Editorial

From Allosteric Drugs to Allo-Network Drugs: State of the Art and Trends of Design, Synthesis, and Computational Methods

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Abstract: Allosteric drugs bind to sites which are usually less conserved evolutionarily as compared to orthosteric sites. As such, they can discriminate between closely related proteins, have fewer side effects, and a consequent lower concentration can convey a lesser likelihood of receptor desensitization. However, an allosteric mode of action may also make the results of preclinical and animal experiments less predictive. The sensitivity of the allosteric consequences to the environment further increases the importance of accounting for patient population diversity. Even subtle differences in protein sequence, in cellular metabolic states or in target tissues, can result in different outcomes. This mini-hot-topic issue of CTMC showcases some successes and challenges of allosteric drug development through the examples of seven-transmembrane (GPCR), AMPA, NMDA and metabotropic glutamate receptors, as well as the morpheein model of allosterism involved in inherent metabolic errors. Finally, the development of allo-network drugs, which are allosteric drugs acting indirectly on the neighborhood of the pharmacological target in protein-protein interaction or signaling networks, is described.

Keywords: Allo-network drugs; allosteric drugs; glutamatergic transmission; GPCR receptors; networks; quaternary structure; SAR landscapes; schizophrenia.

1. INTRODUCTION

On the one hand, allosteric drugs (targeting distant, allosteric regulatory sites of proteins) may be more promising than orthosteric drugs (binding to ligand binding sites or active sites of enzymes). Allosteric drugs bind to sites which are usually less conserved evolutionarily than orthosteric sites, which are occupied by very similar ligands, such as hormones or ATP. Thus, allosteric drugs may discriminate between closely related proteins (receptors, protein kinases, etc.), and usually have less side effects than orthosteric drugs. Moreover, allosteric drugs are less likely to encounter problems such as overdose and receptor desensitization. On the other hand, the development of allosteric drug action is a challenging process. The lower evolutionary pressure on allosteric sites, and in particular the sensitivity of the conformational consequences – agonist or antagonist – to slight changes in the drug, or the environment, including even changes in protonation states, make the results of preclinical and animal studies less predictive with regard to the effects of the drug in humans. This is especially challenging when considering a highly diverse patient population [1-7].

The successes of allosteric drugs are exemplified well by the seven-transmembrane receptor family (G-protein coupled receptors, GPCRs). GPCRs signal a wide range of extracellular stimuli ranging from photons of light, to peptides, lipids, neurotransmitters, and hormones. Historically, GPCRs have become the most successful drug targets, with almost one third of currently available therapeutics acting on GPCRs. This success was highlighted by the Nobel Prize in chemistry in 2012 [1, 2, 8, 9]. Despite the wide use and importance of the receptor family, only a small fraction of known GPCRs are currently targeted, leaving much room for future novel pharmacological applications. The first two contributions of this issue [10, 11] assess drug development aspects of this target family.

The hurdles faced by allosteric drug development are exemplified by the complex challenge of identifying allosteric leads. The structure-activity relationship (SAR) landscape of allosteric ligands is often modular, composed of 'flat' segments where modifications of the chemical structure of the ligand do not induce major changes in its activity, and 'rough' segments where minor chemical changes of the ligand may lead to significant [12-14], even opposing agonist/antagonist effects. The apparent modularity of allosteric SAR landscapes compared to orthosteric SAR landscapes may be due to the highly anisotropic nature of allosteric action [15] as compared to the pronounced centrality of the active site in protein structure networks. These challenges are reviewed by the examples of the last three contributions extending the scope of allosteric drugs to AMPA receptors, NMDA receptors and metabotropic glutamate receptors [16], as well as to quaternary protein structure dynamics [4, 17] and to allo-network drugs [18, 19] involving the propagation

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1873-5294/13 $58.00+.00

of allosteric effects through protein-protein interactions across signaling networks, beyond individual proteins or closely associated protein complexes.

2. FROM ALLOSTERIC DRUGS TO ALLO-NETWORK DRUGS

In the opening contribution of this series, *Terrence Kenakin* [10] describes the quantitative models available to characterize the allosteric effects in GPCRs in molecular terms, and shows their use to predict allosteric effects in all other systems. He concludes that quantitative analysis "necessitates the assessment of two specific aspects of allosteric ligand function: (1) the direct effect of the allosteric ligand on receptor conformation insofar as it may lad to observable changes such as agonism, and (2) the effects imposed by the allosteric ligand on the action of endogenous ligands such as neurotransmitters and hormones."

