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ORAL PRESENTATION

S1

Update on global HIV prevention research

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While vaccine development is a major theme of IHV meetings, other prevention research approaches are not necessarily on the radar scope of the basic science and clinical researchers seeking state-of-the-art updates. The HIV Prevention Trials Network and the Microbicide Trials Network are engaged a wide variety of prevention clinical trials. Other trials are underway with other sources of support. This presentation will highlight current challenges in:
-Barrier research, including microbicides and diaphragms
-Male circumcision and its rationale
-Use of antiretroviral therapy and transmission prevention
-Use of opportunistic infection and helminth treatment to reduce viral load and infectiousness
-Control of sexually transmitted diseases to reduce HIV transmission efficiency
-Selected highlights in treatment of drug abuse to reduce HIV risk, prevention of mother-to-child HIV transmission, and in behavior change research for prevention.
The goal for this presentation is to challenge the basic science and clinical research communities to identify important partnerships that can enhance the scientific value of key prevention clinical trials, as well as to address underlying mechanisms of approaches that show promise as new tools.

S2

Chemokine receptor CCR5 mediates resistance to West Nile Virus infection in mouse and man

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West Nile Virus (WNV) is a re-emerging pathogen and a well-known agent of fatal encephalitis in several species, including mouse and man; however immunopathogenic mechanisms are poorly understood. We found that WNV induced upregulation of the chemokine receptor/HIV coreceptor CCR5 and its ligand CCL5 in mouse brain, as well as influx of effector leukocytes, including CD4+ and CD8+ T cells, NK cells, and macrophages, of which ~25% expressed CCR5. Infection of CCR5-/- mice was rapidly and uniformly fatal, whereas the majority of CCR5+/+ mice survived. Consistent with this, CCR5 32 homozygotes were overrepresented in three of three cohorts of symptomatic WNV seropositive individuals compared to control populations. And were more likely to have a fatal outcome. CCR5 appears to mediate resistance to fatal WNV infection in mouse and man by coordinating leukocyte recruitment to the infected brain. Thus CCR5 32 homozygosity is a strong genetic risk factor for symptomatic WNV infection in man. The results suggest that therapeutic blockade of CCR5 may carry increased risk of symptomatic and possibly fatal outcome should individuals become infected with WNV.

S3

Genetic variation in HIV-1C: implications for prevention and treatment

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HIV-1C of southern Africa shows higher rates of genomic variation than does HIV-1B. Prevalence rates are far higher in this region as compared to elsewhere in sub-Saharan Africa or in the world. Enhanced rates of transcriptional activation, presumably related to duplication in the LTR NF-kB enhancer region of the genome, have been well documented. This may in turn be associated with better replication in vaginal and GALT tissues, different patterns of mother/infant transmission, and elevated transmission rates. HIV-1C has also been shown to have higher rates of nevirapine resistance in mothers given labor nevirapine, higher rates of K65R resistance to tenofovir after in vitro selection, different patterns of accumulation of thymide analogue mutations to the nucleoside analogue drugs, and different patterns of mutations to the protease inhibitor drugs. HIV-1C also shows different patterns of immunoselection for immunodominant epitopes to both CTL and antibody responses. With the gag gene epitopes, for example, the p17 region is immunodominant in HIV-1B while the p24 region is immunodominant for HIV-1C. How these responses may be related to differences in major histocompatibility alleles in the people of southern Africa is unclear.

S100
Natural and engineered antibodies against HIV

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The humoral arm of the immune system exerts continual selective pressure on HIV replication in the infected person. We have described a conserved epitope within the gp120 V3 loop that is masked in the native Env trimer on CCR5-restricted (R5) HIV-1 virions, but fully exposed on CXCR4-using (X4, R5X4) virions. The ability of a monoclonal antibody against this epitope to selectively neutralize CXCR4-using but not CCR5-restricted primary isolates raises the question of whether in vivo neutralizing antibody selection pressure in the acutely infected person plays a major role in the selective transmission of R5 viruses.

