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In silico redesign and de novo design of MUC1 monoclonal antibodies

Cancer is one of the leading causes of death globally, accounting for 10 million deaths in 2020 with lung, stomach, colon, liver and breast cancers remaining the leading causes.

A hallmark common to these cancers is the altered sugar attachment or glycosylation of the MUC1 protein. In healthy cells, the MUC1 consists of long, branched sugars, whereas in cancer cells, these sugars are truncated. This key difference makes MUC1 a viable target for antibody treatment. The problem with cancer cells is that they are very similar to healthy cells. An effective antibody for treatment and detection of epithelial cancers should therefore be highly specific, recognizing the MUC1 peptide and the truncated sugar. My research will attempt you create this highly specific antibody making use of methods such as docking (PIPER), single state antibody design (Rosetta design), molecular mechanics (MM/GBSA) and molecular dynamics (GROMACS). This study will consider the Tn glycosylated MUC1 ligand as this truncated sugar variant is present in high concentrations in breast cancers.

5445 antibodies were docked against the Tn MUC1 ligand and scored using MM/GBSA. Poses which showed recognition of the Tn sugar and MUC1 peptide region were then selected for single state design with Rosetta to generate a new structure energetically optimized to bind the Tn MUC1 ligand. The newly designed antibodies were then redocked and rescored to confirm the improved binding. The docking and MM/GBSA modules used are part of the Schrödinger Software Suite which is available at the CHPC. These jobs were split into subjobs which were distributed among the 24 threads available on the CHPC serial queue. Simulations run on the CHPC took 10-15 minutes per system compared to when run locally on a 16 thread machine which took 30-45 minutes per system. Rosetta single state design calculations are computationally inexpensive and were performed on a Linux workstation. Designed structures were then selected for Free Energy molecular dynamics (MD) simulations. Free energy MD simulations are currently underway utilizing the GROMACS software and GPU resources available at the CHPC.

Thus far, 14 known MUC1 antibodies have been identified, docked and scored using MM/GBSA. A total of 166 new structures were designed. AR20.5 which is known to bind the MUC1 peptide region only, scored the best using MM/GBSA with a binding affinity of -100 kcal/mol. A computationally designed antibody reported a binding affinity of -97 kcal/mol from MM/GBSA calculation and showed the desired recognition for both the Tn sugar and MUC1 peptide region.

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