Retrovirology

Poster presentation

P05-12. A computationally designed immunogen elicits potent anti-V3 neutralizing antibodies

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Background

Retrovaccinology aims to employ neutralizing monoclonal antibodies isolated from natural infection to guide design of immunogens that 're-elicit' similar neutralizing specificities. With that aim, we are developing computational immunogen design methods that take as input a crystal structure of an antibody-epitope complex and produce as output "epitope-scaffold" immunogens in which the antibody-bound structure of the epitope is transplanted onto and stabilized by scaffold proteins. We report our first results on scaffolding the V3 loop conformation bound by mAb 447D.

Methods

Computational methods were developed within the Rosetta modeling platform. Ten scaffolds were identified by structural search of the Protein Data Bank and subjected to backbone and sidechain grafting to transfer the 447D-bound epitope conformation.

Results

The three epitope-scaffolds with highest affinity for 447D had dissociation constants from 2 to 15 nM as measured by surface plasmon resonance. These three exhibited specificity for 447D in that they showed little or no binding to 9 other anti-V3 monoclonals in Elisa. One epitope-scaffold, from human Interleukin-4, was selected for immunization. Rabbits (N:3) were immunized with epitope-scaffold DNA (0 and 4 weeks; 0.5 mg per animal per immunization) and then with epitope-scaffold protein (12, 19 and 25 weeks; 0.05 mg per animal per immunization) mixed with Ribi. Antisera collected after the protein-boost potently (IC50 > 250) neutralized HIV strains exposing the consensus clade B V3 sequence, but did not exhibit the full breadth of 447D itself.

Conclusion

The epitope-scaffold antisera represent the first potently neutralizing response to a computationally designed HIV antigen and demonstrate that computational design can achieve desired immunological effects. Iterative methods development with biophysical and immunological feedback promises to improve our ability to design immunogens that elicit predictable neutralizing responses.

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