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Exploiting unique interactions in the MKK3/6 and ASK1 kinase active sites through computer-aided drug design

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Since the early 1990's, the concept of structure-based drug design has been demonstrated on a wide array of protein targets, becoming an established and integral part of drug discovery and lead optimization. While now synonymous with this concept, computer-aided modeling is widely recognized as a seminal aspect of structurally enabled drug discovery programs. The ubiquitous exposure to structural information has spawned a scientific enlightenment around the details and nuances of protein structural information. Kinases are one of the most extensively studied protein families based on the vast number of structures currently available in the Protein Data Bank. Although they share similar architectures and substrates, it is still quite common to identify unique interactions within these proteins that can yield highly selective inhibitors. My talk will describe the use of computer-aided drug design in the context of optimizing novel inhibitors of the two kinases: MAP Kinase Kinase isoforms 3/6 (MKK3/6) and the Apoptosis Signal-Regulating Kinase 1 (ASK1). Each of these kinases is found within the MAPK pathway and contain unique residues and interactions in the active site. Using structure-based modeling, these differences were exploited to enhance inhibitor potency and selectivity. These efforts yielded highly efficient and selective tool compounds that were valuable in testing key pharmacological hypotheses in the areas of immunological and cardiovascular diseases.

Biography

Simone Verene Bigi completed her BS from University of Notre Dame in South Bend, Indiana.

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