The complex structure of the Zika virus NS2B-NS3 protease with a boronate inhibitor

Zika virus (ZIKV) is one of the Arthropod-borne viruses. Like the yellow fever virus and dengue virus, it belongs to the *Flaviviridae* family. According to the statistics of the WHO, ZIKV infection cases are reported in 67 countries and territories until July, 2016. ZIKV can trigger the Guillain-Barre syndrome and microcephaly in newborn children. There are no vaccines or antiviral drugs available for protection from or treatment of ZIKV infection.

The NS2B/NS3 protease of ZIKV can cleave the viral polyprotein, which is essential for the virus life-cycle; hence, this enzyme is a potent attractive drug target. A research group headed by Prof. Rolf Hilgenfeld (University of Lübeck, Germany) for the first time reports a complex structure of ZIKV NS2B-NS3 protease with a boronate inhibitor, which can speed up the research for anti-ZIKV drugs.

In the complex structure, the research team found the Boronic-acid inhibitor interacts with glycerol to form a cyclic diester. The new boronate inhibitor could traverse the cellular membrane more readily, then a prodrug might be obtained. Next, the team found a non-conserved Asp that likely accounts for the high catalytic efficiency of the ZIKV protease. Finally, the research group found an unusual dimer, which has not been seen with other flavivirus proteases. This dimer may provide a new assessable model during the virus replication.

Peptide boronic acids have previously been tested as drugs, and the proteasome inhibitor brotezomib (Velcade) has been approved for the treatment of multiple myelomas. The team thinks the new result can be used to design a drug to interrupt the transmission chain via mosquitoes to protect pregnant women.

The paper about this work has been published in *Science* (29, July). The first author is Jian Lei and the corresponding author is Prof. Rolf Hilgenfeld.

Prof. Rolf Hilgenfeld is the director of the institute of biochemistry, University of Lübeck, Germany. His research areas are related to viral-structural biology, viral proteases and anti-viral drug development etc. He was invited to write a paper “Structural and mutational analysis of the interaction between the Middle-East respiratory syndrome coronavirus (MERS-CoV) papain-like protease and human ubiquitin” in the special issue of V. S.