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Report NVVI Travel Grant
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Keystone conference on HIV Vaccines 2013

The Keystone symposia on molecular and cellular biology are a series of international symposia organized to bring together experts in various fields of biology.
I had the opportunity to visit the conference on HIV Vaccines from 10-15 February 2013 in Keystone, Colorado (USA), which was joined with the Keystone conference on B Cell Development and Function.

In my PhD-project, I study the influence of perinatal HIV infection on the development of the B- and T-cell immune system in children. Most previous studies focused on HIV infection in adults. Since the adaptive immune system in young children is highly dynamic and immunological memory needs to be built up, perinatal HIV infection could severely affect this immune development. My results showed that perinatally HIV-infected children had reduced build-up of memory B- and T-cell compartments, despite current antiretroviral treatment protocols. This combined Keystone conference was an optimal opportunity to meet experts in the fields of HIV vaccine development and eradication strategies, as well as B cell function. In addition, I was able to put my findings in the context of studies performed in other research institutes. This is important for better understanding of my findings and to guide me in future directions.

The conference was opened on the first evening by two keynote speakers (M.S. Cohen and M.C. Nussenzweig), who gave an update on state-of-art HIV prevention strategies and broadly neutralizing antibodies to HIV.

The second day of the conference started with a very interesting HIV vaccines-session on 'protective responses in animal models'. Jeffrey Lifson gave an interesting presentation on new approaches to improve vaccination strategies. Current HIV vaccines induce a T-cell response to HIV with mainly a *central memory* phenotype. Infection with the cytomegalovirus (CMV) on the other hand, induces a strong anti-viral *effector memory* T-cell response, which is more effective in controlling an infection. Jeffrey Lifson used this knowledge to improve the HIV vaccination strategies. He showed that a CMV vector-based HIV vaccine induced an anti-HIV *effector memory* T cell response, which was more effective in controlling HIV infection. Another interesting presentation in this session was from Sallie Permar, who talked about immune protection against postnatal HIV1/ SIV transmission. She showed that the B cells (in local tissue) can produce HIV-neutralizing antibodies, which can be secreted in breast milk. Interestingly, these neutralizing antibodies were from the IgG isotype, instead of the well known mucosal IgA isotype. An important question is why some infants are infected with HIV while others are not. Sallie Permar showed that mothers of infants that were not infected had more of these anti-HIV IgG antibodies in their breast milk. By vaccinating mothers to improve the anti-HIV IgG responses in breast milk, this natural protective mechanism could potentially be used in our benefit in new treatment strategies and reduce mother to child transmission of HIV. Altogether, this session helped me to better understand the natural mechanisms of humans/ animals in their protection against HIV infection and how these can be used to improve current HIV vaccination strategies.

The third day focused mainly on the quality of immune responses to HIV and the quality of HIV vaccines. In addition, it focused on the importance of mucosal surfaces in both topics, because mucosal surfaces function as HIV reservoirs and are important routes for vaccination. The fourth day contained talks on $CD4^+$ and $CD8^+$ T cell responses in HIV infection. During both the third and fourth days, some interesting mucosal and peripheral blood T-cell subsets were introduced that might be interesting to analyze in my patient cohort, and that might help me to further unravel the defects that are visible in peripheral blood of HIV-infected children. An important topic in the conference was the identification and definition of peripheral blood follicular helper T cells (T_{FH}), which seem to be important in controlling HIV infection. Multiple presentations including the one from

Shane Crotty and Rafale Cubas indicated the importance of these T_{FH} cells in controlling HIV infection in elite controllers, and the lack of/ reduced numbers of these cells in chronic aviremic patients or viremic patients.

The last day continued with a session on $CD4^+$ T-cell help in anti-HIV responses and the generation of HIV-neutralizing antibodies. Understanding both processes is important to optimize vaccination strategies. Furthermore, this session gave me the opportunity to correlate my results, i.e. defects in memory B- and T-cells, to the slow development and low affinity of neutralizing anti-HIV responses.

During the evening poster sessions, I had the opportunity to present my research and to discuss that of other researchers. This gave me the opportunity to get useful feedback on my research approach and results from various scientists in the field, e.g. Susan Moir, who is a leading scientist in the HIV research. She did a lot of research on defects in HIV infection, including B-cell defects, despite antiretroviral treatment. We compared and discussed the findings from PhD students in her lab and my findings in children.

In addition, I met Katija Jelicic, who described that HIV binding to an α4β7 receptor on B cells impaired their normal functioning and probably delayed anti-HIV antibody responses in these patients. B cells expressing this α4β7 receptor expressed multiple markers, which we and others have observed to be expressed on an aberrant B cell population expressing low levels of CD21. This $CD21^{low}$ B-cell population is frequently described in HIV-infected patients and is less responsive to antigen stimulation. Furthermore, it correlates to HIV virus load in serum and Susan Moir described it to be enriched for anti-HIV responses. Importantly, the underlying mechanism impairing these B-cell responses and the relevance of this population in HIV pathogenesis is not fully understood. It will be very interesting to study whether this $\alpha4\beta7^+$ B-cell population is the same as the $CD21^{low}$ population, as this might explain their impaired functioning and might be an important reason why anti-HIV neutralizing antibody responses are weak and slowly develop. This is definitely a population I will focus on in my further studies.

I would like to thank the NVVI for making it possible for me to join this very interesting and useful meeting.