Graeme Milligan and co-workers [11] summarize recent developments in the pharmacology of free fatty acid sensitive GPCRs, and discuss the potential of allosteric ligands of this receptor sub-family in the treatment of metabolic diseases such as type 2 diabetes and inflammatory conditions. They conclude that "it also appears likely that several additional ligands already described for these receptors are in fact also allosteric, and indeed allosteric agonists and modulators appear destined to play a critical role in future drug development at fatty acid-sensitive GPCRs."

Robert Volkmann and co-workers [16] give a network background of schizophrenia development showing a paramount role of glutamatergic response misfunction [20-22], and address the promises of the use of allosteric glutamatergic ligands to treat schizophrenia. They show that allosteric modulators are better suited to maintaining the highly precise temporal and spatial aspects of glutamatergic synaptic transmission. The paper concludes that allosteric modulators of AMPA receptors, NMDA receptors, and metabotropic glutamate receptors are promising drug candidates for restoring physiological glutamatergic synaptic transmission.

Eileen Jaffe [4, 17] describes the impact of quaternary structure dynamics on allosteric drug discovery in terms of the morpheein model of allostery. She highlights the effects of quaternary structure dynamics on the efficiency of the drug discovery process by the examples of porphobilinogen synthase, phenylalanine hydroxylase, HIV integrase, pyruvate kinase, tumor necrosis factor α and transthyretin. In these proteins, the discovery of ligands stabilizing a particular quaternary structure conformation may help reverse disease-inducing shifts of quaternary dynamics causing enzyme dysfunctions related to inborn errors of metabolism.

In the closing contribution of the mini hot topic special issue, *András Szilágyi et al.* [19] extend the earlier concept of *Ruth Nussinov et al.* [18] on allo-network drugs showing that most intra-protein conformational changes may be transmitted across protein-protein interaction and signaling networks of the cell. Allo-network drugs influence the pharmacological target protein indirectly, using specific inter-protein network pathways. Allo-network drugs may rewire the networks of human cells, and can be designed to have specific effects in a diseased state. The contribution is concluded by the suggestion of several methods to identify allo-network drugs including determination of network centralities, network hierarchy, controllability, assessment of perturbation propagation in networks, the analysis of correlated motions, reverse engineering methods to reveal central and less frequently used pathways, as well as analysis of evolutionary conservation, disease-related systems biology data, or system level responses of the cell to drugs. The development of allo-network drugs appears as a promising new trend of drug design.

Collectively, these studies highlight the promises and challenges of the development of allosteric drugs [10, 11, 16, 17, 19], and draw attention to novel areas of this promising aspect of drug design such as free fatty acid sensitive GPCRs [11], receptors involving the correction of glutamatergic response in schizophrenia [16], the morpheein model of allostery involving the quaternary structure dynamics changed by mutations causing inborn errors of metabolism [4, 17], as well as allo-network drugs [18, 19]. The discovery of the structural background of allosteric action has a history of half a century [23-25]. The contributions of this hot-topic issue clearly demonstrate that despite reaching the status of a 'senior citizen', this concept, which is now better understood based on the free energy landscape [26], still deeply influences our understanding of drug action, and opens up new, promising avenues in drug design.

CONFLICT OF INTEREST

The author(s) confirm that this article content has no conflict of interest.

ACKNOWLEDGEMENTS

Work in the authors' laboratory was supported by research grants from the Hungarian National Science Foundation (OTKA K83314, K105415), by the EU (TÁMOP-4.2.2/B-10/1-2010-0013). This project has been funded, in part, with federal funds from the NCI, NIH, under contract HHSN261200800001E. This research was supported, in part, by the Intramural Research Program of the NIH, National Cancer Institute, Center for Cancer Research. The content of this publication does not necessarily reflect the views or policies of the Department of Health and Human Services, nor does mention of trade names, commercial products, or organizations imply endorsement by the U.S. Government.

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Received: December 27, 2012 Revised: December 29, 2012 Accepted: December 30, 2012

PMID: 23409761