Preface

The phenomenon of allosteric transitions within proteins was elegantly described in the 1960s by Monod, Wyman, and Changeux. However, the concept of allosteric modulation of G protein-coupled receptors (GPCRs) remained little more than a pharmacological curiosity until the 1990s when functional cell-based assays overtook traditional radioligand binding methods as the high-throughput screening method of choice, revealing a multiplicity of GPCR-interacting ligands. As we enter 2020, it is timely to consider the progress made toward the discovery, mechanistic understanding, and development of allosteric modulators of GPCRs as new therapeutics.

The term *allosteric*, from the Greek *allos* (other) and *stereos* ("solid" or "shape"), defines binding sites (and their ligands) that are topographically distinct from that utilized by the endogenous agonist for a receptor (the *orthosteric* site). As such, allosteric modulation confers a unique set of properties onto a GPCR, including probe dependence (different responses depending on the cobound orthosteric ligand), saturability of effect (driven by the level of cooperativity between the two cobound ligands), and often enhanced receptor selectivity.

The past two decades have seen the advent of hundreds of discovery projects targeting allosteric modulators of GPCRs. A critical element of success has been developing improved methods for understanding the (at times complex) mechanistic pharmacology of this class of ligand. This spans from exploiting recent advances in GPCR computational and structural biology through to considering how the inherent properties of allosteric ligands translate into efficacy in disease states, both in animal models and patients.

With 4 allosteric GPCR drugs now approved, and a further 22 in active clinical development (Table 1), it is an opportune time to review the landscape. What we have learnt, and what remains unanswered in our understanding of GPCR allosteric modulation—and how we can bring these concepts to the development of improved therapeutics?

This volume includes contributions from experts across the field of GPCR allosterism, spanning the spectrum from computational chemistry through to evaluation of allosteric modulators in preclinical models of disease. In Chapter 1, Gary Tresadern (Janssen) and colleagues outline ligand- and receptor model-based computational approaches that have been used for drug discovery targeting metabotropic glutamate (mGlu) receptors.

Table 1 Allosteric modulators of GPCRs either approved or in active clinical development (as of March 2020; data from Cortellis Competitive Intelligence database search[a]).

Drug	Main indication(s)	GPCR target	Mode[b]	Clinical Phase
Maraviroc	HIV infection	Chemokine CCR5	NAM	Launched
Evocalcet	Hypercalcemia; secondary hyperparathyroidism	Calcium sensing receptor	PAM	Launched
Etelcalcetide	Secondary hyperparathyroidism	Calcium sensing receptor	PAM	Launched
Cinacalcet	Hypercalcemia; secondary hyperparathyroidism	Calcium sensing receptor	PAM	Launched
Cenicriviroc	NAFLD/NASH[c]; primary sclerosing cholangitis	Chemokine CCR2/CCR5	NAM	Phase III
SK-1403	Secondary hyperparathyroidism	Calcium sensing receptor	PAM	Phase III
LY-3154207	Alzheimer's disease; Parkinson's disease	Dopamine D_1 receptor	PAM	Phase II
ASP4345	Schizophrenia	Dopamine D_1 receptor	PAM	Phase II
Dipraglurant-ER[d] Dipraglurant-IR[d]	Dystonia L-DOPA-induced dyskinesia	Metabotropic Glu5 receptor	NAM	Phase II
Foliglurax	Parkinson's disease	Metabotropic Glu4 receptor	PAM	Phase II
RVT-1502	Insulin-dependent and non-insulin-dependent diabetes	Glucagon receptor	NAM	Phase II
Mavoglurant	Obsessive compulsive disorder	Metabotropic Glu5 receptor	NAM	Phase II
ADX-71149	Epilepsy	Metabotropic Glu2 receptor	PAM	Phase II
ASP-8302	Bladder disease	Muscarinic M_3 receptor	PAM	Phase II

Table 1 Allosteric modulators of GPCRs either approved or in active clinical development (as of March 2020; data from Cortellis Competitive Intelligence database search[a]).—cont'd

