Editorial

Continuing for many decades, and even into this post-genomic era, the G protein-coupled receptors (GPCRs) remain attractive targets for the discovery of small molecule therapeutics and still constitute the largest single fraction of the "druggable proteome", with GPCR-targeted drugs having annual sales in the tens of billions of dollars worldwide [1,2]. Further exploitation of this rich treasure trove of targets, however, demands adding novel, creative approaches of identifying GPCR signaling modulators to the continued application of traditional high-throughput screening and medicinal chemistry efforts. In two special issues of CCHTS, we have compiled accounts from a cross-section of strategies in the hopes of illuminating the breadth of available and emerging approaches to identifying small molecules that modulate GPCR signal transduction in valuable ways.

In this issue (*CCHTS* Vol. *11*, No. *5*), Kenakin considers the emerging realm of allosteric modulators of GPCR signaling and the attendent modifications to screening strategies required to maximize their discovery in high-throughput screens of biological function. The number of such HTS-amenable biological readouts of GPCR action are ever-expanding; Crouch and Osmond discuss the use of labelled antibody monitoring of ERK phosphorylation status in this context, whereas Fang and co-workers consider the emerging realm of label-free, intact cell readouts. Johnston and colleagues review their work in identifying novel phage display peptides with nucleotide-state-selective affinity for heterotrimeric G-protein alpha subunits, as well as applying them in developing non-radioactive assays of G-protein activation by GPCR signaling. Smrcka and co-workers review their work in identifying novel phage display peptides with affinity for heterotrimeric G-protein beta/gamma subunits and their application to *in silico* compound screening for Gbeta/gamma inhibitors. Finally, Kimple *et al*. round out this collection of articles with the most speculative assay development concept, involving a target considerably distant from the orthosteric binding site of GPCRs – namely, the interaction of heterotrimeric G-protein alpha subunits with the GoLoco motifs of G-protein signaling regulators LGN and RGS12.

In next issue (*CCHTS* Vol. *11*, No. *6*), Houston and colleagues describe a *tour-de-force* application of iterative chemical synthesis and biological testing towards the rational design of ligand tools (antagonists, agonists, radioligands) for a single GPCR -- the purinergic $P2Y_1$ receptor that represents an important therapeutic target in platelet aggregation. Jensen and Roth describe a converse, post-genomics approach of screening single molecules against a multitude of receptors, and the consequent surprises and biological insights that can result from such screening. As a unique means to identify new GPCR-binding compounds in an unbiased fashion, Whitehurst and Annis describe the use of affinity selection-mass spectrometry (AS-MS) as applied to HTS of GPCRs. This newly-emergent technique relies on obtaining quantities of purified (and functional) receptor; the multitude of strategies for this technical hurdle are enumerated in encyclopedic detail in the following paper by Chiu and colleagues. In addition to enabling AS-MS and structural biology pursuits, purified GPCR preparations should also greatly facilitate antibody generation; the use of state-selective anti-GPCR antibodies in HTS and drug development is considered in the paper by Gupta and co-workers.

We thank all the authors who participated in this project for their creative inputs. We hope that, in the aggregate, these articles spark renewed excitement towards GPCR signaling as a drug discovery platform and also highlight some of the novel and innovative approaches yet to be fully explored in this tried-and-true field.

REFERENCES

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