14th International Conference on **Microbial Interactions & Microbial Ecology**
&
11th Edition of International Conference on **Advances in Microbiology and Public Health**
August 19-20, 2019 Vienna, Austria

Structure-assisted discovery of antivirals targeting chikungunya virus protease

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Chikungunya virus (CHIKV), a pathogenic arbovirus that poses a public health threat. Currently, no specific antivirals are available against CHIKV infection. CHIKV nsP2pro is the virus specific protease, which splices the nonstructural polyprotein into individual non-structural proteins essential for the viral replication complex formation. Hence, constitutes an attractive target for antiviral drug development. In this study, the crystal structure of nsP2pro has been determined and structure analysis done that revealed the presence of a variable loop gating the active site. Structural comparison of CHIKV nsP2pro with other alphavirus nsP2pro has disclosed the presence of substrate binding residue Asn547 on this variable loop. The Asn547Ala substitution led to three fold reduction in nsP2pro activity, indicating the specificity of Asn in substrate recognition & binding. Furthermore, based on the crystal structure of CHIKV nsP2pro, two peptidomimetics compounds (PepI & PepII) were identified and a fluorescence resonance energy transfer (FRET) based CHIKV nsP2 protease assay was developed to assess the nsP2pro activity with its fluorogenic substrate peptide. This FRET assay was utilized to evaluate the inhibition potential of Pep I & Pep II. Both the compounds were found to inhibit nsP2pro with IC50 values of 34μM and 42μM, respectively. The inhibition constant (Ki) value is 33.34±2.53 μM for Pep-I and 45.89±4.38 μM for Pep-II. Moreover, plaque reduction assay and RT-PCR analysis revealed that these compounds specifically inhibit CHIKV replication. Our studies of structure-asisted identification of nsP2pro inhibitor molecules pave way to the rational approach for development of novel antivirals against CHIKV.

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