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Antigenicity, structure and immunogenicity of the HIV-1 trimeric envelope glycoprotein spike

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The development of broadly neutralizing antibodies (bNAbs) to HIV-1 is often thought to be a key component of a successful vaccine. A common target of bNAbs is the conserved primary receptor CD4 binding site (CD4bs) on the HIV envelope glycoprotein (Env) trimeric spike. Although CD4bs-directed bNAbs have been isolated from infected individuals, elicitation of such bNAbs by Env vaccination has proven difficult. To help understand the limitations of current immunogens, we structurally characterized vaccine Env trimer-elicited CD4bs-directed non-bNAbs isolated from primates. We demonstrate that these vaccine-elicited antibodies, which cannot neutralize most circulating HIV isolates, attempt a vertical approach to the CD4bs, thereby clashing with the variable region of the trimeric spike cap. In contrast, CD4bs-directed bNAbs adopt angles of approach lateral to the viral membrane that avoid such clashes and achieve potent and broad neutralization of most HIV primary isolates. This analysis has informed our vaccine design efforts to generate more well-ordered trimers to limit routes of access to the CD4bs. We have developed new designs and methods to generate soluble, properly folded trimers that both present the conserved CD4bs and other trimer-specific, conserved quaternary epitopes on the HIV-1 spike revealed by newly discovered bNAbs. Antigenic, biophysical, structural electron microscopic and immunogenicity analysis of selected trimers will be presented, focusing on the capacity of these trimers to to elicit HIV-1 neutralizing antibodies.

Biography

Richard T Wyatt received his PhD in 1991 from Tufts University School of Medicine at the Sackler School of Graduate Biomedical Sciences in Boston, MA. He served on the editorial board of the Journal of Virology, is a member of the Scripps CHAVI-ID, the NIH Vaccine Discovery Research Group, the UCSD CFAR Grant Review Committee, is a member of the American Foundation for AIDS Research (AmFAR) Scientific Advisory Committee, the American Association for the Advancement of Science, and reviews for AIDS FONDS Grant Applications (The Netherlands). He has co-authored over 120 peer-reviewed articles, predominantly focused on the HIV-1 envelope glycoproteins. He was formerly a Senior Investigator and Chief of the Structural Immunology Section at the Vaccine Research Center at the NIH in Bethesda, MD, was on the faculty of Harvard University, and is a charter member of IAVI's Neutralizing Antibody Consortium and Neutralizing Antibody Center at Scripps. His research focuses on the structure, function and especially the immunogenicity of the HIV-1 envelope glycoproteins (Env). Of late, his laboratory is exploring interaction of model Env soluble and particulate immunogens with B cells and CD4+ T cells to learn rules of immunogenicity to forward HIV -1 vaccine development.

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