ashm
Supporting the HIV, Viral Hepatitis and Sexual Health Workforce

HTLV-1 Round Table – Summary.

Tuesday 15 November, 2016
4:00 – 7:30pm

Agenda

1. **Acknowledgement of traditional owners** (delivered by Damian Purcell)

2. **Introductions** (roundtable brief self-introduction/background)

Meeting attended by:

- David Anderson, The Burnet Institute
- Lisa Bastian, WA Health
- Josh Booth, Virology research student, HTLV-1
- James Cooney, Walther and Eliza Hall, Pelligrini Lab, PhD Student
- Levinia Crooks, Policy support, ASHM
- Lloyd Einsiedel, Alice Springs Infectious Diseases Specialist/Researcher
- Kath Fethers, Melbourne Sexual Health Physician, formerly Alice Springs SHC
- Colleen Hayes, Flinders University
- Vicki Krause, NT Health
- Ricky Mentha, Baker IDI
- Mark Pelligrini, Walter and Eliza Hall, Pre-clinical Research
- Damian Purcell, Doherty Institute, Translational Research
- Kerry Taylor, Flinders University
- Paul Young, University of Queensland, HTLV-1 vaccine research
- James Ward, Aboriginal and Torres Strait Islander Health Researcher
- Kim Wilson Scientist, National Serum Reference Laboratory
- David Yurick, Doherty Institute, Purcell Lab, PhD Student
- Skye McGregor, Kirby Institute, UNSW Sydney
- John Zaunders, , Kirby Institute, UNSW Sydney
- Apologies: John Kaldor, Kirby Institute, UNSW Sydney
  Simon McKeon, Macquarie Bank, Monash University

3. **Introduction to HTLV-1 infection and diagnostics** (Damian Purcell)

General description of HTLV-1 discovery, retroviral structure, modes of transmission, and comparison of Australian HTLV-1 subtype C with the international strain HTLV-1 subtype A. Comparisons were drawn with the closely related HIV-1 retrovirus that infects and kills T-lymphocytes leading to the release of many new virus particles, but while HTLV-1 infects the same cells it does not kill these cells nor lead to the release of new virus particles. Instead integrated HTLV-1 DNA lodged in

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the cell genome expresses viral proteins that reprogram T-cell function for competent immunity. The Purcell lab has sequenced full HTLV-1c genomes and discovered differences in the nucleotides that should code for the protein p12, which could impact immune function leading to disease pathogenesis. A quantitiative drop digital PCR assay that accurately and sensitively measured the levels of HTLV-1c DNA in the T-lymphocytes was developed and shows that the infection is even more widespread that first thought. Several seronegative samples tested positive for low levels of HTLV-1 DNA using the ddPCR. While about half the samples in a longitudinal study showed that the levels of HTLV-1 were steady through time, the others mostly showed increasing levels of HTLV-1. A smaller number of other samples showed that some individuals controlled the virus and reduced the levels of virus DNA. Brief discussion of future research direction to address the mechanisms used by HTLV-1 to alter immune functions of the infected cells, hurdles to funding, delivering scientific findings and translating discovery back to the Indigenous community.

4. **Historical context of HLTV-1 in central Australia, impacts on research & public health policy** (Kerry Taylor and Colleen Hayes, Ricky Mentha)

General description of POCHE Center for Indigenous Health and Well-being, work output in central Australia in an NT context. Touched on "examples of concern", offering Indigenous insights into cultural safety of medical practices, undertaking clinical and scientific research in primary language, and respect for "cultural gate-keeping". One recent area of concern was the publication of specific shire names identifying high HTLV-1 prevalence, potentially stigmatizing Indigenous areas of central Australia. Concluded with reminder that without Indigenous leadership these projects will not advance! Indigenous Health Research Officers, Ricky and Colleen, spoke with great clarity and insight into the pervasive nature of HTLV-1 infection in the community and their work to disseminate information about this infection in local language terms that resonate with the community. They described an understanding of the issues, but were concerned that they could not suggest any guidance or therapies.

5. HTLV-1 epidemiology, clinical disease, and current research in central Australia

Indigenous communities in central Australia have extremely high rates of HTLV-1 infection. In this setting HTLV-1 infection contributes to morbidity and death, largely through HTLV-1 associated pulmonary disease. Several studies out of Alice Springs Hospital (ASH) were presented highlighting the very high prevalence of HTLV-1 within central remote Indigenous communities; >60% for adult in-patients from communities to the south of Alice Springs and >40% for adults in one community recently surveyed. Clinical conditions observed at ASH include ATLL and HAM/TSP but the most common HTLV-1 associated disease observed in >500 HTLV-1 infected adults at ASH is bronchiectasis which affected 10% of subjects. The mean age of death due to bronchiectasis in Indigenous adults is similar to that for subjects in the USA in 1940 for bronchiectasis; 42.5 years. Risk factors for bronchiectasis in a case-control study included HTLV-1 seropositivity which included risk 2.5 fold in a multivariable model and HTLV-1 pro-viral load (pVL) among subjects who were HTLV-1 infected 5 fold. In a whole of community survey that included >70 Indigenous adults, 40% were HTLV-1 infected. Moreover, chronic lung disease was only found among HTLV-1 infected subjects (7 out of 30 HTLV-1+ patients in a whole of community survey also diagnosed with chronic lung disease, 3 of which were ataxic). HTLV-1 infection also increased the risk of life-threatening blood stream

