



Virology Division

HIV/AIDS Research Unit

BACKGROUND

The AIDS Virus Research Unit comprises 3 laboratories, namely the Virology Laboratory headed by Prof Lynn Morris who also serves as the head of the Unit, the Cell Biology Laboratory headed by Prof Caroline Tiemessen and the Immunology Laboratory headed by Prof Clive Gray. The Unit is the largest at the NICD and conducts research projects primarily on the virology and immunology of HIV. It also serves important functions for drug resistance surveillance for the National Department of Health as well as performing validated end-point assays for HIV vaccine trials. The Unit raises a large amount of external funding for the various projects with numerous collaborators and serves an important role in training and capacity building, including running workshops. The total number of staff and students in the AIDS Unit in 2007 was 63.

ACTIVITIES, HIGHLIGHTS AND ACHIEVEMENTS

RESEARCH PROJECTS

The C3-V4 region is a major target of autologous neutralizing antibodies in HIV-1 subtype C infection

The early autologous neutralizing antibody response in HIV-1 subtype C infections is often characterized by high titers, but the response is type-specific with little to no cross-neutralizing activity. The specificities of these early neutralizing antibodies are not known, however the type specificity suggests they may target the variable regions of the envelope. Here we show that cross-reactive anti-V3 antibodies developed within 3-12 weeks in 6 individuals but did not mediate autologous neutralization. Using a series of chimeric viruses, we found that antibodies directed at the V1V2, V4 and V5 regions contributed to autologous neutralization in some individuals, with V1V2 playing a more substantial role. However, these antibodies did not account for the total neutralizing capacity of these sera against the early autologous virus. Antibodies directed against the C3-V4 region were involved in autologous neutralization in all 4 sera studied. In two sera, transfer of the C3-V4 region rendered the chimera as sensitive to antibody neutralization as the parental virus. Although the C3 region, which contains the highly variable alpha 2-helix

was not a direct target in most cases, it contributed to the formation of neutralization epitopes as substitution of this region resulted in neutralization resistance. These data suggest that the C3 and V4 regions combine to form important structural motifs and that epitopes in this region are major targets of the early autologous neutralizing response in HIV-1 subtype C infection. *This study is in press at Journal of Virology.*

4E10 Resistant Variants in an HIV-1 Subtype C Infected Individual with an Anti-MPER Neutralizing Antibody Response

The broadly neutralizing monoclonal antibody (MAb) 4E10 recognizes a linear epitope in the C-terminus of the membrane proximal external region (MPER) of gp41. This epitope is particularly attractive for vaccine design because it is highly conserved amongst HIV-1 strains and neutralization escape *in vivo* has not been observed. Multiple *env* genes were cloned from an HIV-1 subtype C virus isolated from a 7 year old perinatally infected child who had anti-MPER neutralizing antibodies. One clone (TM20.13) was resistant to 4E10 neutralization as a result of an F673L substitution in the MPER. Frequency analysis showed that F673L was present in 33% of the viral variants and in all cases was linked to the presence of an intact 2F5 epitope. Two other envelope clones were sensitive to 4E10 neutralization, but TM20.5 was 10-fold less sensitive than TM20.6. Substitutions at 674 and 677 within the MPER rendered TM20.5 more sensitive to 4E10, but had no effect on TM20.6. Using chimeric and mutant constructs of these two variants, we further demonstrated that the LLP-2 domain in the cytoplasmic tail affected the accessibility of the 4E10 epitope, as well as virus infectivity. Collectively, these genetic changes in the face of a neutralizing antibody response to the MPER, strongly suggested immune escape from antibody responses targeting this region. *This study is in press at Journal of Virology.*

Development of phenotypic HIV-1 drug resistance following exposure to single dose nevirapine

The HIVNET 012 single dose nevirapine regimen (sdNVP) used to prevent mother-to-child transmission of HIV-1 results in the selection of genotypic drug resistance mutations. To determine the level of phenotypic resistance conferred by these mutations we examined the ability of sample-derived HIV-1 reverse transcriptase to function in the presence of NVP. Plasma samples from HIV-1 pregnant women before

and after exposure to sdNVP were used to extract viral reverse transcriptase for the CaviDi ExaVir[®] Drug Susceptibility Assay. The fold increases in phenotypic resistance for each sample were compared to the genotypic profiles determined by population-based sequencing. None of the 49 women sampled before sdNVP exposure had phenotypic resistance (median fold increase 0.7). Seven weeks after sdNVP, there was a 16-fold increase in phenotypic resistance among 44 women who had NVP resistance mutations compared to only a 1.9 fold increase among 31 NVP-exposed women with wild-type virus (Figure 1). Overall 89% of samples with genotypic mutations had phenotypic resistance at 7 weeks. Phenotypic resistance decayed with time coincident with the fading of genotypic mutations and by 18 months all samples were phenotypically susceptible. In conclusion, exposure of pregnant women to sdNVP was associated with the transient appearance of viral populations that displayed phenotypic resistance to NVP.

