Designing and screening altered peptide ligands for the treatment of HLA type II autoimmune disorders using computational chemistry.

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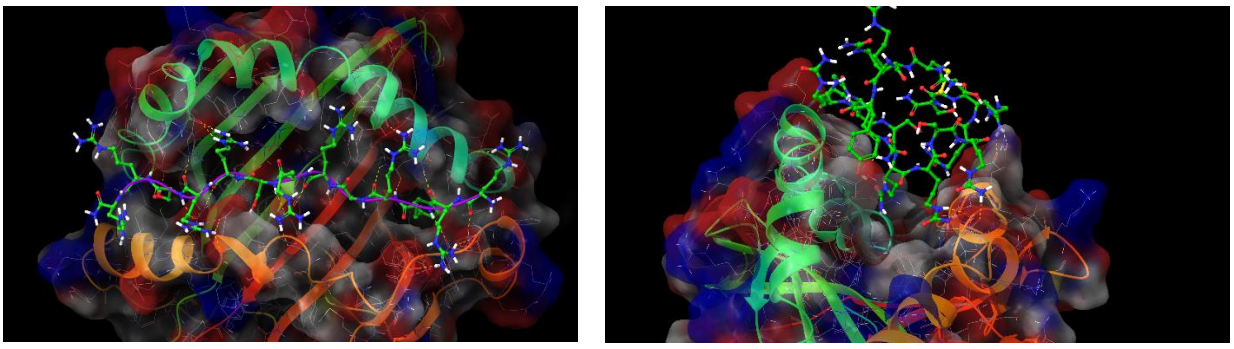
HLA type II autoimmune disorders (e.g. Rheumatoid Arthritis, Diabetes, Celiac), affect a significant portion of the population and are becoming more common. These diseases result from the misrecognition of small peptides by mutated human leukocyte antigen (HLA) receptors which present these peptides to T cell receptors (TCR) of the immune system, initiating an incorrect immune response. Currently, no drug exists capable of stopping or reversing the disease. A proposed solution is the use of altered peptide ligands (APLs), which are peptidomimetics capable of binding the HLA in place of the misrecognized peptide, potentially halting or even reversing disease progression by preventing immune system activation. The problem with the design of APLs is that it is extremely difficult to screen or predict their activity without costly *in vitro* testing, coupled with an often long and challenging synthesis of non-natural amino acids and subsequent peptide. Our objective is the high throughput screening of APLs using computational chemistry techniques consisting of three steps: 1) Docking 2) Molecular Dynamics Simulations (MD) 3) Molecular Mechanics-generalized Born and surface area continuum solvation (MM-GBSA) calculations. Docking of a set of peptides to HLA-DQ2 with known affinities shows good correlation to experimental IC50 values and is an effective initial screening step, with low cost allowing for high throughput screening. Several APLs based on the Rheumatoid Arthritis HLA-DR4 binding motif were examined using this process. These ligands were docked, then 50 short molecular dynamics simulations were performed per peptide which was then used to calculate their binding affinity using MM-GBSA. Binding affinities show large standard deviations which highlights the need for many simulations in order to obtain statistically converged results. Predicted binding affinities agree with observed binding trends of these peptides to the DR4 receptor showing that this approach can be used to screen and rank APLs.



Linear APL bound to the HLA-DR4 binding groove (left) and cyclic APL bound to the same binding groove (right). A molecular surface has been applied showing the electrostatic regions of the pocket (red=negative, blue=positive, gray=neutral). Hydrogen bonds are shown by hashed yellow lines.