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Extended Abstract

Targeting Novel Allosteric Sites with Confidence: Methods and Applications †

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Allosteric sites create opportunities to act on novel targets when their orthosteric sites are not druggable. However, they also provide increased selectivity and can modulate their targets in unique ways, such as enzymatic activation or change in protein levels, localization or quaternary structure. The discovery of allosteric modulators has traditionally been serendipitous, resulting from random (often phenotypic) screening and subsequent elucidation of their mechanism of action. Computational tools developed in our group for druggability prediction, binding site mapping, and virtual screening have enabled us to identify and tackle novel allosteric sites with confidence. In this talk, I will give an overview of our approach, which combines molecular dynamics with mixed solvents (MDmix) [1–4] molecular docking [5] dynamic undocking (DUck) [6,7] and, finally, experimental screening of a shortlist of candidate molecules in low-throughput assays. I will provide examples of successful discovery of allosteric binders, including non-competitive pharmacological chaperones for the treatment of rare diseases.

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