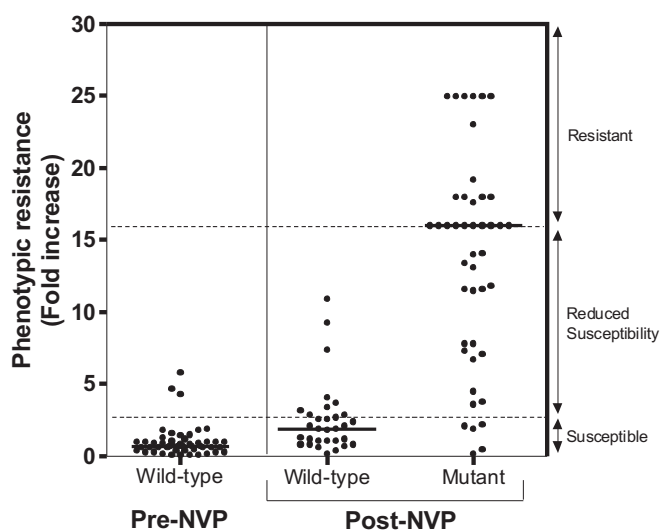


Figure 1: Phenotypic susceptibilities pre- and post-NVP. Wild-type designates samples that contained no genotypic resistance mutations while mutant designates samples that contained NVP genotypic resistance mutations. Results are shown as fold increases in IC₅₀ values relative to wild-type controls and classified as susceptible, with reduced susceptibility or resistant.

Persistent K103N mutations among women exposed to single-dose nevirapine prophylaxis and virologic response to non-nucleoside reverse transcriptase inhibitor-based therapy

To investigate whether there are persistent effects of exposure to single-dose nevirapine (sdNVP) on the virologic response of HIV-infected women to NNRTI-based therapy an observational epidemiologic study was conducted in Johannesburg, South Africa. Initial and sustained virologic response to NNRTI therapy was compared between 94 HIV-infected women exposed to sdNVP 18-36 months earlier and 60 unexposed women with a pregnancy within a similar interval. Viral load was

measured every 4 weeks to 24 weeks and every 12 weeks to 78 weeks. Time to achieving viral suppression (<50 copies/ml) and confirmed viral rebound (>400 copies/ml) were compared. Pre-treatment samples were tested for K103N mutations using an allele-specific PCR. Population sequencing was done among those with inadequate virologic responses. Almost all women, 97.5% of sdNVP-exposed and 91.3% of unexposed women ($p=0.21$), suppressed by 24 weeks and similar percentages in each group, 19.4% of sdNVP-exposed and 15.1% of unexposed women, rebounded within 78 weeks post-treatment ($p=0.57$). K103N was detected by allele-specific PCR among 10.6% of sdNVP-exposed women pre-treatment. Detection of K103N in either viral RNA or DNA was strongly predictive of inadequate viral response: 60.9% of women with the mutation did not suppress or rebounded within 78 weeks compared to 15.1% of women without ($p<0.001$). K103N mutations below detection thresholds of conventional assays reduce the likelihood of and durability of virologic suppression with an NNRTI-based regimen. Since these mutations persist among a minority only of sdNVP-exposed women there is negligible impact of exposure to sdNVP >18 months earlier on response to NNRTI treatment. *This work was done in collaboration with Dr Ashraf Coovadia, Elaine J. Abrams, Gayle Sherman, Tammy Meyers, Scott Hammer and Louise Kuhn.*

Understanding protective immunity to HIV using maternal-infant HIV transmission as a model

Innate immunity needs to become a more integral component of studies on HIV vaccines, as understanding the interplay between innate and adaptive immunity may hold the key to understanding what constitutes protective immunity to HIV. Our work over many years has focused on studies of uninfected infants born to HIV-infected mothers as a model, as they provide a unique human experimental model to extend our understanding of these phenomena.

