

SYMPOSIUM 06: REFINING IMMUNOGEN DESIGN

S06-01

Structural basis of broad neutralization of HIV-1

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To develop an effective HIV-1 vaccine, it is critical to understand how to elicit broadly neutralizing antibodies against the virus. Thus far, only a handful of human antibodies have been identified that neutralize a wide-range of different HIV-1 isolates. We have analyzed crystal structures of four of the five broadly neutralizing antibodies, as well as many clade-specific antibodies, free and in complex with their viral epitopes, to determine how they neutralize and why some are more effective than others. A common theme derived from these structures is that HIV-1 has found many ways to circumvent the immune system, but the antibody repertoire is sufficiently diverse to find novel solutions for recognition of the most highly conserved, functional epitopes of gp120 and gp41. The antibodies include: b12, that recognizes the deeply recessed CD4 binding site; 2G12, that recognizes a high-mannose cluster of self-carbohydrates on the gp120 surface; and 4E10 and Z13e1 that recognize the membrane proximal region (MPER) on gp41. In addition, we have determined structures for several anti-V3 antibodies (447-52D, 2219, and F425-B4e8) that recognize this region, which is more variable, but is implicated in co-receptor binding; each antibody uses a different strategy for recognition. This structural information is now being used in a retrovaccinology approach to design immunogens that focus the immune response onto these critical epitopes and induce antibodies that have similar, broadly neutralizing properties. Crystal structures and immunological experiments with such designed antigens are in progress.

S06-02

Primary immunization influences the magnitude, quality and breadth of Gag specific T cell responses following an rAd-5 boost

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A fully effective vaccine against HIV will require broadly neutralizing antibodies to prevent infection and CD8+ T cells to control viral spread. Prime-boost immunization regimens with heterologous vaccine formulations are an effective approach for inducing such broad-based adaptive immunity. In this regard, protein-based vaccines have been used to generate antibody responses with HIV envelope proteins while viral vectors have been optimal for inducing CD8+ T cell responses to envelope and structural proteins. Recent evidence from pre-clinical mouse and non-human primate (NHP) studies show that protein vaccines are also capable of inducing potent Th1 cell responses to HIV or SIV Gag antigens. Furthermore, depending on the formulation and the type of adjuvant, Gag proteins can elicit CD8+ T cell responses through cross-presentation. Thus, since protein vaccines are not limited by pre-existing or vaccine induced immunity, they provide a flexible platform for use in heterologous prime-boost HIV vaccine regimens with viral vectors. In a series of studies, NHP were immunized with Gag protein/Poly I: C with or without formulation in a liposomal emulsion and then boosted with rAd-5 expressing Gag. We assessed the T cell responses after primary immunization and their effect on the magnitude, quality and breadth of CD4 and CD8+ Gag specific T cell responses following the rAd-5 Gag boost. Remarkably CD4 and CD8 + T cells induced following primary immunization differentially influence the CD8+ T cell response after the rAd-5 boost. These studies provide insight into the mechanism by which primary immunization enhances CD8 T cell immunity following a viral rAd-5 Gag boost. In addition the studies show how protein based vaccines may be used in HIV vaccine development.

S06-03

New applications for mosaic antigen designs

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We proposed a vaccine antigen design approach called mosaic vaccines aimed at contending with viral diversity, and this strategy has since shown some experimental promise in terms of elicited T-cell responses with greater breadth and depth than natural proteins in animal models. Mosaics vaccines are based on in silico recombinant proteins that provide a nearly optimal solution for potential epitope diversity coverage in a population for a given number of proteins to be included in a cocktail. Mosaics align well with natural proteins, do not carry unnatural breakpoints, and minimize the inclusion of rare variants. So far they have been well expressed and immunogenic. I will first briefly review how mosaics are designed, and provide comparisons that resolve common questions and misconceptions about the design strategy. Then discuss two possible novel strategies for 2nd generation mosaic vaccines. The first strategy is a simple application of mosaics to an old concept already being studied by other groups: restricting vaccines to the inclusion of only highly conserved regions. Even the most conserved regions of HIV have some diversity in T cell epitope length fragments. Mosaics simultaneously provide definitions of conserved regions and select the most common variants for inclusion in vaccines. The second idea is optimizing coverage of potential B cell epitopes defined by spatial proximity, where every amino acid is considered together with its nearest neighbors in 3-dimensional space. When viewed this way, potential B-cell epitope diversity is vast, and highly subtype dependent. A modified version of this approach could be used to design cocktails of spatially determined regional variants for targeting specific epitopes.

S06-04

HIV-1 mosaic antigens expand cellular immune breadth and depth in Rhesus Monkeys

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Viral diversity represents an enormous challenge for the development of an HIV-1 vaccine. In particular, natural sequence antigens have been shown to elicit only limited breadth of cellular immune responses in both nonhuman primate studies and clinical trials to date. Here we explore the potential utility of HIV-1 mosaic antigens as compared with consensus antigens and natural sequence antigens expressed by Ad26 vectors in rhesus monkeys. We demonstrate that HIV-1 mosaic antigens expand cellular immune breadth, which theoretically may improve coverage of global virus diversity. We also show that HIV-1 mosaic antigens augment cellular immune depth, which we define as the capacity to elicit responses simultaneously to multiple epitope variants, and which theoretically may inhibit viral escape or exact a higher fitness cost for escape. These data suggest that further evaluation of HIV-1 mosaic antigens in clinical trials is warranted.