Drug	Main indication(s)	GPCR target	Mode[b]	Clinical Phase
Vicriviroc	Colorectal cancer	Chemokine CCR5	NAM	Phase II
Nimacimab	NAFLD/NASH[c]	Cannabinoid CB_1 receptor	NAM[e]	Phase II
HME-0266	Movement disorders	Metabotropic Glu5 receptor	NAM	Phase I
JNJ-55375515	Neurological disease; psychiatric disorder	Metabotropic Glu2 receptor	NAM	Phase I
SX-682	Various cancers	Chemokine CXCR1/2 receptor	NAM	Phase I
VU-319	Mild cognitive impairment	Muscarinic M_1 receptor	PAM	Phase I
LY-3154885	Parkinson's disease dementia	Dopamine D_1 receptor	PAM	Phase I
CVL-231	Schizophrenia	Muscarinic M_4 receptor	PAM	Phase I
ASP-8062	Drug dependence	$GABA_B$ receptor	PAM	Phase I
HTL-14242	Multiple CNS indications	Metabotropic Glu5 receptor	NAM	Phase I

[a]Search in Cortellis Competitive Intelligence for drugs with "*Any Action (G protein coupled receptor modulator) AND Any Text (allosteric)*" filtered for "*Highest Status*", "*Launched; Phase 1 Clinical; Phase 2 Clinical; Phase 3 Clinical,*" with manual curation for missing, duplicated or incorrectly annotated entries.
[b]PAM, positive allosteric modulator; NAM, negative allosteric modulator.
[c]NAFLD, nonalcoholic fatty liver disease; NASH, nonalcoholic steatohepatitis.
[d]IR, immediate release formulation; ER, extended release formulation.
[e]Monoclonal antibody.

In Chapter 2, Kirstie Bennett, John Christopher and Benjamin Tehan (Sosei-Heptares) elegantly describe computational and medicinal chemistry, along with structural biology approaches, to the identification of novel mGlu5 negative allosteric modulators.

In Chapter 3, Guy Servant (Firmenich) and colleagues provide an overview of the broad range of allosteric modulators that have been discovered

and developed for the human sweet taste receptor, and apply state-of-the-art analytical models to better understand their function. Completing the set of chapters on molecular understanding of allostery at Class C GPCRs, in Chapter 4, Julie Kniazeff (IGF, CNRS) outlines mechanisms of modulation the $GABA_B$ receptor, which encompass not only small molecule ligands, but also allosteric interactions that occur across the obligate dimer and higher order oligomers. In Chapter 5, Augen Pioszak (University of Oklahoma) and Debbie Hay (University of Auckland) extend the notion of allosteric modulation of GPCRs by endogenous protein partners by exploring the effect of receptor activity modifying proteins (RAMPs) on the function of calcitonin and calcitonin-like Class B GPCRs. In Chapter 6, Alice Berizzi and Cyril Goudet (IGF, CNRS) outline the opportunities to interrogate receptor function and GPCR allostery by using photo-switchable ligands, which have most notably been applied to Class C GPCRs, but have broad applicability to interrogate physiology of any receptor. In Chapter 7, Francis Willard, Joseph Ho and Kyle Sloop (Lilly) describe the discovery of a small molecule allosteric modulator of the Class B glucagon-like peptide-1 receptor, BETP, and its utility in terms of understanding receptor function and tractability as a drug target for medicinal chemistry.

In Chapter 8, Kari Johnson (Uniformed Services University of the Health Sciences) and David Lovinger (NIAAA) summarize the Class C mGlu receptor family as drug targets for the treatment of alcohol use disorder, outlining the preclinical evidence base, most notably for mGlu2 and mGlu5 receptors. In a similar vein, Leigh Walker and Andrew Lawrence (Florey Institute of Neuroscience and Mental Health) highlight recent advances in allosterically targeting the muscarinic M_1, M_4 and M_5 receptor subtypes in the context of alcohol and other substance use disorders in Chapter 9. Miriam Scarpa, Sarah Hesse and Sophie Bradley (University of Glasgow) complete the volume with a summary of the progress toward the development of selective muscarinic M_1 receptor ligands as an approach to both symptomatic and disease modification in Alzheimer's disease in Chapter 10.

I am enormously grateful to all of the authors who so willingly gave up their time to contribute to this venture. It is only through projects such as this that we have the opportunity to take a broad view of the field, assess our progress, and establish what will still have to achieve. The road to the discovery and development of better GPCR therapeutics may be a long and challenging one, but it is no doubt slightly shorter and easier to traverse thanks to the colleagues who have assembled this volume. I would like also

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