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GPCR Drug Discovery: Emerging Targets, Novel Approaches and Future Trends

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G-protein coupled receptors (GPCRs) are a class of seven-transmembrane proteins that have attracted tremendous interest in both the pharmaceutical industry and academia for decades owing to their physiological and therapeutical importance and accessibility for small molecule drug discovery. GPCRs play critical roles in physiological responses to a variety of stimuli such as ions, small molecules, macromolecules, peptides and other proteins, which are associated with the vast biological functions mediated by GPCRs. Aspects of cognition, immune response, and cellular organization as well as many others, are regulated by GPCR signaling. The pharmacological regulation of GPCRs provides leverage for the treatment of various human diseases including those of the central nervous system (CNS), cancer, viral infections, inflammatory disorders, metabolic disorders, and others. Moreover, the location of GPCRs in the cellular membrane allows unique pharmacological access to these proteins while the effectors and second messenger systems coupled to the receptors allow for efficient drug action and drug targeting in the discovery of novel therapeutics. Intriguingly, GPCRs represent the largest family of druggable proteins in the human genome and unsurprisingly are targeted by more than 30% of marketed drugs worldwide.

This issue contains a diverse collection of reviews covering the cutting-edge biology and medicinal chemistry in GPCR drug discovery, with special attention to new approaches in traditional targets, emerging targets, and future trends. As a traditional drug target, the dopamine D1 receptor (D1R) is essential to neurotransmission in various brain pathways where it modulates key functions including voluntary movement, memory, attention and reward. Recent chemistry breakthroughs and innovative approaches to selectively target and activate the D1R also holds promise for creating pharmacotherapy for several neurological diseases. Allen and colleagues provide an overview of the major classes of D1R selective ligands including antagonists, orthosteric agonists, non-catechol biased agonists and positive allosteric modulators, highlighting their structure activity relationships and medicinal chemistry [1]. An impaired signaling capacity of the serotonin (5-HT) 5-HT_{2C} receptor (5-HT_{2C}R), another traditional drug target in class A GPCRs, contributes to the

neurobehavioral processes that underlie addictive disorders as well as other chronic health issues (*e.g.*, depression, impulsivity disorders, obesity). The recently solved crystal structures of 5-HT_{2C}R co-complexed with ligands are expected to significantly facilitate small molecule drug discovery by targeting this receptor. Zhou and colleagues highlight the biological significance, the biological context for signaling and function, as well as the current status of emerging approaches developing various agonists and positive allosteric modulators (PAMs) of the 5-HT_{2C}R [2]. The pituitary adenylate cyclase-activating polypeptide (PACAP)-selective PAC1 receptor (PAC1R, ADCYAP1R1) is a member of the vasoactive intestinal peptide (VIP)/secretin/glucagon family of GPCRs. Enhancing PAC1R signaling has the potential to mitigate cellular damage associated with cerebrovascular trauma (including stroke), neurodegeneration (such as Parkinson's and Alzheimer's disease) or peripheral organ insults. Given the diverse PAC1R-mediated biological activities, the receptor has emerged as a relevant pharmaceutical target. Li and colleagues provide a comprehensive review on targeting the PAC1 receptor for neurological and metabolic disorders, and highlight the opportunities and insights to accelerate structure-based drug design for PAC1R and other class B GPCRs in the treatment of a number of disease conditions [3]. The cannabinoid receptor 1 (CB1R) is involved in a variety of physiological pathways and has long been considered an important therapeutic target for the treatment of obesity, metabolic disorders and drug addiction. However, the first-in-class CB1R ligand rimonabant, with therapeutic use for obesity treatment and smoking cessation, displays serious psychiatric side effects, including anxiety, depression and even suicidal ideation, resulting in its eventual withdrawal from the European market. Zhang and colleagues present the recent progress towards overcoming the psychiatric side effects of the cannabinoid CB1 receptor antagonists, and highlight the current approaches for therapeutics development by targeting this receptor [4]. Type II diabetes is a major health issue worldwide with complex metabolic and endocrine abnormalities. Insulin signaling regulates metabolic homeostasis by regulating glucose and lipid turnover in the liver, skeletal muscle and adipose tissue. Vasudevan and Gupta summarize the emerging antidiabetic therapeutics including classes of drugs targeting GPCRs in the liver, adipose tissue and skeletal muscle, and highlight several shared intermediates between insulin and GPCR signaling cascades opening potential novel avenues for diabetic drug discovery. Adenosine receptors (AR) are a class of purinergic GPCRs. Alterations of AR function and expression have been studied in neurological diseases such as epilepsy, Alzheimer's disease, and Parkinson's disease, cardiovascular diseases, cancer, and inflammation and autoimmune diseases [5]. The positron emission tomography (PET) imaging probes have provided valuable information for diagnosis and therapy of diseases related to alterations of AR expression. Chen and colleagues provide a concise overview of various AR-targeted radioligands for PET imaging in diseases, and highlight the most recent advances in PET imaging studies by using AR-targeted probes. Recent success in immunotherapy has advanced cancer treatment from traditional chemotherapy, irradiation therapy and targeted therapy into an exciting new era, representing a promising future trend in cancer drug discovery and development [6]. The discovery of more targets that regulate the immune system and chronic inflammation, such as GPCRs, offers novel alternative strategies for enhancing antitumor immunity. Chen and colleagues provide an update on recent advances in small molecular regulators targeting GPCRs that are associated with oncology immunomodulation, including chemokine receptors, purinergic

receptors, histamine receptors, prostaglandin E receptor EP4 and opioid receptors. In addition, they outline how such modulators affect tumor immunity and neoplasia by regulating immune cell recruitment and modulating tumor stromal cell biology, and highlight the recent clinical advances in small molecular regulators targeting these GPCRs, in combination with immune checkpoints blockers such as PD-1/PDL-1 and CTLA4 inhibitors for the treatment of human cancers [7].

Acknowledgments

As the Guest Editors, we would like to thank all the authors for their tremendous effort, dedication, and excellent contribution to this special issue of *Current Topics in Medicinal Chemistry*. We hope that this issue will serve as a key reference work for medicinal chemists, chemical biologists, structural biologists, pharmacologists, and other research investigators engaged in or interested in GPCR drug discovery and development.

Biographies

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