HIV-1 specific cellular immune responses are elicited in a proportion of infants born to HIV-1 infected mothers and are associated with protection against vertical transmission. To investigate correlates of these HIV-1 specific responses, we examined levels of the immune activation markers neopterin, β_2 -microglobulin (β_2 -m), soluble L-selectin (sL-selectin), the immunomodulatory and haematopoietic factors interleukin-7 (IL-7), stromal cell-derived factor 1 alpha (CXCL12), granulocyte-macrophage colony-stimulating factor (GM-CSF) and the immunoregulatory cytokine interleukin-10 (IL-10) amongst a group of newborns born to HIV-1 positive mothers who did not receive any antiretroviral drugs for prevention of perinatal HIV-1 transmission. Cellular immune responses to HIV-1 envelope (Env) peptides were also measured. We aimed to determine whether newborns who elicit HIV-1 specific cellular immune responses (Env⁺) and those who lack these responses (Env⁻) exhibit unique immune features. Our data confirmed that no Env⁺ infants acquired HIV-1 infection.

Among exposed-uninfected infants, Env⁺ infants had reduced immune activation (as measured by β_2 -m and sL-selectin levels in cord blood plasma) compared to Env⁻ infants as well as reduced GM-CSF levels in cord blood plasma. There was also a reduced ability of cord blood mononuclear cells to be induced to produce GM-CSF among Env⁺ infants. Maternal viral load was lower in Env⁺ infants suggesting that exposure to low levels of antigen may be responsible for priming the protective responses. These findings suggest that infants who are able to develop apparently protective HIV-1 specific cellular immune responses have immunological features and viral exposure histories that distinguish them from their non-responder counterparts, providing new insights into the development of HIV-1 protective immunity. Building on earlier work on maternal-infant transmission of HIV-1, where we have identified CCL3/CCL3L1 as an important CC chemokine in protective immunity to HIV-1, studies are in progress to establish the relationship between the presence of HIV-1 specific immune responses in exposed-uninfected infants and expression of the CC chemokines (CCL3, CCL4, CCL5), given that they also play an important role in directing adaptive immune responses.

Host CCL3L1 gene copy number in relation to HIV-1 specific CD4⁺ and CD8⁺ T cell responses and viral load in South African women

HIV-specific T cell responses play an important role in control of HIV-1 infection. Since CCL3 can direct adaptive immune responses and can block entry of CCR5-utilizing strains of HIV-1, we hypothesized that host CCL3 genotype (*CCL3L1* gene duplications) would influence the development of effective HIV-specific immune responses. Copy numbers of *CCL3L1* were determined for 71 HIV-infected women, and HIV-specific CD4⁺ and CD8⁺ T cell responses to overlapping peptide pools spanning the HIV-1 subtype C genome simultaneously measured by an interferon- γ and interleukin-2 whole blood flow cytometric assay. Host *CCL3L1* copy number correlated negatively with viral load ($r=-0.239$; $P=0.045$), as did magnitudes of Gag CD4⁺ ($r=-0.362$; $P=0.002$) and CD8⁺ ($r=-0.261$; $P=0.028$) T cell responses. Patients with a Gag CD4⁺ response ($P=0.002$) or dominant Gag CD8⁺ ($P=0.006$) responses had significantly lower viral loads than those whose dominant response targeted another region of the genome, whereas a dominant Nef-specific CD8⁺ T cell response was associated with higher HIV viral load. *CCL3L1* copy number greater than or equal to the population median of 5 was significantly associated with increased magnitude of CD4⁺ Gag responses ($P=0.017$), and women who had both CD4⁺ and CD8⁺ Gag-specific responses had significantly lower viral loads ($P=0.004$) and higher *CCL3L1* copy number ($P=0.015$) than those women with only CD8⁺ Gag-specific responses. Findings suggest that demonstrable Gag-specific CD4⁺ T cell responses are indicative of better immune integrity and function and can serve as markers of more effective Gag-specific CD8⁺ T cell responses, and we propose that *CCL3L1*

production capacity, here inferred by *CCL3L1* copy numbers, influences T cell responsiveness by having an “adjuvant effect”, or by preserving CD4⁺ T cell function through contributing to control of viral replication. Maintenance of responses in a milieu of higher CCL3 production is clearly advantageous to the host. Our data are consistent with findings of vigorous HIV-specific CD4⁺ T cell responses associated with virus control in long term non-progressors that was linked to enhanced production of CC chemokines, and further highlight the importance, in particular, of CCL3 as an innate immune factor, and of CD4⁺ Gag-specific T cell responses in control of viremia.

