Chapter 1

INTRODUCTION: THE UNTAPPED PHARMACOLOGIC POTENTIAL OF GPCRs

G protein-coupled receptors, known familiarly as GPCRs, or more correctly as 7TMRS (7-transmembrane receptors), have served as extremely popular drug targets for the pharmaceutical industry. Depending on one’s definition, anywhere from about 30%–40% of marketed drugs target one or another GPCR. One reason why GPCRs have been so popular is that there are so many of them, up to 1,000 if genome sequence extrapolations can be believed, although half or more of those are sensory receptors and not terribly relevant for drug discovery.

Despite their extreme popularity, one can easily argue that the pharmacologic potential of GPCRs is far from exhausted. A very few targets, mainly those for which endogenous ligands are biogenic amines, correspond to a large majority of all the GPCR-based drugs that have made it to market. A key reason for this limitation is that early high-throughput screening efforts were based largely on competitive ligand-binding assays, for which the biogenic amines were highly amenable.

GPCR-based drug discovery has come a long way since these first-generation drugs made it through the pipeline. Medicinal chemistry and structure-based drug design have advanced to the point where it is relatively easy to selectively target receptor subtypes, a capability that goes a long way toward improving drug safety. Perhaps even more importantly, screening technologies have evolved from mainly measuring binding to elucidating a variety of functional parameters, which has opened the door to working with a great many more receptors than were previously accessible. For this and other reasons, drugs currently in the R&D pipeline target a great many more GPCRs than are represented among currently marketed products.
This is the first known structure of a human G protein-coupled receptor.

_Credit: Courtesy of the Stevens Laboratory, The Scripps Research Institute._
Still, deorphanization remains an important issue. A number of deorphanized GPCRs are currently active in drug discovery, including ORL-1 (nociceptin/orphanin FQ ligand) agonists for stress and pain, histamine H₃ antagonists and inverse agonists for dementia, histamine H₄ antagonists for inflammation, orexin antagonists for sleep disorders, ghrelin agonists for catabolic disorders, et al. At least one prominent drug discovery company, Arena Pharmaceuticals, has developed a screening technology capable of identifying hits for orphan GPCRs (see Chapter 4).

### 3.3. Allosteric Modulators

No single topic in the GPCR world currently generates more justified excitement than allosteric modulation. Although the formal, historically based definition of allostery is complex, a commonly accepted definition of the allosteric site is attributed to May and coauthors:

“A binding site on the receptor that is topographically distinct from (does not overlap with) the orthosteric site.”

Another relevant definition offered for allosteric interaction by the same authors is:

“An interaction between ligands that bind to distinct, nonoverlapping but conformationally linked recognition sites on the receptor molecule.”

And finally, the converse of an allosteric site, the orthosteric site:

“The primary binding site on the receptor that is recognized by the endogenous agonist for that receptor.”

So an allosteric modulator of a GPCR is one that binds to an allosteric site on the receptor. GPCRs are natural proprietors of allosteric sites, since endogenous and other agonists induce conformational changes in the receptor that allow it to enter into protein-protein interactions with other proteins. The sites for these interactions may also bind small molecules, which may be expected to modulate receptor activity toward compounds that bind at the orthosteric site. Vincent Mutel, PhD,
Of the 32 drugs listed in Table 4.12, all but six are primarily antihypertensives. Three drugs are listed as cardiotonics, one as an antiarrythmic, one a coronary vasodilator, and one for treating glaucoma. By contrast, only two beta1 modulators are known to be in development (Table 4.13), one for treatment of asthma, the other as a coronary vasodilator.

### Table 4.13. Drug Candidates for the Beta1-Adrenergic Receptor

<table>
<thead>
<tr>
<th>Source</th>
<th>Generic Name</th>
<th>Target</th>
<th>Principal Treatment Area</th>
<th>Clinical Status</th>
</tr>
</thead>
<tbody>
<tr>
<td>Inverseon</td>
<td>nadolol</td>
<td>beta1-adrenergic receptor</td>
<td>Antiasthma</td>
<td>Phase II</td>
</tr>
<tr>
<td>ARCA Discovery</td>
<td>bucindolol</td>
<td>beta1-adrenergic receptor</td>
<td>Vasodilator, coronary</td>
<td>Phase III</td>
</tr>
</tbody>
</table>

Source: Insight Pharma Reports

Bucindolol, a beta blocker currently in Phase III as a treatment for heart failure, has an interesting history from a pharmacogenetic perspective. A report in 2006 on the BEST clinical study showed that while the drug was not very effective in a general population, it showed 38% improvement in survival versus placebo for a group with arginine at a particular position in the target. People with glycine at that position showed no advantage over placebo.35

A great many launched drugs aimed at treating asthma target the beta-2 receptor (Table 4.14). Out of 21 launched drugs listed, 15 target asthma, one is an antitussive, and two (levomoprolol and penbutolol) target hypertension.

