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Structure-based drug design of the EG5 inhibitor NVP-BQS481

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Several biological functions, particularly chromosome segregation, require the generation of motile force. The generation of this force relies heavily on a class of proteins known as motor proteins. Motor proteins such as Kinesin Spindle Protein (KSP), also known as Eg5, utilize the energy derived from ATP hydrolysis to generate motile force. High-throughput screening of Eg5 identified several hits which were non-competitive with ATP with micromolar IC50's capable of inhibiting the motor protein. Using structure-based drug design, these hits were progressed to NVP-BQS481, a clinical candidate with an IC50 of 700 picomolar. The talk will present the design concepts and optimization techniques used to advance the series to the pre-clinical stage.

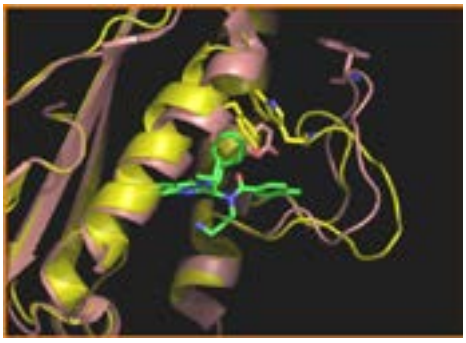

Figure1: *Eg5 compound exosite illustrating conformational changes occurring upon compound binding*

Biography

Dirk Bussiere has his expertise in biochemistry, biophysics, computer sciences and structural biology to the discovery of novel therapeutics for the treatment of disease. He received his BA in biochemistry from Northwestern University, has completed MS in Molecular Biophysics and Biochemistry from Yale University, and PhD in Microbiology, Immunology and Molecular Biophysics from Duke University. He also has an MBA in Entrepreneurship, Management of Technology, and Finance from the Haas School of Business, University of California-Berkeley. He was named a Novartis Leading Scientist in 2007. He is currently the director of the Structural and Biophysical Chemistry group in Global Discovery Chemistry at the Novartis Institutes for Biomedical Research in Emeryville, California.

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