Identifying cytokine phosphorylation profiles as novel immune monitoring tools

According to the dominant role that cytokines play in regulating the immune response such as differentiation and/or proliferation, the goal of our research is to study the phosphorylation profiles of T cell subsets and antigen-specific CD4⁺ and CD8⁺ T cells in response to exogenous cytokine engagement. The aim is to identify signalling cascades associated with efficient or impaired immune responses. We have conducted STAT-5 phosphorylation profiles in response to IL-2, IL-7 and IL-15 in memory T cell subsets of HIV+ and HIV- individuals. No significant differences were detected between HIV+ and healthy controls in response to IL-2 and IL-15 in the different memory subpopulations in both CD4⁺ and CD8⁺ T cells, despite lower levels of IL-2R α on CD8⁺ T cells from HIV-infected individuals. For IL-7 triggering, there was reduced p-STAT5 expression in CD8⁺T memory subsets from HIV-infected individuals when compared with healthy controls, which may be accounted for by the lower level of IL-7R α (CD127) expression. No significant differences were observed in response to IL-7 activation in the CD4⁺ T cell compartment between healthy and HIV+ individuals. These data show that the STAT-5 signalling pathway in CD8⁺ memory T cells from subtype C HIV infected individuals seems to be impaired in response to IL-7 triggering, and which may be associated with downregulation of IL-7R α expression. These data have implications for the long-lived ability of CD8⁺ T cell memory cells to respond to in vivo survival/growth signals.

Identifying T cell recognition profiles at the acute stage of subtype C HIV-1 infection

Investigating HIV-specific T cells responses at the acute stage of infection is considered important as these responses may indicate which recognition profiles may be important for subsequent disease progression. These may form the foundation for identifying relevant vaccine-induced responses in subsequent clinical vaccine trials. Fifty-three subjects with acute HIV-1 infection have been screened for HIV-1 specific T cell responses using a set of 432 overlapping peptides spanning the entire HIV-1 proteome in an IFN- γ Elispot assay. The peptides are arranged in a pool-matrix

format to allow for detail characterization of regions rich in potential T cell epitopes. Using IFN- γ Elispot assay, we were able to quantify the evolution of HIV-1 specific T cell responses over time from as early as 3-5 weeks post infection up to 6-months. Our preliminary data shows that Nef was by far the earliest dominant responses at 3-5 weeks post infection with almost 71% of epitopic regions targeted in this protein, followed by Pol and Gag (41%), Env and Vif (29%), Vpr (24%), Rev (18%) Vpu (12%) and Tat (6%). In addition, there was an overall increase in the frequency of individuals recognizing epitopic regions within Nef, Pol and Gag from 3-5 weeks up to 6 months. Almost all individuals at 6 months post infection responded to epitopic regions within Nef, with 73% to Pol, 64% to Gag, 44% to env, 42% to Vif, 29% to Vpr, 16% to Rev, 9% to Vpu and Tat. Our data suggest that immunodominant regions within Nef, Pol and Gag may be important in the design and testing of candidate HIV-1 vaccines.

Identifying common HLA allele frequencies at high resolution and associations with viral burden

Genetic variation at the HLA loci plays an important role in determining host immune response to human immunodeficiency virus type 1 (HIV-1) infection. Variation in Class I HLA genes (A, B and Cw) causes restriction of CD8+ T cell cytotoxic responses, whereas Class II (including DRB1) variation restricts CD4+ T cell responses. The aim of this project is to study HLA variation in both HIV+ and HIV- southern African individuals to determine the HLA profile of the southern African population, and to determine which alleles are important in disease susceptibility and disease progression. Individuals from southern Africa were classified into broad ethnic groups (African, Caucasian, Coloured) and described as HIV-infected or uninfected. High resolution HLA genotyping for the A, B, Cw and DRB1 loci was performed by sequence-based typing. Where possible, viral loads and CD4 counts of HIV-infected individuals were determined. We characterised the spectrum of HLA-A, B, Cw and DRB1 alleles present in African HIV-infected, African HIV-uninfected and Caucasian HIV-uninfected groups. In the African HIV-infected samples (N=127), a total of 32 HLA-A and 34 HLA-B alleles were observed. The most common HLA-A alleles in this group were A*2301 (10.3%), A*3002 (9.9%) and A*6802 (8.7%), and the most common HLA-B alleles were B*5802 (11.8%), B*1503 (11.0%), B*4403 (11.0%) and B*1510 (9.8%). In African HIV+ individuals, allele A*2902 was significantly associated with low viral load (<10 000 RNA copies/ml) and alleles A*4301, A*0101 and A*2902 were significantly associated with high CD4 counts (>500) and may be associated with slower disease progression. Alleles A*3004, B*0801, B*5801 and B*4101 were significantly associated with high viral loads (>50 000 RNA copies/ml), whilst alleles A*2301, A*3004 and B*0801 were significantly more frequent (P<0.05) in individuals with low CD4 counts (<250), and may signify susceptibility to disease progression. These unique associations underscore the different HLA distribution profile of individuals in southern Africa.

