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Allosteric Drugs: New Principles and Design Approaches for Gaining Comprehensive Control of Drug Properties and Actions

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Design of allosteric drugs is a promising biomedical implication of allostery, leading to the paradigm change in drug design in general and providing a powerful toolbox for emerging precision medicine. Important characteristics of allosteric sites, effectors, and their modes of actions distinguishing them from the orthosteric counterparts are determined and described here, calling for new principles and protocols in the quests for allosteric drugs. In particular, it is important to consider both binding affinity and allosteric signalling in establishing the structure-activity relationships (SARs) toward design of allosteric effectors. To this end, pairs of allosteric sites and their effector ligands – the site-effector pairs - should be generated and adjusted simultaneously in the framework of what we call directed design protocol. We implemented the protocol in a broadly applicable computational framework for obtaining allosteric site−effector pairs, providing targeted, highly specific, and tunable regulation to any functional site. To demonstrate performance of the framework allosteric effectors and binding sites were designed and optimized for the switch regions of K-RasG12D oncoprotein. The proposed generic framework will be instrumental in developing allosteric therapies aligned with a precision medicine approach.