Modulation of Protein-Protein Interactions for the Development of Effective Therapeutics - From a Joint Perspective of Experiment and Computation

Many proteins present in living organisms act as obligate oligomers – that is to say - they require other protein partners to function properly. Oligomerization does not only lead to the formation of physical interactions, which are required to hold individual protomers together in these assemblies, but it also triggers the cross-talk within the oligomer, so that individual protomers can regulate and modulate each other’s function in the form of either inhibition or activation. Consequently, this notion has changed the classical “single-target” pharmacology to “multi-target” one, urging the development of novel approaches in the field of drug discovery. In general, modulation of the function of a particular complex can be done by means of small-molecules developed specifically to target the interface between the protomers. This requires atomistic-level knowledge regarding the structure and dynamics of the system. As such, numerous experimental techniques were established in order to identify the partners in these assemblies. However, data solely based on these experimental techniques do not provide a mechanistic insight on the system as it cannot provide atomistic-level information per se regarding inherent allosteric interactions that govern the function of the complex. In this respect, computational methods act as indispensable tools to complement and to provide careful experimental data interpretation. The combination of these two worlds paves the way to the development of new, efficient and specific therapeutics.

In this special issue, the status and the prospects of small-molecule inhibition of protein-protein interactions were reviewed with a special emphasize on MDM2/X and TNF/RANKL by Santos et al. [1] and Afantitis et al. [2] respectively. The authors thoroughly checked available experimental methods that target and modulate the function of these specific systems by pointing out both advantages and disadvantages. In the former, the importance of a multi-target approach was also discussed.


Besides the experimental perspective on modulation of protein-protein interactions, the status and prospects of computational approaches were also covered by Tuncbag et al. which made an extensive assessment on the methodological approaches currently used for structure prediction [4]. These authors also revisited protein-protein targeting from a system biology perspective and discussed other non-structural approaches.

Finally, the guest authors of this issue, Dr. Sensoy and Dr. Moreira and their collaborators made thorough review on both experimental and computational methods/tools used to identify/predict and target interaction interfaces of specific G Protein-Coupled Receptor (GPCR) oligomers [5]. This class of membrane receptors are known to form extensive oligomers to respond precisely to the needs of the cells and are targeted by nearly 40% of currently prescribed drugs. Authors emphasized the relevance of merging both types of techniques to develop efficient therapeutics with unwanted side effects. They also connected this information to diseases that emerge upon misregulation of pathways involved in oligomer formation.

As guest editors, we would like to express our great gratitude to all the authors who contributed to this special issue and made a great effort to bring light to the status and prospects in the field of protein-protein modulation from a joint perspective. Finally, we would like to thank the main editors for giving us this opportunity to act as guest editors of the journal “Current Topics in Medicinal Chemistry”.
REFERENCES


---

**Irina Sousa Moreira, Ph.D.**  
*Guest Editor*  
*Current Topics in Medicinal Chemistry*  
Group Leader – Data Driven Molecular Design  
Center for Neuroscience and Cell Biology  
Rua Larga, FMUC, Polo I, 1ºandar,  
Universidade de Coimbra, 3004-517 Coimbra,  
Portugal  
E-mail: irina.moreira@cnc.uc.pt  
URL: [http://www.moreiralab.com/](http://www.moreiralab.com/)

**Özge Şensoy, Ph.D.**  
*Guest Editor*  
*Current Topics in Medicinal Chemistry*  
Assistant Professor  
Department of Computer Engineering; School of Engineering and Natural Sciences  
Istanbul Medipol University  
Kavacik Mah., Ekinciler Cad. No:19, 34810 Beykoz, Istanbul  
Turkey  
E-mail: osensoy@medipol.edu.tr