Retrovirology

Poster presentation

P12-06. A 'non-self' mimic of the natural epitope of anti-HIV antibody 2G12 shows enhanced antigenicity

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

Published: 22 October 2009

Retrovirology 2009, **6**(Suppl 3):P172 doi:10.1186/1742-4690-6-S3-P172

This abstract is available from: http://www.retrovirology.com/content/6/S3/P172

Background

The broadly neutralizing antibody 2G12 binds a cluster of high mannose oligosaccharides on the glycan shield of HIV. In particular, it recognises the Manα1,2Man linkages of the D1 and D3 arms of the oligosaccharide. Immunogens that resemble the 2G12 epitope are therefore a desirable component of a future HIV-1 vaccine. Vaccine candidates displaying self-carbohydrates have thus far been unsuccessful at eliciting 2G12-like antibodies. Inspired by the observation that the non-self sugar D-fructose (which resembles D-mannose when displayed in its pyranose form) had a higher affinity for 2G12 than D-mannose, we proposed to chemically synthesise D1 arm mimics displaying fructose-like non-self sugars at the terminus to enhance antigenicity and immunogenicity.

Methods

Small alkyl groups were chemically introduced into the C-3, C-5 and C-6 positions (supported by modeling) of the terminal mannose of the D1 arm. IC50s were measured using competitive ELISA. The structural basis of the enhanced inhibition was determined using X-ray crystallography. These 'non-self' sugars were conjugated to Qbeta virus particles using click-chemistry.

Results

Non-self mimics of the D1 arm were successfully synthesized. Introduction of non-self modifications were not only tolerated in the 2G12 binding site but in one particular case, the C-6 methyl structure, showed higher affinity for 2G12 than the natural substrate. A crystal structure of this sugar in complex with Fab 2G12 dimer revealed additional hydrophobic interactions were responsible for the enhanced antigenicity. Conjugation of these oligosaccharides to Qbeta virus scaffold created high affinity glycan shield mimics for use as immunogens.

Conclusion

A non-self D1 arm mimic has been synthesized and shown to bind with higher affinity to 2G12 than its natural epitope. Conjugation of this oligosaccharide to Qbeta was shown to be an effective mimic of the HIV-1 glycan shield. We anticipate that these non-self oligosaccharides are good candidates as synthetic carbohydrate anti-HIV immunogens and are currently under investigation.