Allosteric modulation in drug discovery

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In the drug discovery process, small molecules are traditionally designed to bind to the primary active (or orthosteric) site of their biological targets in order to induce a therapeutic effect. This therapeutic effect could be the result of either preventing natural substrates from binding to the active site (inhibitor or antagonist) or directly activating the target (agonist). Despite the significant efforts to achieve both high affinity and high selectivity of small molecules targeting the active site, the similarity between orthosteric pockets among most of the protein families, leads to adverse effects caused by these compounds. A new emerging direction in drug discovery is the use of alternative, non-orthosteric binding sites where small molecules can bind and modulate the biological target's function. These sites are called allosteric sites while the respective small molecules are called allosteric modulators. In the efforts to discover drugs to be used as effective allosteric modulators one needs first to identify the allosteric sites and then design the molecules that can bind to these sites and have tailored functionalities. In this presentation, I will describe our efforts towards this direction applied on phosphoinositide 3-kinase alpha (PI3Kα),[1,2] a target of particular pharmacological interest for anti-cancer drug development.

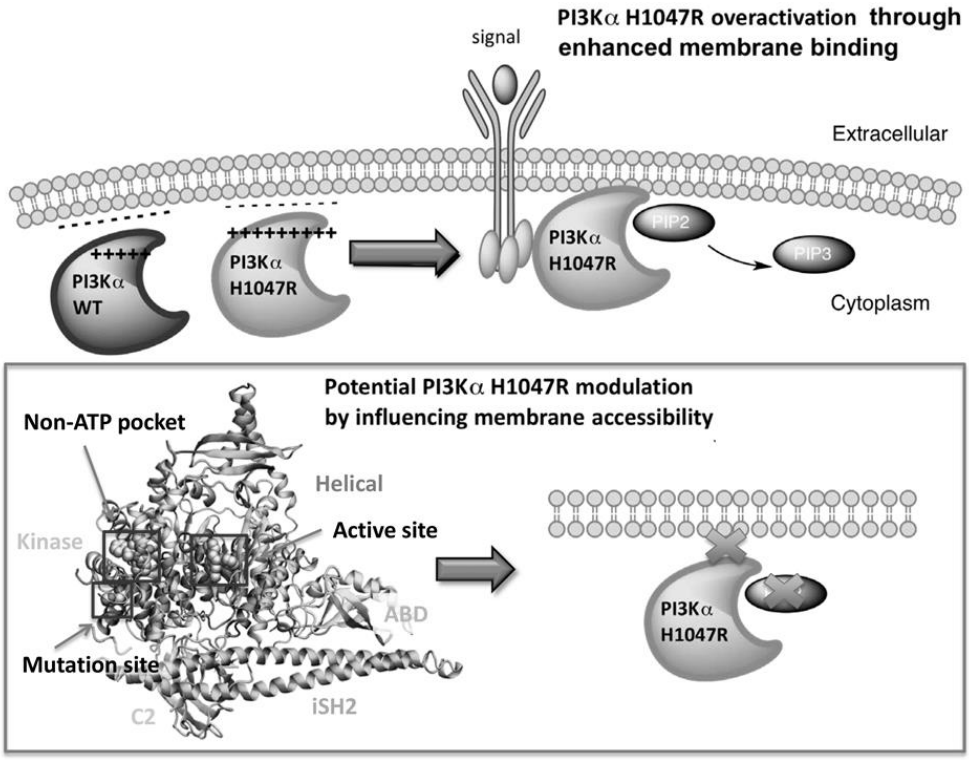

Figure 1. Proposed allosteric mechanism for H1047R PI3Kα targeting.

Bibliography :

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