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Structure-based Design of Broadly Neutralizing HCV Antibody and Vaccine

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Presenter Information
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Comments
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Structure-based design of broadly neutralizing HCV antibody and vaccine

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Hepatitis C virus (HCV) chronically infects nearly 200 million people worldwide. Antibodies have the potential to prevent establishment of chronic HCV infection in individuals exposed to the virus. Several broadly neutralizing monoclonal antibodies capable of binding HCV surface glycoproteins have been identified, including HCV1 identified by MassBiologics at UMMS, which targets a highly conserved linear epitope.

We utilized the recently solved structure of the HCV1-bound epitope to identify regions of the antibody that could be modified to potentially improve binding to a mutation (N415K) which facilitates escape from neutralization. Based on systematic in silico mutagenesis of HCV1 residues in the Rosetta protein modeling program, a number of single or double antibody mutants were selected for in vitro evaluation. The mutated antibodies were synthesized and their ability to neutralize HCV pseudoviruses expressing either wild-type epitope sequence or the N415K variant was evaluated. Antibodies with mutations on the heavy chain, R65Q and V50L, demonstrated improved neutralizing activity against the N415K escape mutant without impacting their ability to neutralize wild type virus.

We also sought to design a novel HCV vaccine that could focus the response to a small conserved neutralizing epitope of the virus defined by HCV1. The HCV1 epitope structure was used to search a large dataset of known protein structures from the Protein Data Bank, resulting in designs of scaffolds that were predicted to stably accommodate the epitope. These epitope-presenting scaffold proteins have been made and will be screened in animal studies to determine their potential as vaccine candidates for HCV prevention.