infections, a risk that was closely associated with higher HTLV-1 pVL among subjects who were HTLV-1 infected. In a prospective cohort of 840 subjects followed for up to eight years, HTLV-1 infection was associated with an increased risk of death, an effect that was largely mediated by HTLV-1 associated lung disease. HTLV-1 pVL >1% PBL increased the risk of death >four fold in a multivariable model. Concluded with future research directions including PVL longitudinal study underway but held up by funding issues, but hopes of 2017 grant approval in this area; closer look into pulmonary disease and its implications for bronchiectasis, identifying risk factors and potential strategies for intervention. Finally, touched briefly on researching sepsis as a potential HTLV-1-associated condition due to immune dysregulation and identifying risk factors and intervention ideas.

6. **Animal models of HTLV-1 infection** (Marc Pelligrini, presented by James Cooney)

The mouse model that installs a human-immune system into mice, generally referred to as the humanised mouse model, was described. The potential for these humanized mice for studying HTLV-1-associated cancer, inflammatory disease, and hematopoiesis was introduced. Reported model validation of HTLV-1-infectability via MT2 cell line and reported data showing 16-week study measuring HTLV-1 pVL using ddPCR (with credit to Purcell lab for ddPCR assay). Final pVL in some 16-week mice was greater than 10^6 copies/10^6 PBMCs, indicating there is multiple infection of provirus per cell. Also reported an increase in cell proliferation and observed HTLV-1 related symptoms (splenomegaly, hepatomegaly). Histology of hepatocytes showed classical ATLL morphology and "logs-greater" number of tumor infiltrates lymphocytes.

7. **Control and prevention of HTLV-1 around the world** (Kath Fethers)

Personal anecdotal introduction justifying why HTLV-1 is an important issue especially in Aboriginal communities, personal ties to the Indigenous community of Alice Springs, and perspective as a sexual health practitioner with central Australian experience. Presented topic of mother-to-child transmission (MTCT), and stressed the sensitivity and guidance necessary to advise when it is/isn't appropriate to advise alternatives. Mentioned MTCT intervention strategies that have proven successful in Japan (limited breastfeeding intervals and even freeze-thawing breast milk) and potential for pVL testing as an indicator for safe/unsafe breastfeeding periods. Resource poor regions such as Brazil have successfully adopted the Japanese model of prevention of HTLV-1 MTCT. Kath suggested that antenatal testing should/could be a regional guideline, not indigenous specific, as with universal screening in HIV. This is preferable for several reasons; HTLV-1 has various routes of transmission, is endemic in the region and universal screening would also avoid stigmatising indigenous women in antenatal care.

8. **Future research directions and research structure** (Damian Purcell, James Ward)

Agreed that HTLV-1 future directions largely remain an issue of funding projects and coordinating Indigenous leadership. Paul Young suggested looking into philanthropic resources such as Welcome Foundation Funding (https://wellcome.ac.uk/funding), and not so much towards the Gates Foundation (http://www.gatesfoundation.org). There was mention of the HIV Observational Database (http://kirby.unsw.edu.au/projects/australian-hiv-observational-database-ahod) which is believed to be NIH funded. James Ward emphasized the importance for

HTLV-1 research to remain in central Australia and with Indigenous leadership. James Ward also mentioned the "Purple House", which had a previous fund raising success that resulted in the Alice Springs Hospital Dialysis Centre. Is there potential for fund raising (i.e., Indigenous artwork) to establish principal funding? Finally, there was mention of personal contacts with members of Parliament, television programs and media outlets that might be utilized to gain visibility. However, it is paramount that the HTLV-1 story does not create anger, instill fear, or propagate stigmatism within Australia, the world, and especially in Aboriginal communities themselves.

9. Open forum

Due to time, moved directly to next steps and closing segments of roundtable.

10. Next Steps

Most of what was mentioned in 'future research directions and future research structure' was reiterated as part of 'next steps'. Future years may have greater inclusion of HTLV-1 in track A of the ASHM Conference, and could provide a multidisciplinary sub-theme for next year's Australasian HIV/AIDS Conference. There was some clarification from James Ward to Levinia Crooks that acknowledgment of HTLV-1 as a significant issue was still pending. Instead, in the Fourth National Aboriginal and Torres Strait Islander Blood-Borne Virus and Sexually Transmissible Infections Strategy HTLV-1 was still considered an emerging issue, which needs to be rectified to gain deserved attention. Paul Young offered to submit this roundtable to the Aus J Med for recordkeeping.

11. **Close** (Damian Purcell and James Ward)

The purpose of this first meeting was to get a better understanding of the science of HTLV-1 and get an update on what work is being done in HTLV-1. We included representatives of affected communities from the outset and acknowledged their importance as crucial components of this round table. We have also included representatives from the jurisdictions most impacted by HTLV-1. Hopefully, this meeting is the first of many, and historically marks a foundation for HTLV-1 strategic development inclusive to Indigenous Australians.