### Table 4.14. Launched Drugs Targeting the Beta2-Adrenergic Receptor*

<table>
<thead>
<tr>
<th>Source</th>
<th>Product Trade Name or Status in US (generic name)</th>
<th>Target</th>
<th>Principal Treatment Area</th>
<th>2007 Worldwide Sales (in millions of USD)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Abbott</td>
<td>Preclinical (tulobuterol)</td>
<td>beta2-adrenergic receptor, surface</td>
<td>Antiasthma</td>
<td>NA</td>
</tr>
<tr>
<td>Astellas</td>
<td>Foradil</td>
<td>beta2-adrenergic receptor, surface</td>
<td>Antiasthma</td>
<td>NA</td>
</tr>
<tr>
<td>Astellas</td>
<td>NA (tiaramide)</td>
<td>beta2-adrenergic receptor, surface</td>
<td>Antiasthma</td>
<td>NA</td>
</tr>
</tbody>
</table>

Continued
Metabotropic Glutamate Receptors

Metabotropic glutamate receptors (mGluRs) are found in pre- and post-synaptic neurons of the brain's hippocampus, cerebellum, and cerebral cortex. They are also found elsewhere in the brain and in peripheral tissues, and serve to modulate the function of other receptors, such as NMDARs. They are involved in learning, memory, anxiety, and perception of pain. Eight receptors are known (mGluR\textsubscript{1} through mGluR\textsubscript{8}), with further division into subtypes.\textsuperscript{59}

Again, no launched drugs exist in this category, and relatively little development has yet emerged. Three mGluR\textsubscript{1} modulators are in preclinical development for diverse neurological applications (Table 4.37). Two mGluR\textsubscript{2} modulators are under development as neuroleptics, one preclinical and the other Phase II. A single mGluR\textsubscript{4} compound is in preclinical development for treatment of Parkinson's disease. Four mGluR\textsubscript{5} modulators are in development, two as antispasmodics, one as an antidepressant, and one as a neuroleptic, at stages ranging from preclinical to Phase II.

<table>
<thead>
<tr>
<th>Source</th>
<th>Generic Name</th>
<th>Target</th>
<th>Principal Treatment Area</th>
<th>Clinical Status</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pfizer</td>
<td>CVX-096 (recombinant peptide)</td>
<td>glucagon-like peptide-1 receptor</td>
<td>Recombinant, other</td>
<td>Preclinical</td>
</tr>
<tr>
<td>Eli Lilly</td>
<td>LY-548806</td>
<td>glucagon-like peptide-1 receptor</td>
<td>Antidiabetic</td>
<td>Phase II</td>
</tr>
<tr>
<td>Ipsen</td>
<td>taspoglutide</td>
<td>glucagon-like peptide-1 receptor</td>
<td>Antidiabetic</td>
<td>Phase II</td>
</tr>
</tbody>
</table>

Source: Insight Pharma Reports

Table 4.36. Drug Candidates for Glucagon and Glucagon-Like Peptide-1 Receptors (cont.)
signal both through G proteins and in a G protein-independent manner. There is some tantalizing evidence that one can identify molecules that regulate G protein signaling but not G protein-independent signaling, and vice versa. If that appears to be a genuine phenomenon, then I suspect that five years down the line we may well have many examples of molecules that only show efficacy in disease if they regulate the appropriate pathway.

Deorphanization and Unfamiliar GPCRs

About 100 GPCRs remain in orphan status, and efforts to find endogenous receptors for these appear to have slowed somewhat in recent years. Dr. Milligan had the following to say on this issue:

“Genome sequencing revealed a whole series of GPCRs in the genome with unknown function, which have come to be called orphans. A number of companies have tried to work these up into drug targets, and we’re only now just starting to see some level of fruition in terms of those programs leading to novel drugs. I think there will be a few that come from those programs, but probably nowhere near as many as I think the leaders of the industry who drove this expected in the first place. One issue that remains pertinent, despite GPCRs’ importance as drug targets, is that there is a core of maybe 25 or 30 receptors with therapeutic drugs targeted against them. Of course there are another 400, and maybe many of these only have small effects on biology and not the major effects needed for a drug to either a mask or remedy a symptom of the disease.”

The aforementioned big pharma screening director commented:

“There remain around 100 family A GPCRs, particularly, that have not been liganded. I think a challenge for the next decade will be trying to understand why we have failed to identify ligands for these receptors and then translate those receptors into drug targets. It may be that they don’t signal through G proteins. It may be that one could only assay them with a label-free detection system. I think that is a major challenge for the next several years.”
CHI: Maybe it depends less on pharma's internal health than it does on the availability of venture capital funds for small companies to do some of this work.

Dr. Conn: Yes, that's right. There are many pieces to that puzzle. One problem we have right now, in addition to the stress for big pharma, is that the venture funds for innovative ideas in smaller companies are much harder to come by. On the good side, I think the shift of NIH-funded investigators to start thinking more seriously about translational research is a good thing. It is going to take some time for that community to really come up to speed on what it takes to do that effectively. But that is one way of filling a gap that has been left with venture money starting to shrink.

6.5. Sidney Topiol, PhD

Associate Director, Computational Chemistry; Lundbeck Research

CHI: Please start by telling me a little bit about your background, how you got involved with GPCRs, and what you are doing today.

Dr. Topiol: Going back to my graduate work, I was originally a quantum chemist. I did my graduate and post-doctoral work on quantum chemical methods applied to larger systems than were possible at the time. We were streamlining computational methods to increase the size of the system. I worked with Jules Moskowitz, PhD at NYU, Mark Ratner, PhD at Northwestern, and John Pople, PhD at Carnegie-Mellon, who won the Nobel Prize for computational chemistry. After a number of years of doing post-doctoral work on how to develop methods for studying larger molecules, I thought it would be interesting to actually use methods to study large systems. An opportunity came up at Mount Sinai School of Medicine, where there was a faculty position in the pharmacology department with a molecular pharmacology bent to it. There were actually a few computational chemists there, and at the time we were looking mostly at small molecules. The subject was molecular pharmacology dealing mainly with the CNS.

So this is how I became involved in looking at drugs and ligands for GPCR targets. At the time, the most we really knew about the actual structure was drawing little cartoons, representations of what the receptor might look like. So it was kind of a dream, if you will, to be in a position where you could actually look at the real coordinates of the