Considerations for Target Selection in CNS Drug Discovery Programs

Stephen A. Hitchcock, PhD

Envoy Therapeutics
Jupiter, Florida
Considerations for Target Selection in CNS Drug Discovery Programs

The Druggable Genome
Currently approved drugs mediate their therapeutic effects via a relatively small subpopulation of the druggable genome. Contemporary estimates suggest that approximately 3000 druggable genes exist, yet current drugs act on only ∼400 defined unique molecular targets (Rask-Andersen et al., 2011). These statistics suggest that the vast majority of the druggable genome is, as yet, unexploited by pharmacotherapy. The current repertoire of drugged targets is dominated by cell surface receptors, transporters, and soluble enzymes (Fig. 1). The drugged members within these target families are considered by many to represent the “low-hanging fruit” within the druggable genome, implying that the next generation of targets will be substantially more challenging.

The concept of small-molecule druggability has evolved from an analysis of the overlap between druggable biological target space and oral drug-like chemical space. The convergence of these two concepts requires first that the target play a role in human disease and second that it has the potential to be modulated in a selective manner by a small molecule that has oral, drug-like physicochemical properties. A target’s druggability is usually estimated by classifying it with known gene families that have previously been successfully targeted with drugs. However, this approach has some inherent limitations, so for targets of known structure, researchers have used a mathematical model that uses structural information about a target’s binding site in order to estimate a maximal achievable affinity for a drug-like molecule (Cheng et al., 2007).

The concept of oral drug-likeness has its origins in the mid 1990s and initially centered on the relationship between compound properties and solubility and permeability. The Lipinski Rule of Five (Lipinski, 2004) provided guidelines for oral drug-likeness based on lipophilicity, as defined by the logarithm of the octanol/water partition coefficient (logP ≤ 5), hydrogen bond donor count (HBD ≤ 5), hydrogen bond acceptor count (HBA ≤ 10), and molecular weight (MW ≤ 500 Da). Further analyses of druggable chemical space have revealed additional relationships between compound properties and other absorption, distribution, metabolism, excretion, and toxicity (ADMET) properties that must be satisfied for a successful drug candidate (Meanwell, 2011). Favorable ADMET properties and biological target potency generally show a diametrically opposed relationship with respect to MW and logP. There is also a growing body of evidence that compound promiscuity on average increases with increasing MW and logP. This characteristic suggests that the level of potency sought in a candidate molecule must be carefully balanced with physical properties, ADMET characteristics, and promiscuity — especially for CNS targets (Gleeson et al., 2011).

The CNS Druggable Genome
Despite recent advances in technology demonstrating the delivery of antibodies across the blood–brain barrier (BBB) in animal models (Atwal et al., 2011), drugged CNS targets remain exclusively within the domain of small-molecule therapeutics. The nonfenestrated endothelium of brain capillaries that constitutes the BBB physically limits the passive permeability of compounds and presents a metabolic barrier to CNS entry in the form of metabolizing enzymes and transport proteins. A further refinement of the concept of drug-likeness is therefore required for compounds intended for CNS targets in order to account for the limitations imposed by BBB permeability. The fact that CNS-accessible chemical space represents a subset of oral drug-like space can be illustrated by plotting simple physiochemical descriptors such as MW, polar surface area (PSA), and calculated LogP (cLogP) of drugs marketed for CNS indications against those intended for peripheral targets (Fig. 2). For example, there is greater latitude for higher PSA in drugs that do not require entry into the CNS. The same is true of MW. The greater stringency around CNS compound properties translates into a

Figure 1. Percent distribution of the targets of approved therapeutics by target class (Rask-Andersen et al., 2011). LGIC, Ligand-gated ion channel; NR, nuclear receptor; RTK, receptor tyrosine kinase; SLC, solute carrier class; VGIC, Voltage-gated ion channel.

© 2011 Hitchcock
lower likelihood of simultaneously achieving good BBB permeability and potent activity for targets with large and/or polar binding sites.

