

# Fourth Annual Conference

## ABSTRACTS OF SUBMITTED PRESENTATIONS

### S41 VaxGen's Global Strategy to Develop and Evaluate an HIV Vaccine, AIDSVAX™

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Several impediments to HIV vaccine development and evaluation have emerged, including HIV genetic variation, lack of knowledge of the immune correlates of protection, the different routes of HIV transmission, and social/behavioral aspects such as stigma and discrimination, reluctance of high-risk persons to volunteer for clinical trials, and fear that participation in a trial would increase risk behavior. VaxGen, Inc. has initiated the first two phase III efficacy trials to evaluate the protective efficacy of AIDSVAX™, the first in the U.S., Canada, and The Netherlands among over 5400 homosexual men and women at high risk of HIV infection, and the other in Bangkok, Thailand among 2545 injecting drug users.

**Objectives:** To determine the protective efficacy of AIDSVAX™ and the significance of HIV genetic variation on vaccine protection, to define immune correlates of protection, and to overcome the social/behavioral obstacles of performing clinical trials in persons at high risk of HIV infection.

**Methods:** Multivalent gp120 vaccines (B/B and B/E) have been developed to approximate the prevalent HIV strains circulating in the trial populations. The trials are randomized, double-blind, placebo-controlled, and powered to detect at least 30% efficacy. After providing informed consent, volunteers are immunized at months 0, 1, 6, and every 6 months thereafter up to 30 months. Genetic sequencing of infecting viruses will be conducted and a "sieve analysis" used to determine the significance of genetic variation on vaccine protection. Assays for binding, blocking, and neutralizing antibodies will be performed. Measures have been developed and implemented to ameliorate potential adverse social/behavioral outcomes related to trial participation.

**Results:** Both trials are fully enrolled and have thus far experienced excellent follow-up. Vaccinations have been well tolerated with no serious vaccine-related adverse events reported. Risk behavior has not increased with trial participation and social harms have been minimal. The first interim efficacy analysis will be conducted in late 2001, with final results expected in 2002.

**Conclusions:** The two ongoing trials, if successful in showing protective efficacy, will provide critical information on the significance of HIV genetic variation, immune correlates of HIV infection, and the potential value of a global multivalent HIV vaccine to target the five major HIV subtypes in the world.

### S42 Phase III Efficacy Evaluation of AIDSVAX™ B/E HIV Vaccine in Bangkok, Thailand – An Update

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In March 1999, the first HIV vaccine efficacy trial in a developing country was initiated among injecting drug users (IDUs) in Bangkok, Thailand.

**Objectives:** To determine the protective efficacy of AIDSVAX™ B/E HIV vaccine in IDUs; confirm the safety of AIDSVAX™ B/E; and determine if vaccine can prevent chronic infection or disease by reduction of viral load.

**Methods:** The study is a randomized, double-blind, placebo-controlled trial powered to detect at least 30% efficacy. IDUs attending 17 Bangkok Metropolitan Administration drug treatment clinics were randomized to receive either AIDSVAX™ B/E (300 µg of each antigen) vaccine or placebo at months 0, 1, and 6, with boosters every 6 months up to 30 months. The trial is monitored by an independent Data and Safety Monitoring Board every 6 months for safety, with an interim efficacy analysis at 30 months. The protocol was extensively reviewed and approved by local and international bodies in Thailand and the U.S., as well UNAIDS.

**Results:** Between March 1999 and August 2000, 4646 IDUs were screened and 2545 eligible volunteers enrolled. As of January 2001, immunization compliance has been 96%—2513 received the second, 2142 received the third and 1294 received the fourth doses respectively. Thus far, 11 have been lost to follow-up and 37 deaths have occurred (none vaccine related). Immunizations have been well tolerated and no serious vaccine-related adverse events have occurred. Since enrollment, reported risk behavior (sexual and injecting) has declined and trial-related social harms have been minimal, indicating that trial participation has not resulted in adverse social effects.

**Conclusions:** The first phase III efficacy trial of an HIV vaccine among a high-risk population of IDUs has been initiated in Bangkok, Thailand. To date, recruitment and enrollment is complete, follow-up is excellent, and adverse effects are minimal. An interim efficacy analysis is expected in late 2002, and the trial will conclude in late 2003.

### S43 Immunization of HPV+ patients with high-grade anal dysplasia using a microsphere encapsulated DNA vaccine (ZYC101) results in HPV specific immune responses.

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A dose escalation, phase I trial was conducted in HPV+ patients with high-grade anal dysplasia to test the safety of a microsphere encapsulated DNA vaccine candidate (ZYC101). The vaccine expresses multiple HLA-A2 restricted CTL epitopes derived from the HPV type 16 E7 protein. Twelve male patients who are both HPV type 16 and HLA-A2 positive were given 4 intramuscular injections 3 weeks apart. The drug was well tolerated in all patients at all dose levels tested. Patient PBMC were isolated at each clinical visit. Direct ELISpot assays were set-up to enumerate IFN-γ producing cells present prior to and post treatment. Re-stimulated PBMC cultures were also evaluated for the presence of T cells specific for the peptide epitopes encoded within the drug. Ten of 12 patients have completed the trial and their immune responsiveness have been evaluated. Nine of 10 patients have a demonstrably increased CTL response to the peptide epitopes encoded within the ZYC101 formulation. Additionally, 9 of 10 patients have significant CTL responsiveness at their 6 month follow up visit. These data suggest a significant proportion of the patients mount an antigen-specific immune response after receiving the ZYC101 vaccine candidate.

### S44 Therapeutic Vaccination Against Alzheimer's Disease

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Alzheimer's Disease (AD) is a neurodegenerative disease characterized by overproduction of (Aβ)-amyloid from amyloid precursor protein (APP) with the subsequent pathologic deposition of Aβ into extracellular plaques in regions of the brain important for memory. It is estimated that during the next 50 years the number of cases of AD in the US will increase from 4 to 10 million underscoring the need for effective therapies. Recently we, as well as others, have demonstrated that vaccination of a transgenic mouse for AD (expressing mutant presenilin-1 and APP) with an Aβ peptide (aa 1-42) resulted in amelioration of neural pathology as well as protection of these mice from functional memory deficits. The objectives of this study were to (a) examine the longevity of the anti-Aβ response after vaccination; (b) determine the location of the major B cell reactivities using different truncated Aβ peptides in a competition assay and (c) measure anti-Aβ isotype specificities for the determination of T helper cell responses. Anti-Aβ response time course analysis indicated that at least 3 vaccinations (each 100µg) were necessary to elicit a significant anti-Aβ half-maximal titer. Subsequent vaccinations resulted in half-maximal antibody titers of at least 10,000 and these titers were maintained for at least 2 months after the final boost. Peptide binding competition studies indicated that highest humoral response are generated against the first 16 amino acids of the Aβ peptide. Finally, measurement of specific murine Ig isotypes in Aβ vaccinated mice demonstrated predominantly a IgG1 and IgG2b response indicating primarily a type 2 (Th2) T helper cell immune response. These data indicate that immune responses to the first 16 amino acids of Aβ contribute significantly to the protective immunity mediated by vaccination. In addition, the generation and maintenance of high titer antibodies is possible with this vaccination regimen. Finally, the preponderance of IgG1 and IgG2b responses, indicative of Th2 responses, is further indicative of the important role of humoral immunity. These findings may be important in the development of other vaccines against Aβ which may have prophylactic and/or therapeutic potential against human AD. Supported by NIH grant AG18478 to M. Gordon, K. Ugen and D. Morgan.