Protein Activation in Drug Discovery - Part-I

In direct contrast to the inhibition of protein functions, the activation is another important strategy drug hunters employ to achieve desired therapeutic effects in their practice. This could be accomplished through a diverse set of pharmacological agents, such as orthosteric agonists, allosteric agonists, and positive allosteric modulators (PAM). While the topic is very broad, we intend to sample protein activation in drug discovery in multiple therapeutic area in different development stages. We also want to highlight some current advances in the recently developed concepts of bitopic and biased activations in the G-protein coupled receptor (GPCR) field. In addition, we are interested in structural insights that could potentially allow design of ligands with better potency and target selectivity.

In this thematic issue of Protein Activation in Drug Discovery, five manuscripts encompassing multiple protein classes are presented. Chan et al. review the development and potentials of non-peptidyl activators of the insulin-induced and brain-derived neurotrophic factor (BDNF)-induced signaling pathways in type 2 diabetes mellitus (T2DM) treatments [1]. Lian et al. summarize both cyclic dinucleotide (CDN) and non-nucleic acid derived STING agonists that have generated enormous interest and been intensely pursued in this new era of cancer immunotherapies [2]. McGowan describes recent developments in the small molecule activation of the Toll-like receptors (TLRs) 7 and 8 in the innate immunity signaling [3]. Goldsmith updates on the activation of N-methyl-D-aspartate receptor (NMDAR) with a diverse chemotypes of positive allosteric modulators (PAMs) that could potentially lead to new treatments in neurological and psychiatric disorders [4]. Atobe reviews recent advances of agonists of transient receptor potential vanilloid (TRPV) and their application as disease-modifying osteoarthritis drugs (DMOADs) [5].

We are grateful to all the authors who contributed to this special thematic issue and referees who provided insightful feedbacks. We also want to thank Dr. Allen B. Reitz (Editor-in-Chief) and Ms. Ambreen Irshad (Associate Editor) for their help during the preparation of this issue. The success of this issue is not possible without their help.

REFERENCES