Future of GPCRs in Drug Discovery: Novel Technologies, Leading Companies, and Opportunities for Target Expansion

GPCRs are being actively pursued as a target class for developing new therapeutics for various indications. This report discusses the developments in targeting selected, recently deorphaned GPCRs.

Scope

- Analysis of specific GPCRs that have been exploited or explored.
- Novel approaches to targeting GPCRs and their benefits, such as selectively modulating distinct GPCR signaling pathways.
- Case histories highlighting how enhanced selectivity can be achieved by exploiting improved knowledge of GPCR targets.
- Potential GPCR targets for major under-treated diseases.
- Commercial outlook for drugs targeting GPCRs.
- Assessment of the level of activity in GPCR research.

Research and analysis highlights

The pharmaceutical industry has more effectively exploited GPCRs than it has any other target class, with GPCRs accounting for about 30% of exploited targets and revenues of over $60 billion in 2009.

The vast majority (about 80%) of GPCRs have yet to be effectively or commercially exploited, for a variety of reasons, thus offering many opportunities.

Successful pursuit of such approaches, together with effective targeting of currently unexploited GPCRs, is critical to compensating for the loss of revenues as patent expirations impact upon the sales of leading branded GPCR-targeted drugs.

Key reasons to purchase this research

- Understand how new opportunities in the GPCR field are not confined to underexploited or orphan GPCRs.
• Gain awareness of the multiplicity of opportunities that are, or will become, available as knowledge of specific GPCRs improves.
• Understand which specialist companies offer technologies that would make them most relevant as potential partners.
• Identify which new approaches might be most relevant to specific project goals.
• Gain insight into the predicted development of the market in GPCR therapeutics.
Table of Contents

The Future of GPCRs in Drug Discovery

Executive summary 10

Introduction 10
Characteristics of GPCRs 10
Commercial exploitation 11
New approaches 12
New opportunities 13
Specialist company profiles 14
Market outlook for drugs targeting GPCRs 14

Chapter 1 Introduction 18

Summary 18
Introduction 18
GPCRs in the human genome 19
Additional opportunities 20
The leading class of drug targets 21
Commercially validated targets 23

Chapter 2 Characteristics of GPCRs 28

Summary 28
Introduction 28
Protein structure 29
Functional receptors 31
Second messengers 31
Agonists, antagonists, partial agonists, and inverse agonists 33

Chapter 3 Commercial exploitation 36

Summary 36
Introduction 37
Current successes 37
Targeted GPCRs 44
Unexplored targets 47
Difficult targets 50
Opportunities 50

Chapter 4 New approaches 54

Summary 54
Introduction 55
Screening methods 56
Structure-based methods 57
Knowledge-based methods 60
Allosteric modulators 62
Bifunctional ligands 65
Dimeric receptor targeting ligands 66
Biased ligands 68

Chapter 5 New opportunities 72

Summary 72
Introduction 73
Enhanced selectivity 73
Atypical antipsychotics 75
Lorcaserin 78
Figure 1.1: Commercially exploited targets by target type 22
Figure 1.2: Exploited and unexploited GPCRs by class 23
Figure 2.3: Heptahelical structure of Class A and Class B GPCRs 29
Figure 2.4: Schematic diagram of Class C GPCRs 30
Figure 2.5: GPCR signaling 32
Figure 2.6: Schematic dose response curves to different types of GPCR ligand 33
Figure 3.7: Exploitation of class A GPCRs 38
Figure 3.8: Schematic phylogenetic relationship between groups of Class A GPCRs 45
Figure 3.9: Relative exploration of groups of class A GPCRs 49
Figure 4.10: Strategic opportunities in targeting GPCRs 55
Figure 4.11: Timeline of GPCR 3-dimensional structural information 58
Figure 4.12: Potential advantages with allosteric modulators of GPCR function 62
Figure 4.13: Schematic of allosteric modulator approach 63
Figure 4.14: Comparison of biased ligands and conventional GPCR ligands 69
Figure 5.15: Approach to more selective antipsychotic drugs 76
Figure 5.16: Lorcaserin, enhanced 5-HT2C receptor selectivity 78
Figure 7.17: Continued opportunities to exploit GPCRs 109
Figure 7.18: Angiotensin AT1 antagonists - the patent cliff in the US 113

List of Tables

Table 1.1: Classes of GPCRs 19
Table 1.2: Sales of GPCR-directed drugs achieving sales of >$250m in 2009 24
Table 3.3: Sales of AT1 receptor antagonists ($m), 2009 42
Table 5.4: GPR119 agonists in development for the treatment of type 2 diabetes 82
Table 5.5: DP2 antagonists in development for the treatment of asthma 83
Table 6.6: GPCR pipeline of 7TM Pharma 93
Table 6.7: GPCR pipeline of Actelion 94
Table 6.8: GPCR pipeline of Addex Pharmaceuticals 96
Table 6.9: GPCR pipeline of Arena Pharmaceuticals 97
Table 6.10: GPCR pipeline of Domain Therapeutics 101
Table 6.11: GPCR pipeline of Euroscreen 102
Table 6.12: GPCR pipeline of Tranzyme Pharma 105
Table 7.13: Drugs in advanced development, targeting unexploited GPCRs 115