Our understanding of the G protein-coupled receptor (GPCR) family of cell surface receptors continues to advance at a pace. Driven by a flow of new atomic level structures and novel insights into receptor signal transduction, we are learning more of the fundamental biology of this therapeutically important class of receptors. In this Special Edition of *ACS Pharmacology and Translational Sciences* we have attempted to capture some of these advances in a mixture of articles that includes reviews, original research papers, a perspective and the outcome of a workshop.

Not surprisingly a number of articles have focused on the question of ligand bias or functional selectivity. Understanding the rules that govern the rational-design of GPCR ligands that drive receptor signalling towards pathways that promote clinical efficacy and away from pathways that mediate toxicity/adverse outcomes has been the aim of many of the world's leading GPCR research groups[1-5]. Here the challenges of the identification and characterisation of biased ligands is exemplified in an article by **Wouters *et al.*** who focus on the cannabinoid CB1 receptor to discover novel biased ligands. The mechanism of bias signalling is an area of intense investigation and is covered here in an article by **Verweij *et al.,*** where the role played by receptor phosphorylation in driving differential signalling is considered using the histamine H4 receptor as an exemplar. It is now clear that mechanisms other than those centred on receptor phosphorylation[6] and arrestin interaction[7] may underlie bias signalling, a point made clearly in the article by **van der Velden *et al.,*** where ligand binding kinetics is considered not only in the context of functional selectivity but also as an important contributing factor to *in vivo* efficacy of class A GPCR ligands. van der Velden also touches on the importance of signalling not from the membrane but from endosomal compartments a topic expanded on in a review article by **Plouffe *et al.*** In this contribution Plouffe *et al.* not only provide an update on the latest advances in our understanding of GPCR signalling from intracellular compartments, but importantly places this process in a physiological and pathophysiological context by focusing on the importance of intracellular compartmental signalling in cardiac function.

The Plouffe article is just one of a number of contributions that draws a link between molecular pharmacology and translational science. Prominent among these is an article by **Abd-Elrahman *et al.*** where they present evidence that the Type 5 metabotropic glutamate receptor (mGluR5), contributes to the pathology of Alzheimer's disease. The translational theme is also taken up by **Eiden *et al.*** in a slightly different contribution summarising the outcome of a workshop that draw together the world's experts in peptide-liganded receptors asking what are the best receptor classes and strategies to target peptide-liganded receptors in the treatment of neurological and psychiatric disorders? Among the most relevant areas of translational research in the GPCR field is that of the role of GPCRs in inflammation. Here the review article by **Dahlgren *et al.*** addresses the role of GPCRs in neutrophil biology and how allosteric modulators and biased ligands targeting neutrophil GPCRs might offer novel therapeutic approaches to the control of inflammation.

Where would a special edition focused on GPCRs be without an article on atomic structure? In a contribution from **Liang *et al.,*** cryo-electron microscopy structures provide an atomic level understanding of ligand specificity of the calcitonin receptor-like receptor (CLR). This receptor, when dimerised with its chaperon protein RAMP-1, generates the calcitonin gene-related peptide receptor (CGRP), whereas dimerization with RAMP2 and RAMP3 results in the

adrenomedullin receptors 1 and 2, respectively. The paper by Liang *et al.* provides an explanation behind the allosteric modulation of CLR by the RAMP-family. Staying with this class B receptor family **Garelja *et al.*** investigate the mechanism of differential signalling of CLR when dimerised with RAMP1, 2 and 3 and in a separate contribution **Gingell *et al.*** describes how CLR dimerization with different RAMP proteins promotes different mechanisms of receptor internalisation. Continuing with the theme of Class B receptors **Fang *et al.*** provide a mechanistic understanding of the internalisation of the glucagon-like peptide-1 receptor.

Finally, our *Special Edition* presents a series of articles demonstrating the importance of novel post-translational modifications. **Goth *et al.*** reviews the area of post translational modification of extracellular domains on GPCRs. This includes the importance of glycosylation, tyrosine sulphation, modification of proteolytic cleavage sites and extracellular sites of phosphorylation. The importance of extracellular post-translational modifications is expanded on further in the contribution by **Marullo *et al.*** where they review the role of N-glycan chains located at the N-terminus of GPCRs that act as mechano-sensors playing a role in cell:cell interactions that can provide a means of mechanical activation of GPCRs.

This special edition has drawn a number of contributions from the newly established European network of scientists drawn together under the banner of the European Network on Signal Transduction (ERNEST). This exciting collaborative network that brings together scientists from within the European Union and also associated countries to tackle unresolved questions in GPCR signal transduction and biology. The aims, objectives and work packages of ERNEST are presented in an article by **Sommer *et al.***

Overall, we hope that you find this special edition both informative and enjoyable.

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