

# 13th Conference on Retroviruses and Opportunistic Infections



Denver, Colorado - February 5-8, 2006

## GLOBAL HIV-1 VARIATION AND ITS IMPLICATIONS FOR VACCINE DESIGN

*Conf Retrovir Opportunistic Infect 2006 Feb 5-8;13:abstract no. 13*

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**BACKGROUND:** Creating a vaccine to prevent transmission of HIV, or at least to limit its pathogenic and epidemic potential, is one of the great challenges of our time. HIV is extraordinarily diverse globally, and evolves rapidly even within a single infected individual. As a consequence, immune evasion mutations are acquired during the course of an infection. I will briefly review of the emergence of the virus in the human population, current patterns in global diversity, and the implications for vaccines. The importance of factoring in variation when performing and interpreting immunological tests will be illustrated—traditional studies using a single sequence to generate peptides to probe the immune response gives a skewed view of both the magnitude and the number of responses in an individual. Recent studies have suggested an abundance of strong correlations between viral mutational patterns and HLA alleles in the host. However, new analysis methods that track mutations through a phylogenetic tree, show that most of the observed correlations are better explained by an interaction of founder effects, immune escape, relative fitness, overlapping epitopes, and structural constraints. While some clear HLA-HIV mutation correlations are found, they are relatively rare. Finally, to better contend with viral diversity, strategies for using currently available global sequence sampling to rationally design vaccine antigen cocktails for stimulating broad immune responses will be presented. Progress has been made in the areas of using artificial proteins based on consensus sequences, or reconstructed models of ancestral sequences, as well as using polyvalent vaccines including representatives of diverse natural strains.

**CONCLUSIONS:** Several promising approaches from different groups will be reviewed. Building on these concepts, a new design strategy has been developed by a team at Los Alamos that utilizes machine learning methods to create sets of artificial proteins specifically designed to maximize the number of potential T-cell epitopes in proteins

incorporated in a vaccine cocktail. Theoretical results suggest a small number of proteins may have the potential to give global coverage.

2006-02-05  
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