Production and validation of HIV-specific MHC Class-I tetramers

According to the different HLA prevalence within the South African population, we are producing HIV-specific MHC Class-I tetramers restricted to the most prevalent HLA observed in the South-African population (HLA-A*2301, A*3002, A*0301, A*7401, B*1503, B*0801, B*3501). We have made one Nef tetramer and two monomers have been synthesized. Figure 2 shows successful labelling of CD8+ T cells specific for HLA-A*2301 restricted Nef RW8 epitope.

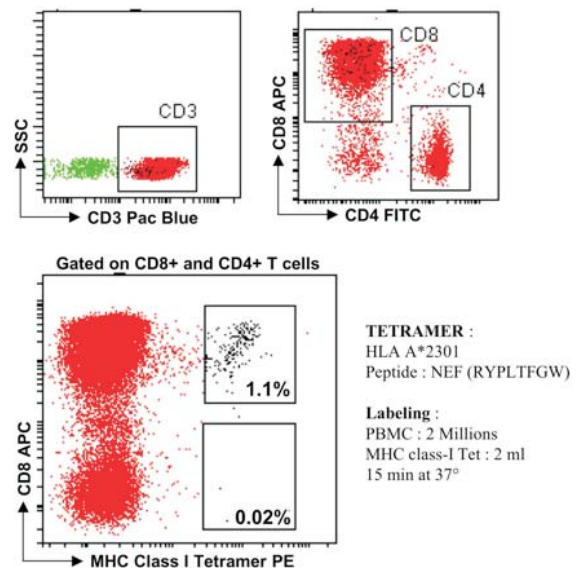


Figure 2: Identification of Nef-specific CD8+ T cells using MHC class I tetramers. PBMC from an HIV infected individual were stained with CD3, CD4, CD8 and MHC class I tetramer. TET+ cells, represented in black, were found exclusively within the CD8+ T cell compartment.

Polychromatic Flow Cytometry

We have introduced polychromatic flow cytometry (12 colour flow cytometry) for identity of functional panels of up to five cytokine expressions at the single cell level and have spent a large amount of time optimizing staining and the quality control of the instrumentation. The LSRII has now been calibrated, optimized and a daily QC incorporating target values established. Baseline values for each parameter on flow cytometer (i.e. lowest CV in a linear range, highest signal to noise ratio and PMT linearity) were determined. Optimization of all the parameters was established using single stained beads to determine the primary fluorescence. The median fluorescent intensity (MFI) was recorded for each parameter based on the voltages determined by the primary fluorescence. These values represent the target values that are quality controlled on a daily basis thereby ensuring that each experiment is conducted under the same conditions and ensuring reproducibility and validity of assay results. An 11 colour intracellular cytokine staining protocol was developed consisting of

a dump channel (V-amine, CD14 cascade blue), anchor marker subsets (CD3 APC-Cy7; CD4PE-Cy5.5 and CD8 QDot705), memory markers (CD27 PE-Cy5; CD45 RO PE- Texas Red; CD57 QDot 605) and functional markers (IFN γ FITC; MIP1 β PE; TNF α PE-Cy7; IL2 APC and CD107 Alexa 680). The panel was optimized on a common source of PBMC in a concordance study between the NICD and Duke University and showed 100% binary concordance between the two institutions. Variation between Duke and the NICD ranged from 3.6-9.8% CV for gated subsets. For the cytokine profiles the %CVs ranged from 18.1 - 43.5 % CV with a median of 31.8% for CD4 and 27.8% for CD8. Correlation between NICD and Duke functional profiles showed in excess of 80% agreement.

Measurement of Antigen Specific Immune Response using 11 Colour flow cytometry

The 11 colour panel was used to measure the cytokine profile and memory status of HIV specific T cells from chronically infected participants. PBMC from participants were stimulated with 5 peptide pools corresponding to full length HIV-1 Gag and Nef. Figure 3 shows a representative plot for two patients displaying the integrated flow data using Boolean gating in Spice software. The pie charts are colour coded to match the coloured blocks beneath the bar chart. CD8 T cell functional responses represented in the pie charts are grouped by number of functions and in the above example range from single functions (yellow) for both patients to two functions (turquoise) for patient 10 and four functions (blue) for patient 37 at a single cell level.

