BIFUNCTIONAL LIGANDS FOR INHIBITION OF TIGHT-BINDING PROTEIN-PROTEIN INTERACTIONS

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The human interactome has grown immensely within the last two decades [1]. Increased number or protein-protein interactions (PPIs) has accompanied high interest in using inhibitors to regulate dysfunctional cellular signaling and therefore cure diseases that have previously been incurable. We introduce a biligand approach for disruption of strong PPIs, which tend to fall short due to the flat and wide interfaces of PPIs for small-molecule inhibitors (SMIs). We demonstrate this novel approach by disrupting the tight-binding (K_D = 100 pM) tetrameric holoenzyme of cAMP-dependent protein kinase (PKA) in a lysate of genetically engineered cell-line [2]. X-ray analysis of cocrystals supported the construction of bifunctional inhibitors (ARC-inhibitors) that associated simultaneously with the ATP-pocket and the PPI interface area of the catalytic subunit of PKA (PKAc). Bifunctional inhibitor ARC-1411 with a supreme K_D value of 3 pM toward PKAc induced the dissociation of the PKA holoenzyme with a low-nanomolar IC_{50}, whereas the ATP-competitive inhibitor H89 bound to the PKA holoenzyme without disruption of the protein tetramer. These inhibitors pose a distinct influence on the intracellular signaling pathway of PKAc through their difference in inhibition mechanism.

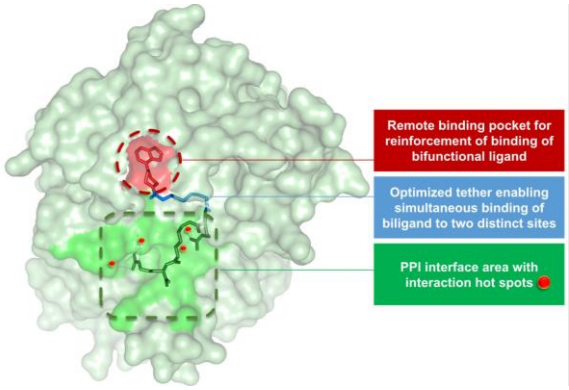

Fig.1 Proposed strategy for building a potent bifunctional protein-protein interaction inhibitor [2].

References

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