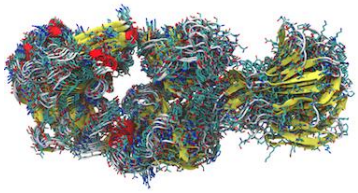

IV ASBioSim – Advanced School on Biomolecular Simulation: Protein Engineering with Rosetta, from fundamental principles to tutorials
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Rational Design of a High Affinity Nanobody Binding ZIKV NS1 Protein Aiming at Serological Differential Diagnostic

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Abstract:

The outbreak of Zika flavivirus (ZIKV) infection and the clinical severity of associated neurological disorders constitute a challenge for the scientific community. An accurate and low-cost diagnosis is a key aspect against the transmission of this viral infection. The diagnosis of ZIKV infection has hitherto been essentially clinical, while viral isolation or serology have been employed as laboratory confirmatory test. However, these strategies have not been successful as unequivocal detection methods. Genomic and symptoms similarity among flavivirus are a major hurdle to the development of diagnostic strategies, mainly where co-circulation occurs, as it happens to dengue virus (DENV), a ubiquitous virus in the tropic. In the present work, we propose an approach to computational design of a high-affinity single heavy chain domain of a heavy-chain antibody (referred to as nanobody) to ZIKV NS1 protein, an important marker to the immune recognition to the host. To assure differential binding between ZIKV NS1 and DENV NS1, the design is directed towards a specific region present only on the ZIKV NS1 surface, in such a way binding affinity of our designed protein can be used to discriminate between the different antigens. To this end, two different strategies were employed: 1) A library containing a set of 130 nanobodies were redesigned to improve specific residue – residue interactions providing a higher affinity for ZIKV NS1; 2) Using the same library, novel nanobodies were designed through the graft of CDRs from an antibody database. Protein engineering was performed using Rosetta suite v. 3.10, and molecular dynamics jointly with associated accelerated techniques were used to elucidate and clarify atomistic details on the protein – protein interface. Molecular biophysics and immunology techniques are going to be synergistically applied to confirm if our designed nanobody binds the target and whether it is functional through the assessment of immunoreactivity against patients' sera (ZIKV+/DENV-, ZIKV-/DENV+ and control ZIKV-/DENV-). Ultimately, our results envision the application of the designed nanobody on diagnostic kits capable to differentiate between ZIKV and DENV infection.

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