is of questionable value given a >50% risk of dementia. Current trends of decreased investments in CNS drug development will be reversed as we better integrate knowledge from basic, translational, and clinical neuroscience.

The term 'novel' refers to any mechanism that has not been explicitly elucidated as critical to the action of some established therapy and/or is hypothesized to be relevant to the pathophysiology of a condition on the basis of modern neuroscience. Examples of such novel targets are Nav 1.7 antagonism for pain or secretase inhibition to reduce beta amyloid, which emerged from identification of genes underlying congenital insensitivity to pain and early-onset Alzheimer's. Targets in systems hypothesized to be involved in the pathophysiology of a condition such as depression—eg CRF-1 receptors and a stress response network—also fit into this definition of novel.

A 'target' is a molecular site the function of which can be altered by a range of interventions, such as orthosteric agonists or antagonists, allosteric modulators, and inhibitors of enzymes in relevant pathways. Industry generates compounds that are potent and selective for such targets using high throughput *in vitro* assays designed to detect these pharmacological classes. If the rationale for a particular target is accepted by the field, enormous resources will be found to generate appropriate molecules for studies in humans. Such has been the case for beta secretase inhibition whereby hundreds of chemists across several companies worked for a decade before identifying a suitable molecule.

The major barriers to clinical success have been the limited predictive value of pre-clinical models and the difficulty in establishing presence or absence of clinical validity for any specific target (Paul *et al*, 2010). For instance, in the case of CRF-1 antagonism we only hypothesize that the effects in animal models are likely to have analogous system function effects in humans and do not know if compounds taken into the clinic actually blocked CRF-1 receptors in human brains so as to test the hypothesis. Until very recently, most clinical trials of CNS compounds have been a black box exercise in which one relates blood concentration to behavioral effects that are inferred to be mediated by events in the brain. One exception is the development of benzodiazepine hypnotics for which EEG measures reliably reveal brain effects related to reports of improved sleep.

These 'lessons learned' from CNS drug development over the last two decades when integrated with advances in basic, translational and clinical neuroscience can deliver a new era of iterative, hypothesis testing, and validating studies. Three interacting disciplines—molecular genetics, systems neuroscience, and translational medicine—make this possible. In the 1980s, neuroscientists optimistically predicted the rapid introduction of novel treatments based, retrospectively, on a naïve hope that we would discover many one gene, one disease, and one-target relationships. It is now clear that single gene etiologies apply mostly to rare diseases although these may prove informative for the more prevalent disease forms. Thus, the excess amyloid deposition associated with certain genetic determinants of familial early-onset Alzheimer's disease (AD) is a target for sporadic late-onset AD with its highly complex contributors (eg over 10 genes replicated in large independent cohorts as well as vascular, metabolic, and immune factors). Elucidating such complexity requires efficient genotyping, phenotying, and informatics capabilities applied to large cohorts. And as full genetic sequencing becomes practical and coupled to epigenetic, complex physiological, and biochemical measures informatics will grow in importance. Drug development no longer ignores this complexity but controls for it to the extent possible with the tools of genetics and translational medicine, which most recently includes expanded use of functional brain imaging (Borsook *et al*, 2011).

An example of a tool to study complex brain function is to focus on the degree of association between the brain

*Correspondence: Dr WZ Potter, 8008 Seminole Street, Philadelphia, PA 19118, USA, Tel: +1 267 970 6604, E-mail: wzpottermd@gmail.com
Received 5 August 2011; accepted 5 August 2011

areas (connectivity) as potentially more informative than simpler stimulus/response single region activation paradigms. It now appears that such matrices can be interrogated even in mouse brain allowing one to answer whether action at a specific target effects downstream complex brain functions similarly across species as recently shown in studies of TNF-α in pain (Hessa *et al*, 2011). A similar approach may help address current attempts to assess glycine modification of NMDA function, which is hypothesized to a have therapeutic potential in schizophrenia. In some pre-clinical models an U-shaped concentration response curve is observed, presumably reflecting a complex interaction of neurotransmitters and circuits. A similar phenomenon may occur in humans as suggested by decreased responses at higher doses of a novel glycine 1 transporter (GlyT1) inhibitor (Pinard *et al*, 2010). As PET ligands for GlyT1 are available, action at the pharmacological target can be quantified in humans without, however, relating it directly to the functional brain responses to see if they decrease with increased occupancy. A system neuroscience approach would be to hypothesize that shifting glutamate NMDA receptor function would alter the balance of activity across the brain regions. Based on knowledge of circuits in which NDMA function has a role, one could assess degree of connectivity between certain areas utilizing a measure of brain activity applicable across species. Then a test of whether a GlyT1 receptor occupancy/connectivity relationship was similar in animals and humans becomes possible.