The bar charts are on an absolute scale and indicate the magnitude of each total Gag response (combined response of 5 pools).

HIGHLIGHTS AND ACHIEVEMENTS

Virology Laboratory

- Dr Visva Pillay received a Young Investigator Award for the Conference on Retroviruses and Opportunistic Infections (CROI) in Los Angeles, 25-28 February 2007.
- Johanna Ledwaba was awarded a scholarship to attend the Conference on Retroviruses and Opportunistic Infections (CROI) in Los Angeles, 25-28 February 2007.
- Elin Gray was awarded a scholarship to attend the Keystone Symposia meeting on HIV Vaccines: From Basic Research to Clinical Trials in Whistler, British Columbia, Canada, 25-30 March 2007.
- Prof Lynn Morris was invited by CDC in Atlanta, USA to Chair an international panel to Review Intramural Research at the International Lab Branch, Global AIDS Program, 10-12 July 2007.
- Dr Penny Moore was awarded a Poliomyelitis Research Foundation (PRF) grant entitled "Investigation of the entry efficiency of HIV-1 subtype C using real-time PCR competition assay"
- Dr Basson was awarded a Poliomyelitis Research Foundation (PRF) grant for "Investigation of the development of tenofovir drug resistance in HIV-1 subtypes B and C in vitro, with special reference to the K65R resistance mutation".

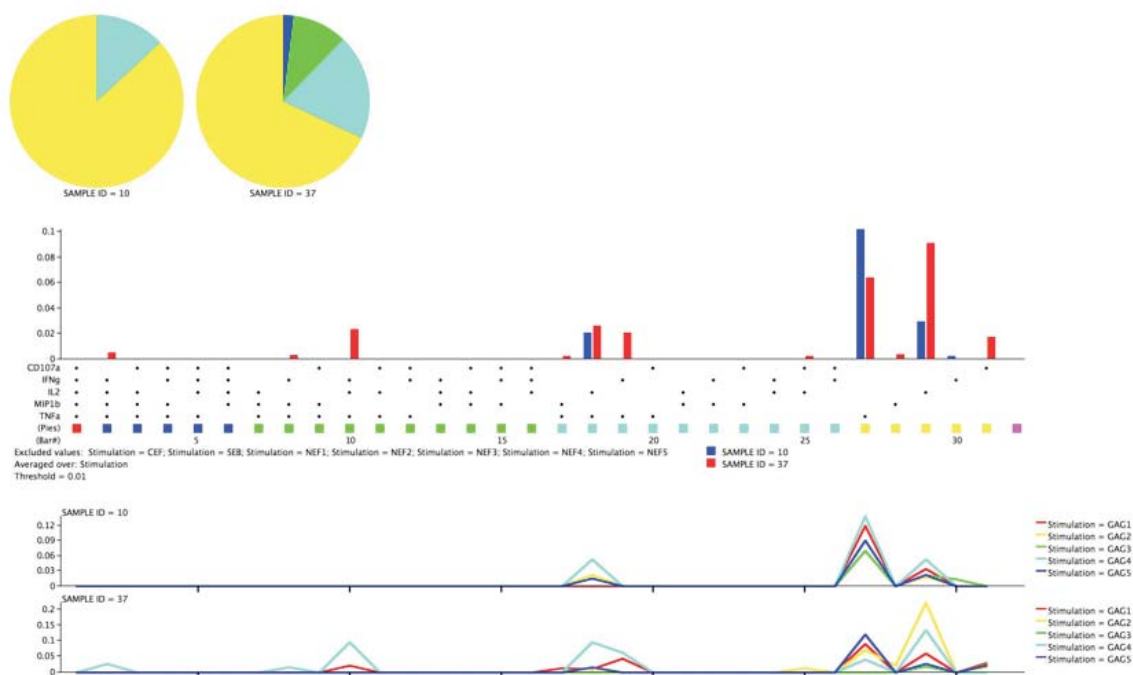


Figure 3: Proportions of CD8+ T cell populations according to differential cytokine expression. Representative plots of cytokine expressing CD8+ T cells from two HIV infected individuals after Gag peptide pool stimulation. Boolean gating was used to ascertain which combination of cytokines CD8+ T cells were expressing.