Retrospective analysis of marketed drugs has revealed that a very low prevalence of P-glycoprotein (P-gp) efflux, coupled with moderately to highly passive permeability, are two key properties that distinguish drugs that engage targets in the CNS from those that act predominantly in the periphery. The efflux properties that differentiate CNS drugs have been quantified using in vitro assays for human and rodent P-gp (Doan et al., 2002; Feng et al., 2008). Efflux properties have also been revealed in vivo by comparing brain drug exposures in P-gp (mdr1a/b−/−) knock-out mice with those observed in wild-type mice (Doran et al., 2005). Despite the lore that correlates compound lipophilicity with brain exposure, LogP is not correlated with brain unbound drug levels, which are the true determinants of pharmacologically relevant exposure. In fact, molecular descriptors related to hydrogen bonding (PSA, HBD, HBA) dominate the relationship with the steady-state unbound brain-to-plasma concentration ratio (Kp,uu,brain) (Fridén et al., 2009). This finding likely results from the additive effect that PSA, HBD, and HBA have on simultaneously reducing passive permeability while increasing the probability of interactions with efflux transporters.

Figure 3a shows the relationship between PSA and average P-gp efflux ratio (ER) of 4125 compounds tested in LLC-PK cells transfected with human multidrug resistance 1 (MDR1) cDNA (P-gp). Compounds with ER >3 are considered to be P-gp substrates. Figure 3b illustrates the average PSA of CNS drugs, all marketed oral drugs (MKT), and kinase inhibitor drugs (KID) (Chico et al., 2009). The high PSA generally required for potent ATP-competitive kinase inhibition explains the generally poor CNS penetration of this class of compounds.

Approved CNS drugs are dominated by compounds that directly engage biogenic amine receptors or indirectly modulate their activity by inhibiting neurotransmitter metabolism or uptake. This circumstance owes much to capacity for achieving high affinity at such targets with low-molecular-weight compounds (high ligand efficiency) that have relatively low PSA and is aided by a traditionally low stringency for biological target selectivity.

The industry shift from phenotypic screening and polypharmacology to single-targeted therapeutics has been particularly hard on CNS drug discovery (Swinney and Anthony, 2011). The orthosteric binding sites among many biogenic amine G-protein coupled receptor (GPCR) family members are
No T
highly conserved. Thus, the quest for subtype-
selective ligands for even these low-hanging targets
has required reliance upon additional interactions
in nonconserved binding regions, thus driving up
the molecular weight of compounds. The surge
of interest in allosteric receptor modulators is
a direct response to the challenge of attaining
selectivity within the confines of CNS-accessible
chemical space (Conn et al., 2009). The origins
of low success rates at each stage of drug discovery
are multifactorial, but the limited structural space
available to achieve target engagement in the brain
is a major contributing element to the high attrition
in CNS programs. Despite the large industry-wide
investment in new targets, only four new CNS drugs
that act by previously unexploited mechanisms have
been launched in the past decade in the United
States (Table 1).

Table 1. CNS Drugs launched during 2000–2010 that act on new targets.

<table>
<thead>
<tr>
<th>Drug</th>
<th>Target</th>
<th>Gene family</th>
<th>Launch</th>
<th>Indication</th>
</tr>
</thead>
<tbody>
<tr>
<td>Aprepitant</td>
<td>NK1</td>
<td>GPCR</td>
<td>2003</td>
<td>CINV</td>
</tr>
<tr>
<td>Ramelteon</td>
<td>MT1/MT2</td>
<td>GPCR</td>
<td>2005</td>
<td>Insomnia</td>
</tr>
<tr>
<td>Varenicline</td>
<td>α4β2</td>
<td>LGIC</td>
<td>2006</td>
<td>Nicotine addiction</td>
</tr>
<tr>
<td>Fingolimod</td>
<td>S1P1</td>
<td>GPCR</td>
<td>2010</td>
<td>Multiple sclerosis</td>
</tr>
</tbody>
</table>

CINV, Chemotherapy-induced nausea and vomiting; GPCR, G-protein coupled receptor; LGIC, ligand-gated ion channel.

