

PLENARY SESSION 02: IN VIVO RESPONSE TO PATHOGENS AND VACCINES

PL02-01

In vivo dynamics of the immune response as revealed by multiphoton imaging

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Immune responses involve multiple cell-cell interactions within lymphoid tissues, the trafficking of activated cells to sites of effector function, and the migration of effector cells within peripheral tissues. To gain a more detailed appreciation of this dynamic cell behavior, we have used intravital multiphoton microscopy to analyze the interactions of antigen (Ag)-specific T and B cells with each other and with Ag-bearing dendritic cells (DCs).

Our data show that T and B cells follow stromal pathways during migration in LNs. In the fibroblastic reticular cell (FRC)-defined T zone, this constrained trafficking enhances interactions with DCs attached to the same FRC network. Additional guidance cues facilitate interactions among rare antigen-presenting and antigen-recognizing cells. Naïve CD8 T cells are attracted by chemokines to DCs that present antigen to CD4 T cells. These signals are important for CD8 T cell memory responses. Adhesive interactions regulating the duration of cell-cell association are also critical to adaptive immune responses. The absence of the small adapter SAP in T cells leads to a defect in humoral immunity and in the development of germinal centers. The primary effect of this genetic deficiency (equivalent to the human immunodeficiency X-linked lymphoproliferative disease) is to prevent stable adhesion between antigen-specific T and antigen-bearing B cells, which interferes with effective delivery of 'help' to the B cells in both the early interfollicular and late germinal center phases of the B cell response.

These observations show the power of in situ imaging in the acquisition of a more accurate picture of the molecular, cellular, spatial, and temporal aspects of cell function and signaling events in host immune responses, information that will complement data from other more conventional studies in helping to design better vaccines.

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PL02-02

Efficacy of CMV/SIV vectors

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RhCMV/SIV vectors can asymptotically reinfect and persist in RhCMV seropositive hosts, and in the process of reinfection elicit and maintain strong CD4+ and CD8+ "effector memory" T cell responses to SIV gene products. Recent data indicate these responses are uniquely associated with abortive infection following limiting dose intrarectal challenge with highly pathogenic SIVmac 239 and provide protection that is distinct from the gradual and incremental reduction in viral replication afforded by non-persistent vectors and prime-boost approaches. This talk will describe the nature of this protection, and explore its mechanistic underpinnings.

PL02-03

TB vaccine development

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Each year over 9 million new cases of TB are diagnosed and 1.7 million people die from TB. One in four TB deaths is HIV-related, and TB is a leading cause of death in people with HIV. BCG, the current vaccine, is largely ineffective in preventing pulmonary TB disease and is unsafe in HIV+ infants. Efforts are underway to develop safer and more effective recombinant BCG vaccines and non-replicating booster vaccines. rBCG30, which overexpresses Ag85B, induced increased antigen-specific CD4+ and CD8+ T cell responses in humans. rBCG VPM 1002, which disrupts endosomal membranes leading to increased antigen cross-presentation, is in Phase I trials. AERAS-rBCG418 with endosomal disruption, proapoptosis due to deletion of nuoG, and overexpression of over 40 proteins is expected to enter clinical trials in 2010. The booster candidates include recombinant proteins plus adjuvants and viral vectored vaccines. GSKM-72, a recombinant fusion protein, induces CD4+ T cells in adults when given with AS-01 adjuvant, as do Hybrid 1 and HyVac4/AERAS-404 when given with IC31 adjuvant. MVA85A/AERAS-485, a MVA vectored vaccine, induces high levels of polyfunctional CD4+ T cells in adults, TB and HIV+ adults, and infants, and is the first TB vaccine to enter Phase IIB efficacy trials in infants. AERAS-402/CrucellAd35, a non-replicating viral vector expressing three TB antigens, induces antigen-specific, polyfunctional CD4+ T cells and high levels of CD8 + T cells in humans. Efficacy trials in HIV+ individuals with latent TB infection will start in 2009. When given to NHPs as a 2-4 micron sized aerosol, it induces high levels of CD4 and CD8+ T cell in bronchoalveolar lavage cells. When used in prime-boost regimens, all of these vaccines induce protection in animals and should be safe in HIV+ individuals. The goal is for a new vaccine regimen to be available for widespread use by 2016.