We are exploiting antibodies to engineer novel bifunctional proteins against HIV infection. One agent, designated sCD4-17b, is based on the sequential receptor binding mechanism of gp120: first to CD4, then to coreceptor. The sCD4 moiety of the chimeric protein binds and induces the conformational change required to expose/create the highly conserved "bridging sheet" involved in coreceptor binding and containing the 17b epitope. The potent neutralizing activity of sCD4-17b against diverse HIV-1 primary isolates suggests its potential utility as a topical microbicide to protect against HIV-1 sexual transmission [1,2].

References

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2. Dey B, Del Castillo CS and Berger EA: **Neutralization of human immunodeficiency virus type 1 by sCD4-17b, a single-chain chimeric protein, based on sequential interaction of gp120 with CD4 and coreceptor.** *J Virol* 2003, **77:** 2859–2865.

S101
Negative regulation of HIV-1 expression by the natural isoform C-terminus truncated STAT5 (STAT5△)

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We have described a constitutive activation of naturally C-terminus truncated STAT5 (STAT5△) in PBMC of most HIV+ individuals (C. Bovolenta, Blood, 1999). We here report that the chronically HIV-infected promonocytic cell line U1 expresses exclusively a STAT5△ isoform similar to that of PBMC of HIV+ individuals in virtual absence of STAT5FL. Consistently with the presence of functional STAT5 DNA binding sites in the HIV-1 LTR (Selliah et al., Virology, 2006), GM-CSF stimulation of U1 cells led to a modest induction of HIV expression as well as to the activation of both STAT5△ and of an ERK-1/2-AP-1 pathway. Inhibition of ERKs/AP-1 by PD98059 abolished GM-CSF induced HIV expression in U1 cells, whereas inhibition of STAT5△ expression by either AG490 or anti-STAT5 siRNA resulted in a significant enhancement of GM-CSF induced HIV expression in U1 cells. Finally, ex vivo IL-2 stimulation of PBMC from most HIV+ individuals in the presence of anti-STAT5 siRNA resulted in the enhancement of HIV-1 p24 Gag antigen expression. Thus, STAT5△ is likely a novel natural inhibitor of HIV expression both in vitro and in vivo.

S102
A dual defensive role of CIITA against retroviral infections

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We describe how CIITA exerts a dual role against retroviral infection. The first, classical role is the upregulation of MHC class II expression and thus the capacity to present viral antigens to CD4+ T cells. The other, evolutionary new and fundamental role is to inhibit viral replication by blocking specifically the function of the viral transactivators. HIV-1 Tat is inhibited through the competition for cyclin T1 of the P-TEFb complex, whereas HTLV-2 Tax-2 is inhibited through a concerted action which may increase the binding affinity of the CIITA-NFY complex for Tax-2, displacing it from the viral LTR promoter. As expected, two distint sequences in the N-term region of CIITA mediate the inhibitory action on Tat and Tax-2, respectively. Of note, Tax-1 from HTLV-1 seems also to be inhibited by the same sequence that inhibits HTLV-2 Tax-2. Interestingly, only those CIITA fragments containing the minimal inhibitory domains that localize into the nucleus could exert an effective suppressive action. Taken together, our results indicate that CIITA is an extant molecular tool endowed with distinct evolving functions against retroviruses. These distinct properties of CIITA will shed new light on the molecular mechanisms of adaptive coevolution of hosts and pathogens and may be exploited to envisage novel therapeutic strategies aimed at counteracting retroviral infections.

S103
Reduced CD4 type 1 cytokine response by HIV-1 transgenic rat may be correlated with increased SOCS-1 expression from dendritic cells

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Suppressor of cytokine signaling-1 (SOCS-1) is an inducible negative regulator of the JAK/STAT signal pathway; SOCS-1 is expressed in dendritic cells (DCs) and negatively regulates