

S17 Immunologic Considerations: Interference in Combination Vaccines

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Since 1988, the number of injections at each visit in early childhood has risen from one per visit to up to four per visit. With the advent of pneumococcal and meningococcal vaccines, there is the potential for this to rise still further. Combination vaccines that offer the convenience of reducing the number of injections per visit to one or two offer increased convenience and more probable physician and parent compliance with immunization schedules. However, when antigens are combined immunologic interference can be observed which could compromise the ability of the vaccine to provide protection. Interference has been observed to date with several combinations. The significance of the level of interference observed is often not known. However, review of the kinetics of bacterial infection and the immune response suggest that immunologic interference that reduces the number of children who achieve accepted thresholds of antibody concentration may put children at increased risk of infection. Unless specific correlates of protection are available, the use of combination vaccines with decreased immunogenicity may pose an increased risk of vaccine failure and of disease in children.

S18 Mechanisms of Immune Evasion

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In this introductory period an overview of the phenomena known as "Deceptive Imprinting" will be discussed. Subsequent speakers who are advancing this area of research will be providing updates to their research. At the heart of the matter appears to be a mechanism(s) whereby annually reoccurring or chronic-active microbes including cancer cells that have evolved a means of not inducing a durable and broadly protective immune response following natural infection. This appears to be accomplished through one or more of the following mechanism(s) responsible for Deceptive Imprinting: genetic instability/antigenic variation/cross-reactive immunodominant, type-restricted, non-protective or misdirected immune responses, immune dysregulating, disease-enhancing, and/or auto-immunity. These types of acute phase or immune responses appear to short circuit the more conventional primary/secondary responses that are polyclonal in nature, directed at multiple different epitopes, undergo affinity maturation and lead to specific memory. Examples of how it complicates current conventional vaccine design and technological advances to circumvent it will be the focus of the session.

S19 A Critical Role of the Intestinal Flora in Murine Leishmaniasis

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Susceptibility of BALB/c mice to *Leishmania major* infection depends on the rapid production of interleukin-4 (IL-4) by CD4⁺ T cells that react to a single parasite antigen (i.e., LACK).^{1,2} We have shown that LACK-reactive cells have been stimulated prior to infection by mimicry peptides which are derived from bacterial antigens of the intestinal flora. Indeed, decontamination of the digestive tract with antibiotics prevents both the development of memory/effector LACK-reactive T cells and their early activation following infection. Moreover, T cells from antibiotic-treated BALB/c mice are unable to transfer susceptibility when adoptively transferred into acid recipients. Thus, molecular mimicry between parasite-derived epitopes and bacterial antigens of the intestinal flora is critical in triggering the early mobilization of T cells which play a pivotal role in determining the disease outcome.

References:

1. Mougneau et al. (1995). *Science*. Vol. 268, pp 563-566.
2. Julia et al. (1996). *Science*. Vol. 274, pp 421-423.

S20 Immunodominance and Immune Response to Tumor Antigens

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Variant cancer cells that arise from the parent tumor during tumor progression can escape immunity by losing some antigens, but these variants retain other antigens. We have mixed highly immunogenic (A⁺B⁺) murine parental cancer cells with less immunogenic (A⁻B⁻) variant cancer cells to construct a model of a cancer containing escape variants. When such mixtures of cells were injected into normal mice, the variant cells grew out because immune responsiveness to the B antigen on the variant was hindered by dominance of the A antigen on the surrounding parental tumor cells. However, A⁻B⁻ variant cells inoculated alone at a separate site induced B specific cytolytic T cells and were rejected. Moreover, mice immunized with A⁻B⁻ cells rejected a challenge which contained a mixture of variant and parental cancer cells, while immunization with A⁺B⁺ cells was ineffective. Thus, variant tumor cells selected from parental tumor cells by cytolytic T cells *in vitro* can be used to induce protective immunity against variants expected to escape tumor immunity *in vivo*. These results indicate that vaccination with individual antigens at separate sites, rather than with multiple antigens at one site, may be needed to prevent escape of tumor cells or infectious organisms. (*Tissue Antigens* 47:399-407, 1996)