Continuing advances in ways of directly studying drug effects in living animal and human brains—the tools and biomarkers of translational medicine—guarantee that at the very least we can avoid uninformative studies. Given a PET ligand and data on full receptor occupancy as with NK1 antagonism, one is sure that disappointing outcome is not because of too little drug reaching the target. In this instance early positive clinical results generated NK1 antagonist programs in several companies until well-controlled negative Phase III studies were reported using doses established by PET studies to achieve full occupancy (Keller *et al*, 2006).

The scientific and methodological advances described above can impact CNS drug development at a much faster rate if we move beyond our current competitive paradigms. Research relevant to target validation remains competitive whether in academia and industry, and is selectively shared to achieve various ends whether at the level of academic status, establishing intellectual property or advancing one's compound in a company. In this climate, multiple companies put compounds against the same unvalidated novel target into trials, so as to be the first to market in case the mechanism proves effective. Such a paradigm has generated a body of exciting neuroscience therapeutic hypotheses but not an open, transparent, and effective test of the same.

An alternative paradigm is embodied in the Alzheimer's Disease Neuroimaging Initiative launched in 2004 in which government, academia, industry, the FDA, and advocacy groups share, to varying extents, funding and expertize to develop the best tools possible for accelerating the development of novel drugs. Central to this paradigm is an unprecedented agreement that all data are made available as soon as it is generated on an open website. Thus data relevant to validating tools as useful or not are made immediately available.

Would something similar be possible in terms of a pre-competitive effort to validate targets? One could begin with establishing sufficient standardization of experimental designs in basic and clinical space to allow for much more direct comparison of data, even to the level of pooling results. Pre-clinical academic and industry studies are still done in ways whereby lack of reproducibility of findings across groups and even laboratories within the same organization can take years, if ever, to resolve. This practice generates increasingly difficult to resolve type I and II errors as more targets and measures are incorporated into studies. Unless one has access to the actual data, it is almost impossible to know how to compare the high-level results across studies leaving the state of validation of a target a very open question, as there can be other explanations for findings than the one advanced to serve such purposes as getting another grant or advancing a compound to the next stage in a company.

In the open source model, studies focused on potential CNS drug targets would be executed in such a way to allow for immediate sharing of raw data among all interested parties, with the goal of prioritizing those targets for which replication and depth of data were greatest. The field would share the 'risk' of bringing forward any target for studies in humans, and ultimate financial reward would depend on having the best molecule from a potency, pharmacokinetic, and safety viewpoint. The field could align on how many parallel target validation efforts made sense and achieve a balance between resources to rule in or out any single target and number of targets under exploration. More targets could be adequately explored with fewer resources by avoiding multiple groups working in secret with non-standardized methods on the same project. Given the complexity of understanding drug actions in brain, it seems unlikely that even the largest groups working in secret are going to generate the depth of understanding needed for the questions of systems neuroscience. Highly publicized efforts, such as One Mind envisage stakeholders all working much more effectively together to integrate science and drug development. We should consider a paradigm of pre-competitive target validation and tackle the issues of the metrics and rewards that this would require.

DISCLOSURE

Dr Potter was an employee of Merck until January of 2010 and subsequently has consulted for the following companies: AgeneBio, Amgen, AstraZeneca, Bristol Myers Squibb, InVivo, Medavante, Orasi, Pfizer and Theravance. He has no

ownership interest in any of these companies except for stock, which he received as an employee of Merck.

Further information:
http://www.1mind4research.org
http://www.adni-info.org

REFERENCES

Borsook D, Hargreaves RJ, Becerra L (2011). Can functional magnetic resonance imaging improve success rates in central nervous system drug discovery? *Expert Opin Drug Discov* **6**: 598–617.

Hessa A, Axmannb R, Rechb J, Finzelb S, Heindla C, Kreitza S *et al.* (2011). Blockade of TNF-α rapidly inhibits pain responses in the central nervous system. *PNAS* **108**: 3731–3736.

Keller M, Montgomery S, Ball W, Morrison M, Snavely D, Liu G *et al.* (2006). Lack of efficacy of the substance p (neurokinin1 receptor) antagonist aprepitant in the treatment of major depressive disorder. *Biol Psychiatry* **59**: 216–223.

Paul SM, Mytelka DS, Dunwiddie CT, Persinger CC, Munos BH, Lindborg ST *et al.* (2010). How to improve R&D productivity: the pharmaceutical industry's grand challenge. *Nat Rev Drug Discov* **9**: 204–214.

Pinard E, Alanine A, Alberati D, Bender M, Borroni E, Brom V *et al.* (2010). Selective GlyT1 inhibitors: discovery of [4-(3-fluoro-5-trifluoromethylpyridin-2-yl)piperazin-1-yl][5-methanesulfonyl-2-((S)-2,2,2-trifluoro-1-methylethoxy)phenyl]methanone (RG1678), a promising novel medicine to treat schizophrenia. *J Med Chem* **53**: 4603–4614.