Exploring Antibody-Derived Beta Hairpins as Minibinders: A Molecular Dynamics Investigation

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Beta-hairpins are compact structural motifs consisting of two antiparallel beta-strands connected by a short turn. They are frequently found in antibodies where they mediate antigen recognition. Their small size and structural simplicity make them attractive scaffolds for the development of minibinders targeting protein-protein interactions that are difficult to address with conventional small molecules [1, 2]. In this study, we investigated whether antibody-derived β-hairpin sequences retain antigen binding when isolated from their native protein framework.

Eight distinct β-hairpin systems were selected from different antibodies that all interact with the same antigen (RBD domain of the Coronavirus spike-protein). In addition, two mutant sequences for one of the systems (7ls9) were investigated. All peptides were cyclized via a terminal disulfide bond.

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7wd1     -----CATPATYYSGRYYYQSPAGGCDY
7rby     -----CAVPSTYYSGTYYYTSHPGGCDY
7q9m     ------CARHVVALTHLYPDYWC-----
7ps4     -----CRSRVGATGGYYDYYC-------
7orb     --------CVVVVAARNHYYNC------
7neh     ----CYYSARDFYEGSFDIWGQC-----
7kn5     -----CLTVGTYYSGNYHYTSSDDCDY
7ls9     ---CRVHRWAYCINGVCFGAYC------
7ls9-s   ---CRVHRWAYSINGVSFGAYC------
7ls9-a   ---CRVHRWAYAINGVAFGAYC------
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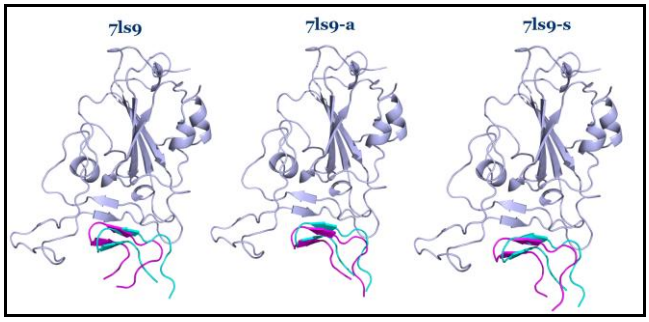

Molecular dynamics (MD) simulations were performed for both free peptides and peptide-antigen complexes with Amber [3]. Structural stability was assessed through backbone RMSD, β-turn conformational stability, and the fraction of native contacts as an indicator of binding interface preservation [4].

Our results reveal that the conformational stability varies considerably across systems: some peptides maintain β-hairpin conformations independently, while others show larger fluctuations both in free and bound states. With respect to their general properties, seven out of ten systems remained bound to the antigen indicating that MD simulations are a suitable tool to assess the conformational stability of complexes. These results suggest that antibody-derived β-hairpins can be viable scaffolds for minibinder development, with some systems retaining their functional β-hairpin structure independently of the full antibody framework.

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