- Prof Lynn Morris was invited to give a talk during a Round Table discussion “Defining the Specificities in Broadly Neutralizing Sera” at the AIDS Vaccine 2007 Conference held in Seattle from 20-23 August 2007. She was also invited to be the Rapporteur for the topics on B cell immunity.
- Prof Lynn Morris was appointed Chair of the AIDS Vaccine 2008 Conference to be held in Cape Town, 13-16 October 2008.
- Dr Penny Moore attended the AIDS Vaccine Conference in Seattle, 20-23 August 2007 and gave a talk entitled “Role of anti-V1V2 antibodies in autologous neutralization of acute HIV-1 subtype C viruses”.
- Eleanor Cave was the recipient of a Fogarty AIDS International Research and Training Award which enabled her to study abroad and acquire specialised laboratory skills. She worked in Dr. Dennis Burton's laboratory at the Scripps Research Institute, La Jolla California, USA, from 25 August to 20 December 2007.
- Prof Lynn Morris was invited to join the five year Review Committee for the Neutralizing Antibody Consortium, International AIDS Vaccine Initiative (IAVI), held in La Jolla, California, USA, from 12-13 November 2007.
- Prof Lynn Morris was invited to give the second James Gear Memorial Lecture at the PRF Training Centre, NHLS Campus on 20 November 2007. The title of her lecture was: “Is a vaccine against HIV possible?”
- Prof Lynn Morris was invited by the Africa Centre, as an external expert, to attend their International Scientific Advisory Board meeting from 22-24 November 2007 at the Africa Centre in Somkhele, KwaZulu-Natal.
- Dr Visva Pillay attended a workshop and gave two talks on the surveillance of HIV drug resistance in Africa which was held in Windhoek, Namibia from 11-13 December 2007. WHO/AFRO in collaboration with CDC, USA and WHO/HQ organised the workshop.
- Mary Phoswa received her certificate on 20 December 2007 for passing her Virology Medical Technician exam which she wrote in October 2007.

Cell Biology Laboratory

- Prof. Tiemessen was reappointed for the 3rd 3-year term (2007-2009) to the Editorial Board: Clinical and Vaccine Immunology
- Prof Tiemessen has been appointed Chairperson of the IBC (Institutional Biosafety Committee) Witwatersrand University as of January 2007

The following presentations were made at the 3rd South African AIDS Conference, Durban, South Africa, June 5-8, 2007:-

- Donninger S, Meddows-Taylor S, Gray GE, Kuhn L, Tiemessen CT. Reduced proportion of CCL3L1 to CCL3 mRNA in HIV-1 infected individuals.
- Kuhn L, Schramm DB, Donninger S, Meddows-Taylor

S, Coovadia AH, Sherman GG, Gray GE, Tiemessen CT. African infants' CC chemokine ligand 3 like 1 (CCL3L1) gene copy numbers influence the risk of perinatal HIV transmission only in the absence of maternal Nevirapine.

- Meddows-Taylor S, Brittan D, Tiemessen CT. Reduced expression of polymorphonuclear neutrophil receptors and impaired chemotactic responses in haemophilia patients with and without HIV-1 infection.
- Mohanlal N, Paximadis M, Songca SP, Tiemessen CT. Developing CC Chemokines as adjuvants for HIV vaccine.
- Paximadis M, Schramm D, Donninger S, Meddows-Taylor S, Gray GE, Sherman GG, Coovadia AH, Kuhn L, Tiemessen CT. Single nucleotide polymorphism and haplotype characterization of the CCL3 and CCL3-L1 genes and investigation of a unique CCL3 haplotype with respect to mother-to-infant HIV transmission.
- Schramm DB, Meddows-Taylor S, Gray GE, Kuhn L, Tiemessen CT. Low maternal viral loads and reduced granulocyte-macrophage colony-stimulating factor levels characterize exposed-uninfected infants who develop protective HIV-1 specific responses.
- Shalekoff S, Meddows-Taylor S, Schramm DB, Donninger S, Gray GE, Sherman GG, Coovadia AH, Kuhn L, Tiemessen CT. Integrity of Human Immunodeficiency Virus-1 Subtype C Specific CD4⁺ and CD8⁺ T Cell Responses in Relation to Viral Load and Host CCL3L1 Copy Number in South African Women.

The following was presented at the Keystone Symposia on Molecular and Cellular Biology: Challenges of Global Vaccine Development, Cape Town, South Africa, October 8-13, 2007.

- Schramm DB, Meddows-Taylor S, Gray GE, Kuhn L, Tiemessen CT. Unique characteristics of HIV exposed-uninfected infants that develop HIV-1 specific cellular immune responses.

