Retrovirology

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Misguiding cues used by HIV to thwart protective immunity

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from 2006 International Meeting of The Institute of Human Virology
Baltimore, USA. 17–21 November, 2006

Published: 21 December 2006

Retrovirology 2006, **3**(Suppl 1):S24 doi:10.1186/1742-4690-3-S1-S24

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Although the specific immune response against HIV-1 envelope trimers is of substantial magnitude, little if any antibody response against the conserved membrane proximal ectodomain region (MPER) is detected in patient sera. Here we report on immunogenicity studies using recombinant truncated constructs of gp41 and show that elicitable response to this MPER segment is minimal. Generation of broadly neutralizing antibodies will therefore require more precise immunogen design. As with the humoral response, we also show that HIV-1 has the ability to drive cellular T lymphocyte responses away from relevant, invariant viral segments, capable of affording broad protection, towards segments harboring more variable epitopes that escape CTL-based destruction. Absent response in HIV-1 infected patients is not a consequence of intrinsic holes in the human T cell repertoire, but rather, the sequelae of chronic exposure to antigens, immunodominance patterns and/or cellular dysfunction. These findings suggest a paradigm shift in HIV-1 vaccine design, focusing on potential immune response in normals to conserved segments of the viral proteins, even if not often observed in chronically HIV-1 infected patients.