S36-3 Design and functional evaluation of dual inhibitors of prenyltransferases targeting identical protein surface structure

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Protein-protein interactions play a central role in numerous biological processes including intracellular signaling pathways. Low molecular weight compounds that modulate such interactions in a selective manner have recently been a focus of intense attention due to their potential to be chemical probes to explore the signaling cascades as well as drug leads for new therapeutic agents to target specific protein interfaces. However, such interfaces involve large and flat protein surfaces that often lack well-defined structural features and are exposed to the bulk of water and solutes. Therefore, disrupting protein-protein interactions by a “drug-like” small molecule still remains a difficult challenge.

We hypothesized that organic agents constructed by assembling a set of small modules, which are designed for binding to multiple sites of the targeted protein surface, may provide a solution for increase affinity for selective binding, reducing molecular size, and introducing antibody-like structural diversity. To this end, we have been studying several methodologies of the module assembly to construct protein surface-directed agents, including a series of enzyme inhibitors that anchor an exterior surface binding module to an interior surface (active pocket) binding module. In this presentation, rational design and functional evaluation of the bivalent compounds for dual inhibition of structurally related protein prenyltransferases, FTase and GGTase-I will be discussed.