Immunology Laboratory

- Mandla Mlotshwa was selected to talk at the Plenary session of the 3rd Annual CHAVI retreat, 29 Sept to 3 Oct 2007: Quality and not quantity of HIV specific T cell responses in HIV-1 subtype C infection is important for control of disease.
- Pholo Maenetje was awarded a Fogarty Fellowship and spent three months at the Vaccine Research Center, NIH, indentifying populations of CD4 T-cell responses in HIV infection associated with the natural control of viral infection using polychromatic flow cytometry.
- The NICD became a partner in a newly funded network: Canadian Africa Prevention Trials (CAPT) Network and the first meeting was held 8-9 March 2007 in Entebbe, Uganda. The aim of the CAPT network is to build training and capacity in clinical trials and laboratory research between Uganda, South Africa and Canada.

- The HIV Immunology Laboratory was involved in coordinating the operations around the HVTN-funded Phambili trial, which commenced enrolment in January 2007. Specifically, we were involved in coordinating HIV diagnostics; pre-existing neutralizing antibody assays to the Adenovirus type 5 vector and the storage and archiving of specimens. This trial was stopped in October 2007 due to the Futility findings of the companion STEP study in the US, Caribbean and Australia.
- We co-organized the first Infectious Diseases in Africa (IDA) symposium held in Johannesburg, 10-11 November 2007. Our organizing partners were Duke University, the California Health Department, the World Health Organisation and National Institutes of Health. The aim was to bring together 13 up and coming African scientists with leading experts in the field of immunology and vaccines.
- Immediately after the IDA symposium, we held the 2nd African Flow Cytometry Workshop at the NICD laboratories and PRF training centre. Twenty junior African scientists were selected to participate in the workshop that focused on 4 and 9 colour flow cytometry and the different ways to analyze the data generated.

Immunopaedia

In 2004, Dr Clive Gray was awarded the International Leadership Award from the Elizabeth Glaser Pediatric AIDS Foundation to develop training and collaborative research materials. One of the developments within this programme is an on-line learning web-site for clinical registrars (www.immunopaedia.org.za). After conducting an extensive Needs Assessment of the paediatric and clinical community in South Africa, we identified that the entrée to immunology learning in a clinical setting is through specific case studies. The site was launched in June 2007 at the Durban AIDS Conference and consists of three main threads of Virology, Case Studies and Immunology where the aim is to integrate each component of the site to achieve a greater understanding of immunology in our target users. A strong component of Immunopaedia is an active Monitoring and Evaluation programme where we are constantly evaluating the strengths and weaknesses of the site. We have an established collaboration with the University of Stellenbosch for piloting materials and web-site use for paediatric registrars.

COLLABORATIONS

Virology Laboratory

Centre for HIV AIDS Vaccine Immunology (CHAVI)
 Centre of AIDS Programme of Research in South Africa (CAPRISA), University of KwaZulu Natal.
 University of Cape Town, Institute of Infectious Disease and Molecular Medicine
 Duke University
 University of Alabama

The Scripps Research Institute
 Torrey Pines Institute for Molecular Studies
 Vaccine Research Centre, NIH
 Stanford University
 South African National Bioinformatics Institute (SANBI)
 Columbia University, New York
 Perinatal HIV Research Unit
 Aurum Health
 Council for Scientific and Industrial Research
 Human Pathogenesis Program, University of KwaZulu Natal

Immunology Laboratory

Vaccine Research Center, NIH.
 HIV Vaccine Trials Network (HVTN)
 University of Montreal
 Center for HIV AIDS Vaccine Immunology (CHAVI)
 Weatherall Institute of Molecular Medicine, University of Oxford
 University of Cape Town, Institute of Infectious Disease and Molecular Medicine
 Centre of AIDS Programme of Research in South Africa, University of KwaZulu Natal
 Perinatal HIV Research Unit, Soweto

Cell Biology Laboratory

Prof. Louise Kuhn, Gertrude H. Sergievsky Centre, and Department of Epidemiology, Mailman School of Public Health, Columbia University, New York

Prof. Glenda Gray, Perinatal HIV Research Unit, University of the Witwatersrand, Johannesburg and Chris Hani/Baragwanath Hospital, Soweto

Prof. Gayle Sherman, Department of Molecular Medicine and Haematology, Johannesburg Hospital, National Health Laboratory Service & University of the Witwatersrand, Johannesburg

Dr. Ashraf H Coovadia, Coronation Hospital, Wits Paediatric HIV Working Group, Johannesburg, South Africa

CAPACITY BUILDING

Elin Gray submitted her PhD Thesis to the University of the Witwatersrand on 14 December 2007. The title of her thesis: "Characterization of neutralizing antibody epitopes on HIV-1 subtype C envelope glycoproteins to support vaccine design".