Retrovirology

BioMed Central

Oral presentation

Open Access

Approaches to Target Conserved Conformational Epitopes in HIV Envelope

Indresh K Srivastava*‡[1], Victoria Sharma[1], Elaine Kan[1], Yide Sun[1], Ying Lian[1], Michael Connolly[2], Ron Zuckermann[2], Claudio Vita[4], Erick Martin[4], Barbara Capecchi[4], Vega Masignani[3], Jan zur Megede[1], Ranjana Srivastava[1], Rino Rappuoli[1,3], John Donnelly[1], Jeffrey B Ulmer[1] and Susan W Barnett[1]

Address: [1]Vaccine Research, Chiron Corporation, Emeryville, CA 94608, [2]Biopharma Research, Chiron Corporation, Emeryville, CA 94608, [3]Chiron Vaccines, Siena, Italy and [4]Department of Protein Engineering, CEA, Gif-sur-Yvette, France

Email: Indresh K Srivastava* - indresh_srivastava@chiron.com

* Corresponding author ‡Presenting author

from 2005 International Meeting of The Institute of Human Virology
Baltimore, USA, 29 August – 2 September 2005

Published: 8 December 2005

Retrovirology 2005, **2**(Suppl 1):S117 doi:10.1186/1742-4690-2-S1-S117

Background

HIV-1 envelope glycoprotein (Env) is the primary target for inducing neutralizing antibodies against the virus Env yet only a small fraction of antibodies elicited are directed against conserved epitopes. Thus, the antibodies produced during infection ad vaccination (to date) have been limited in their ability to neutralize heterologous primary isolates. Since interactions between the virus and its receptor and co-receptor are critical for virus entry into the cell, targeting conserved functional epitopes located in or near the receptor and co-receptor binding sites may be the key for developing an effective vaccine. We as well as others have shown that Env-CD4 complexes are capable of inducing broadly neutralizing antibodies, however use of sCD4 as part of the vaccine has the potential for inducing an autoimmune response.

Materials and methods

Therefore, we are evaluating several approaches, including such as CD4 peptide mimetics (CD4M33), small molecules and novel scaffolds such as invasin and tat (onto which the CD4 binding domain is grafted). This may facilitate targeting of conserved functional epitopes on liganded forms of Env and also reduce immune responses directed towards CD4

Results

We have developed and characterized stable Env-CD4M33 complexes and evaluated them in rabbits for inducing neutralizing antibody responses. In a parallel approach, we have used BMS-853 as a filter to identify 100 structurally similar small molecules, and screened them for their ability to compete with CD4 and b12 for binding to Env as well as their ability to induce conformational change as reflected by enhanced binding to 17b binding. We have so far identified three classes of small molecules that: i) compete for CD4 binding only, ii) induce conformational change in Env without competing for CD4, and iii) compete for CD4 binding and induce conformational changes.

Conclusion

We plan to use small molecules for stabilizing Env in liganded or un-liganded forms for further evaluation of immunogenicity in rabbits. These studies should yield important structural information about the apo and liganded structure of Env and the resulting exposure of conserved epitopes for vaccine applications.