Retrovirology

Poster presentation

P12-13. Structure-guided design and immunological characterization of immunogen constructs presenting the HIV-1 gp120 V3 loop on a CTB scaffold

M Totrov*[1], X Jiang[2], X Kong[2], S Cohen[2], C Krachmarov[3], C Williams[2], T Cardozo[2], M Gorny[2], S Wang[4], S Lu[4], A Pinter[3] and S Zolla-Pazner[2]

Address: [1]M olsoft, La Jolla, CA, USA, [2]NYU Langone School of Medicine, New York, USA, [3]PHRI Center, University of Medicine and Dentistry of New Jersey, Newark, NJ, USA and [4]University of Massachusetts Medical School, Worcester, MA, USA

* Corresponding author

from AIDS Vaccine 2009
Paris, France. 19–22 October 2009

Published: 22 October 2009

Retrovirology 2009, **6**(Suppl 3):P179 doi:10.1186/1742-4690-6-S3-P179

This abstract is available from: http://www.retrovirology.com/content/6/S3/P179

Background

The V3 loop is a major neutralizing determinant of the HIV-1 virus. Cholera toxin subunit B (CTB) is a highly immunogenic protein and it has been used in fusion constructs to enhance immunogenicity of target proteins. We hypothesized that a rationally designed immunogen, based on V3 and CTB, could induce high titers of Abs with binding mode and epitope specificity similar to known broadly neutralizing anti-V3 mAbs.

Methods

We used molecular modeling and available crystallographic structures of the V3 loop in the HIV-1 gp120 context, the V3 loop fragment bound to broadly neutralizing mAbs, as well as the structure of the CTB to design two novel V3-scaffold immunogen constructs: a full-length V3-CTB presenting the complete 35 amino-acid residue V3 loop in a structural context mimicking the V3 in gp120, and a short V3-CTB presenting a smaller segment of V3 in the conformation recognized by mAb 447-52D.

Results

Antigenic properties were evaluated on a panel of 24 anti-V3 human mAbs. The full V3 construct was recognized with high affinity by the large majority of mAbs, with some preference by mAbs derived from clade B-infected individuals. Short V3 construct exhibited high affinity binding to mAb 447-52D and only a few additional mAbs. Immunogenicity of the constructs was evaluated in rabbits using a DNA prime/protein boost protocol. Boosting with the full-length V3-CTB resulted in serum anti-V3 titers that neutralized multiple HIV virus strains from various HIV-1 clades. Short V3-CTB construct was ineffective in boosting the Ab

Conclusion

The results suggest that while (1) a scaffold immunogen that presents a single epitope (designed to fit a single mAb) may result in a poor Ab response, (2) focusing the immune response on a specific immunogenic region, such as the V3 loop, can elicit a robust Ab response, and (3) the CTB scaffold can efficiently present V3