Simple physicochemical guidelines and computational
models can be helpful in altering the probability of
encountering P-gp efflux; however, it is abundantly
evident that compounds with identical physicochemical
properties can have vastly different efflux properties.
As with any small molecule–protein interaction, the
composition and presentation of functionality on a
molecule play a critical role in the recognition process.
However, unlike the typical small molecule–drug
target interaction, P-gp is a highly permissive protein
recognizing a wide diversity of substrates. Biological
targets with larger, more polar binding sites (such as
those that have peptides, amino acids, and nucleotides
as ligands or substrates) are disadvantaged when it
comes to achieving sufficient target affinity within
physicochemical space that is favorable for CNS
entry. However, this limitation does not mean that
reconciling potency, selectivity, and CNS entry for
such targets is impossible; it is simply more demanding.

The aspartyl protease β-amyloid cleaving enzyme-1
(BACE1) is a good example. BACE is a hotly pursued
target in the quest for a disease-modifying therapy for
Alzheimer’s disease (Varghese, 2010). Reconciling
the structural requirements for potency and protease
selectivity with the need for low metabolic clearance,
adequate passive permeability, and avoidance of
P-gp efflux in individual compounds has proven
extremely challenging for those that have tackled
BACE inhibitor optimization. It is worthwhile
contrasting the timeline involved in advancing
HIV protease inhibitors from target discovery
to drug launch with the time that has elapsed
since the first disclosure of BACE as a molecular
target. HIV protease was first disclosed in 1988
and, remarkably, within seven short years, saquinavir
had received FDA approval and was quickly followed by
several other entries. In contrast, BACE was disclosed
in 1999 and only recently have the first inhibitors
begun to enter clinical development, still many
years from potential FDA approval. Although many
factors distinguish HIV infection from Alzheimer’s
disease, a major differentiator
is the absolute requirement
that BACE inhibitors enter
the CNS. The requirement
for CNS penetration imparts
additional confinements
around available structural
and physicochemical space,
reducing the scope of options
for solving potency, selectivity,
and pharmacokinetic
deficiencies.

Numerous other examples highlight successful efforts
to engineer CNS target coverage while maintaining
biological target activity, selectivity, and in many
cases, favorable pharmacokinetic properties for
targets with large and/or polar binding sites. These
include bradykinin, orexin, opioid peptide GPCRs,
GABA, glutamate and glycine receptors, and several
phosphodiesterases and kinases.

Target Selection and Validation
It has been said that a drug target’s relevance to
disease is often inferred with strong belief but fragile
evidence. It can also be argued that, since the complete
sequencing of the human genome, the key task in
biomedical research is no longer target identification
but rather target validation. However, given the
additional limitations around CNS-accessible
chemical space, assessment of potential targets for
the probability of achieving CNS druggability should
be conducted early in the target selection process.
Druggability should then be weighed against other
evidence in support of or against the target. Target
validation is a continuum whereby an increasing
body of data is amassed that culminates in positive efficacy in humans. The initial target selection and subsequent validation path may include evidence from the expression pattern of the target, human and animal genetics, validation in animal disease models (preferably across multiple species), and observations with model compounds (based on human or animal data). The target selection and validation path should also include consideration of a human biomarker, preferably a functional endpoint or surrogate endpoint.

In recent years, there has been a number of high-profile CNS drugs subject to black box label warnings, others subject to outright withdrawal, and FDA rejections of several CNS drug candidates. In many cases, mechanism-related side effects have resulted in an unfavorable risk-to-benefit ratio for the patient. Therefore, in addition to establishing target validation, assessing the likelihood and nature of mechanism-related side effects and the ability to empirically measure and defuse these risks early in the drug discovery process are important. Pursuing targets that have selective expression patterns (preferably limited to the dysfunctional circuit or cell type of interest) would confer the advantage of lowering the probability of mechanism-related side effects.

References


