

Executive Summary

Cell surface G protein-coupled receptors (GPCRs) are extremely popular drug targets, accounting for approximately one-third of approved drugs and for many hundreds of drugs currently in development. Despite the large number of GPCRs that are available as targets, currently approved drugs address only a few receptors, most of which are activated by biogenic amines. Such receptors were amenable to the limited range of screening technologies available at the time. Current advances in functional screening methodologies, medicinal chemistry, and structure-based drug design have generated large increases in the number and diversity of targets for which compounds are currently in development. Furthermore, basic research advances concerning receptor x-ray structures, allosteric interactions, multimerization, and functional selectivity have opened the way for still further exploitation of this large and diverse class of targets.

This report, entitled *GPCRs: Dawn of a New Era?*, explores the basic and applied research advances leading to new directions in GPCR drug discovery, along with the current and likely consequences of these developments. Along with extensive tabulation of marketed drugs and compounds in development arranged by receptor type and subtype, the report includes transcripts of extensive interviews with six recognized academic and industry experts in the field.

Scientific Background and Technologies

Human genome sequencing has revealed about 1,000 sequences known or likely to be GPCRs. More than half of these have sensory functions and are generally not relevant for drug discovery. About 400 GPCRs likely bind endogenous ligands, which have not yet been identified for approximately one-third of these receptors. Approved drugs account for 40–50 GPCRs, which include dopaminergic, serotonergic, muscarinic, purinergic, angiotensin, calcitonin, leukotriene, and prostanoid receptors.

A common classification system refers to Classes A, B, and C receptor families. Class A receptors bind mainly to amines and peptide ligands, Class B to endogenous proteins, and Class C to a variety of ligands including several important neurotransmitters.

Of 371 known GPCR types and subtypes, 125 are targeted by compounds on the market or in development. Of those 125, 37 represent targets for which very few compounds have reached the development stage. Given that there are between 100 and 150 non-sensory orphan GPCRs, these figures suggest there is a great deal of fertile territory yet to explore.

Having selected a target, companies can rely either on diversity screening or augment that with structure-based drug discovery. Classical diversity screening relies on competitive ligand-binding assays, which provide limited information and have been largely supplanted by functional assays that measure changes in concentrations of calcium, cyclic AMP, inositol triphosphate, and other indicators of GPCR-stimulated signaling. Molecular Devices' FLIPR system for measuring changes in intracellular calcium ion concentration is a highly popular example of the genre. Label-free CDS impedance measurement technology systems have become available recently and are receiving a lot of attention in the screening community.

Structure-based drug discovery and design, which previously had to rely pretty much on ligand structures, received a tremendous boost in 2007 with the publication of the beta2-adrenergic high-resolution x-ray structure. The methods used for crystallization open the way for solving additional GPCR structures in the near future.

Basic Research

Key discoveries in recent years have expanded our understanding of GPCRs and their functions in health and disease. Until 2007, the rhodopsin receptor, which is not highly exemplary of those GPCRs which are interesting to pharma, was the only one to have its detailed 3D structure worked out. The beta2-adrenergic structure, which was reported in 2007 and provides detailed information directly relevant to pharmacology, was followed in short order by the beta1-adrenergic structure. These structures, together with previously available structures for extracellular regions of mGluR and several other GPCRs, provide an important boost to already useful ligand-based structural efforts. One key industry participant commented that all the "machinery" is now in place and the real work can begin.

According to one estimate, about 100 of 360 non-sensory GPCRs remain in orphan status, and the rate of deorphanization has decreased markedly in recent years. No new endogenous ligands have been discovered in the past four years. The remaining orphans can be expected to bind small molecules, many of which may be present only at very low concentrations and bind to GPCRs with very high affinity. However, deorphanization remains an important issue, and one company has developed a screening technology capable of identifying hits for orphan GPCRs.

Allosteric modulation of GPCRs is currently generating a great deal of excitement among both basic and applied researchers. Since orthosteric modulators need to compete with natural ligands, they require higher doses, thus raising safety issues. Allosteric modulators do not compete and may be effective at lower, safer doses. Furthermore, allosteric modulators avoid desensitization phenomena that plague orthosteric compounds, and make it possible to discover sought after partial negative modulation. Only two allosteric drugs have so far been approved, but allosteric modulators have been identified for 34 GPCR types and subtypes.

The notion that dimerization might play an important role in GPCR pharmacology has come to light only in the past few years, and its degree of importance is still a subject of controversy and active investigation. Homodimerization is thought to be widespread, but heterodimerization, which possibly is of greater significance, is thought to be relatively rare. Heterodimers have been demonstrated in model systems, but have proved difficult to investigate in primary cells. Considerably more basic investigation is required before pharmaceutical companies can be expected to take an active interest.

The issue of functional selectivity in GPCRs raises further questions whose answers may have great significance for pharmacology. A key observation is that two agonists, for example, can bind to different areas in a receptor's binding site, resulting in different conformational shifts which lead down divergent signaling pathways. Pharmaceutical company researchers have started to take note of functional selectivity and account for it in their programs, but the effort is still in its early stages.

Applied Research

A number of small drug discovery companies focus on GPCR targets, often employing cutting-edge technologies and perspectives derived from basic research. Chapter 4 begins by examining the approaches and drug development activities of a number of these companies, which include 7TM Pharma, ACADIA Pharmaceuticals, Actelion, AcurePharma, Addex Pharmaceuticals, Adenosine Therapeutics (acquired by Clinical Data), Arena Pharmaceuticals, Cara Therapeutics, Dimerix Bioscience, EPIX Pharmaceuticals, and Travena.

The second part of Chapter 4 considers all GPCR types and subtypes for which compounds have either been launched as drugs or are currently in development or pre-registration. Tables and sections are arranged by target class, and information summaries are provided for compounds either in Phase III development or pre-registration. The differences in targets between launched and development compounds reflect a sea change in the pharmaceutical research paradigm superimposed on a growing body of heuristic knowledge permitting greater compound selectivity for GPCR subtypes, and on the benefits of past deorphanization efforts.

General Observations and Conclusions

Chapter 5 of this report draws on interviews with academic and industry experts on GPCR pharmacology. The chapter begins with a series of observations by the experts on a number of critical issues raised elsewhere in the report. Among these observations, we find that the recent diversification in GPCR targets can be expected to continue during the coming decade; big pharma is slow to adopt new basic research methods and perspectives, leaving much of that responsibility to smaller ventures; implementation of diverse functional assays for compound-GPCR interactions has increased the amount of information derived from high-throughput screening and improved pharma's batting average; allosteric GPCR modulators have great benefits to offer in terms of both efficacy and safety, but in some instances they may pose significant challenges beyond those seen with orthosteric modulators; functional selectivity may permit medicinal chemists to target particular signaling pathways, but the reasons for wanting to do this, while potentially valuable, are not always clear. Structure-based drug design has proved valuable in the GPCR world as an adjunct to selection of compounds for screening; the publication of the first truly useful GPCR x-ray structure has a good chance of triggering a quantum leap for the field.