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MOLECULAR DOCKING OF BIVALENT APTAMERS AGAINST HUMAN TROPONIN I

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Cardiac troponin I (cTnI) is well known as a cardiac marker in ischaemic heart disease. In this study, bivalent aptamers (aptamers containing sites that are specific for different epitopes of a target protein) against cardiac troponin I were studied, using the molecular docking approach. Previously, the aptamers having the highest affinity and specificity for the cTnI (PDB ID: 4y99:C) were selected and the screening of aptamer pairs affine to various epitopes of the target was performed using the specially designed bioluminescent solid-phase assay. Different combinations of TnAp2, TnAp10, TnAp12, and TnAp8 with different lengths of linkers between them were tested. Nine aptamer pairs least competing for protein epitopes were selected for further analysis.

To predict the secondary structure of the selected bivalent aptamers the Mfold server was used [1]. The tertiary structures of aptamers were obtained using the RNAComposer server [2]. Low-resolution generic docking with the Global Range Molecular Matching methodology implemented in the GRAMM software was used to obtain protein-aptamer decoys (grid size 4,5 A, rotational step size 10) [3]. The program performs an exhaustive 6-dimensional search through the relative shifts and rotations of the molecules, using only the atomic coordinates of the two molecules (information on the binding sites is not required). For each complex, the top 20000 possible structures were selected as decoys. Further, the Decoys As the Reference State potential (DARS-RNP) was used to assess obtained protein-RNA complexes and select a more native-like structure for each of them [4]. Visualization of selected complexes as well as analysis of intermolecular bonds was carried out using Discovery Studio Visualizer (BIOVIA) [5].

As a result, reduced versions of TnAp8t (40 bp) and TnAp2t (27 bp) with 10 bp long linker between them demonstrated the highest number of molecular bonds with cTnI (22 bonds, 8 of them are electrostatic), while the same aptamer pair with 20 bp linker demonstrated the worst affinity with the protein (5 bonds).

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In addition to the TnAp8t-L10-TnAp2t pair, several pairs of aptamers were selected for further analysis: TnApt12t-TnAp2t, TnAp10-TnAp2t, and TnAp10-L19-TnAp2t forming 17, 16, and 11 bonds with cTnI, respectively.

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