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Structure-based design of covalent inhibitors or protein-protein interactions

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While protein-protein interactions (PPIs) represent in principle a significant number of potential drug targets, their validation is usually hampered by the lack of suitable pharmacological tools with sufficient potency and proper pharmacological properties. HTS and other screening methods traditionally failed at identifying such agents. It is reported in this study that a combination of biophysical methods supported by structural studies can guide the design and synthesis of novel pharmacological tools targeting PPIs. When possible, we found that the design of covalent inhibitors can dramatically increase potency and selectivity of these agents. Examples will be discussed including the E3 ubiquitin ligase Siah, the anti-apoptotic protein Bfl-1, and the EphA4 ligand binding domain. For the first two targets, structure-based design of peptide mimics ultimately led to potent and selective antagonists. For the EphA4 LBD, we also deployed a novel NMR-based screening method of combinatorial libraries that together with structural studies led to a potent inhibitor with *in vivo* activity.

Biography

Maurizio Pellecchia is a medicinal chemist with strong background in biophysics and structure-based drug design. He obtained his PhD in Pharmaceutical Sciences, at the ETH-Zurich, and the University of Michigan. Prior to his recruitment at the Sanford-Burnham in 2002 as Associate Professor, he spent a few years in the pharmaceutical industry. He is currently Professor of Chemical Biology at the Cancer Center of the Sanford-Burnham Medical Research Institute, and is an Adjunct Professor at the Department of Pathology of UCSD, and teaches two graduate courses in drug design.

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