

## PLENARY SESSION 03: CHALLENGES FACING AIDS VACCINE DEVELOPMENT

### PL03.01

#### Correlates of Immunity: RV144 – Lessons Learned

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In September 2009 the Thai Phase III collaboration reported the results of a prime-boost HIV vaccine study in 16,000 18- to 30-year-old Thai men and women. The vaccine showed, for the first time, that a vaccine combination could provide modest protection (31.2%, 95% CI 1.1, 52.1) against infection over a 42-month period of follow-up. There was no effect on post-infection viral load or CD4 T cell counts. Additional analyses and laboratory studies have provided further insight. Laboratory studies have suggested a waning of the humoral immune response. ADCC data appear very similar to prior Phase I/II studies. IFN gamma ELISpot peptide analysis of the vaccinated volunteers shows some differences between vaccine and placebo recipients. Furthermore, analysis of breakthrough infections appears to suggest that the Env predominance of responses seen in HIV negative vaccine recipients persists in vaccine recipients who become infected. Peptide mapping of these responses shows distinct peptide recognition by vaccine and placebo recipients with breakthrough infection and suggests that antigen processing may underlie this difference. Single genome analysis sequencing of breakthrough viruses that infected volunteers early after vaccination is nearly complete, and work has started on the set of “late” breakthrough infections. The ALVAC-HIV and AIDSVAX B/E prime-boost HIV vaccine regimen may reduce the risk of HIV infection in a community-based population in Thailand with largely heterosexual risk and did not affect post-infection viral load or CD4 count. The analysis of cellular and humoral responses to vaccination are beginning to provide a glimpse at immune responses as these relate to infection, and will be complemented by sieve analysis of breakthrough viruses. A plan for next critical path vaccine trials for pox virus prime and gp120 protein boosts will be presented.

### PL03.02

#### Systems biology approaches to HIV vaccine development

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HIV vaccine development still continues to face several important challenges that include the lack of understanding of correlates of immune protection as well as the poor predictability of animal models; the absence of efficacious adjuvants that can be used in humans and delivery vectors that can elicit broad innate, cellular and humoral immune responses has also slowed down HIV vaccine development especially in view of the fact that live attenuated HIV is not an option to be considered. System biology approaches have been used in cancer and in other diseases to stage disease and to monitor the development of novel therapies; our group in collaboration with several large-scale consortia has used OMICs approaches to guide the development of better vaccine vectors and to identify correlates of immune protection in several licensed vaccines and in experimental vaccines in the NHP model. These approaches have allowed us to develop novel generations of pox vectors that have several features of the highly efficacious yellow fever vaccine. Moreover, we have identified several novel molecular pathways of innate immune responses that can predict an immune response to pathogenic SIV leading to control of challenge virus. We are currently validating these pathways at the cellular, biochemical and molecular levels using other OMIC approaches. The use of system biology will accelerate HIV vaccine development by providing unequivocal solutions to several of these pathways.

**PL03.03****The Need for More Efficient Efficacy Trials of HIV Vaccines***L. Corey*<sup>1</sup><sup>1</sup>Fred Hutchinson Cancer Research Center, Seattle, Washington, USA

Efficacy trials of preventive HIV vaccines continue to provide surprising yet critical insights for future HIV vaccines. Vaccine regimens with easily measurable immune responses of high magnitude and frequency, such as the Merck Ad5 gag-pol-nef vaccine, provided little protection from infection or long-term immune control. However, a recent vaccine regimen of a canarypox gp 120 combination vaccine provided nearly 60% efficacy in the first year after vaccination and 30% efficacy overall. This regimen elicited poor CD8+ and mediocre CD4+ T cell responses in phase I and II evaluations. Recent analyses of the longer term follow-up of the Step trial indicate an interaction between receipt of vaccine and lack of circumcision as well as Ad5 seropositivity. The mechanisms of these effects are unclear. Similarly, while NHP models of acquisition are being developed, they are not validated with regards to their predictive efficacy. The above data all indicate that our assays and our current animal models to measure immunogenicity are poor predictors of HIV vaccine efficacy in a human population.

