NUS National University of Singapore | Department of Biological Sciences, Faculty of Science

SEMINAR

Mon 12 Oct 2015 | 2pm | DBS Conference Room 1

Hosted by Professor R M Kini

Protein Engineering of Zymogen Activators and Protease Inhibitors Targeting HGF/MET and BACE1



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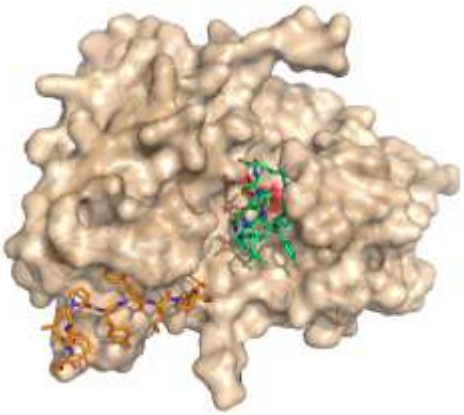
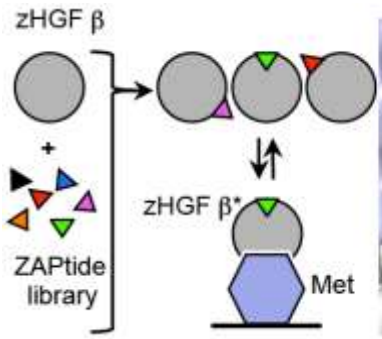
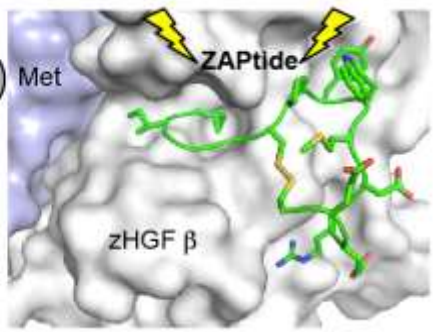
The regulation of proteases and protease-like proteins is a critical aspect of biology. This talk will focus on two different protein engineering stories involving active sites and exosites of proteases. The serine protease-like domain of hepatocyte growth factor (HGF) is critical for Met signaling, which leads to tissue repair and wound healing and, when dysregulated, to cancer. The aspartic acid protease BACE1 is the β-secretase and critical for the formation of the β-amyloid peptide, a key feature of Alzheimer's Disease. By understanding biochemical mechanisms and structures of HGF/Met and BACE1, we have developed novel and diverse inhibitors with potential therapeutic benefit. Using structure-guided peptide phage display combined with activity-based sorting, we engineered potent zymogen activator peptides (ZAPtides) that selectively trap the zymogen in the protease conformation. Molecular mimicry of the trypsin-like N-terminal insertion mechanism by ZAPtides establishes a strategy for reversible pharmacological activation of zymogen serine proteases and protease-like domains.







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