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Structure-based characterisation of small molecule inhibitors against flaviviruses' NS2B-3 protease

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14 September 2021, 2.00pm
Host: Dr Ng Say Kong

Seminar Abstract

In the last decade, there have been increased and larger magnitude of flavivirus' outbreaks. However, there is no specific antiviral treatment for these diseases and patients can only rely on supportive therapy to manage and alleviate the symptoms. With the worsening endemic of flavivirus and the lack of antiviral treatments, flavivirus infection is becoming a major health concern.

Flavivirus' NS2B-NS3 protease is an attractive antiviral target due to its essential role in the viral polyprotein processing process. However, the progress towards designing a potent inhibitor is slow, due to the hydrophilicity and the depth of the protease active site. In this talk, I will highlight the use of a structure-based drug design approach to characterise 2 classes of compounds, small fragment molecules and peptidomimetics inhibitors, against the viral NS2B-3 protease. Firstly, from a fragment compound screening, twenty-two fragments were identified to bind and stabilize the protease. Of which, two fragments were determined to bind S1 pocket of the protease. Secondary, using structural based drug design approach, we reported a series of cyclic, peptidomimetics inhibitors with Ki values within nanomolar range against NS2B-NS3 protease from Zika, West Nile and Dengue Virus. Crystal structures of seven Zika protease inhibitor complexes were determined, and biochemical assays reveal that the inhibitors are very sensitive to cyclic backbone ring size and ring variations. Together, these fragment scaffolds and novel peptidomimetics inhibitors will provide insight and guide future antiviral development with improved potency and biostability.

About the Speaker

Jun Ping received his BSc in Biological Science from Nanyang Technological University in 2016. He was awarded the Nanyang President's Graduate Scholarship to pursue his PhD education at NTU Lee Kong Chian School of Medicine, studying the molecular basis of flavivirus' replication process for antiviral development. Currently, Jun Ping has joined the Animal Cell Bioprocessing team for the development of vaccine against the Scale Drop Disease Virus in Asian sea bass.

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