The pace of HIV vaccine efficacy trials has been slow (currently one trial every 5 to 7 years). If we are to achieve a globally effective vaccine, we need to develop a system to conduct, monitor and analyze efficacy trials in a more efficient and expedient manner, linking laboratory and clinical services more effectively. Adaptive trial designs offer a major advantage over fixed "traditional" models in weeding out ineffective vaccines and providing initial reads on potentially effective vaccine regimens. The use of adaptive designs will be discussed in the context of a more rapid and efficient global clinical trials program.

**PL03.04****Using partnerships in the developing world to accelerate AIDS vaccine development***S. Berkley*<sup>1</sup><sup>1</sup>The International AIDS Vaccine Initiative, New York, New York, USA

AIDS vaccine development has gone through a number of changes since the virus was first discovered more than 25 years ago. Initially, candidates were developed using traditional vaccinology techniques patterned after the successful development of other vaccines and vaccines were tested in the industrialized world. However, the paradigm has shifted to test vaccines in developing countries where the incidence is highest and the need greatest. More than 30 countries have participated in 200 clinical trials enrolling over 40,000 participants. Traditional vaccinology has not been successful and highly innovative vaccine approaches are being developed. We now need a new approach of innovative and rapid iterative trials as part of the research process employing new techniques such as screening test of concept and adaptive trials. To effectively conduct high-quality reproducible trials in the developing world, centers of excellence have to be created where talent can be nurtured and incentives put in place for engaging researchers over the longer term. These centers need flexibility to respond to the changing epidemiology by shifting cohorts for trials. As research moves upstream, scientists in the developing world also have a critical role to play and are well situated via research partnerships to make major contributions. Key new discoveries such as a recent identification of broad and potent broadly neutralizing antibodies and their resultant new vaccine targets are beneficiaries of these North-South research partnerships spanning 3 continents. Understanding the earliest events in infection, including protection and viral escape, is also being pursued. Long-term capacity building along with a culture of research excellence will allow scientists around the world to contribute fully in AIDS vaccine research.

**PL03.05****Impact of Biomedical Prevention Approaches on the Implementation of HIV Vaccine Efficacy Trials***S. Abdool Karim<sup>1</sup>*<sup>1</sup>CAPRISA, University of KwaZulu-Natal, Durban, KwaZulu-Natal, South Africa

The efficacy of HIV vaccines will need to be assessed against the background of existing proven HIV prevention technologies that comprise the “standard of care”. At present this background standard comprises the ABCC, i.e., abstinence, behavior modification, condoms, and circumcision. Of these, only circumcision has been proven through randomized controlled trials (in South Africa, Uganda and Kenya) to reduce HIV incidence. In almost 30 years of HIV research, only a further three of 34 randomized controlled trials have been able to demonstrate an HIV prevention effect. These include the Thai RV-144 HIV vaccine trial, the Mwanza trial of sexually transmitted diseases treatment (seven subsequent trials have failed to replicate this finding), and most recently, the CAPRISA 004 tenofovir gel microbicide trial in South Africa. The latter trial outcome has raised hope that the five pre-exposure prophylaxis (PrEP) trials (VOICE, FEMPrEP, Partners PrEP, iPrEX, and Thai IDU trial) will show protection against HIV. The design of future HIV vaccine trials will be impacted by the choice of HIV prevention strategies, such as circumcision, microbicides and PrEP, implemented in both the active and placebo arms. Three key challenges will need to be addressed:

1. Impact of additional prevention interventions on HIV incidence in the trial.
2. Impact of concomitant interventions, especially antiretrovirals on HIV pathogenesis and vaccine trial endpoints such as set point viral load.
3. Direct and indirect impact of additional prevention programs on trial cost and complexity.

Based on data from the CAPRISA 004 trial, each of these three challenges is quantified, within the constraints of available information. The addition of biomedical prevention such as circumcision, microbicides and PrEP will impact the design and implementation of future HIV vaccine trials; regardless, it should be readily feasible to conduct these trials efficiently and cost effectively with appropriate study designs.