Associations of Host Genetic Variation with Regulation of Inflammatory Gene Expression and HIV Susceptibility

Shanelle N Gingras[1,2], Jeffrey Tuff[1], Naima Jahan[2], Paul Jankowski[1], Salim S. Karim[3], Quarraisha A. Karim[3], Lenine J. Liebenberg[3], Jo-Ann S. Passmore[3,4], Lyle R McKinnon[2,3], Paul J McLaren[1,2]

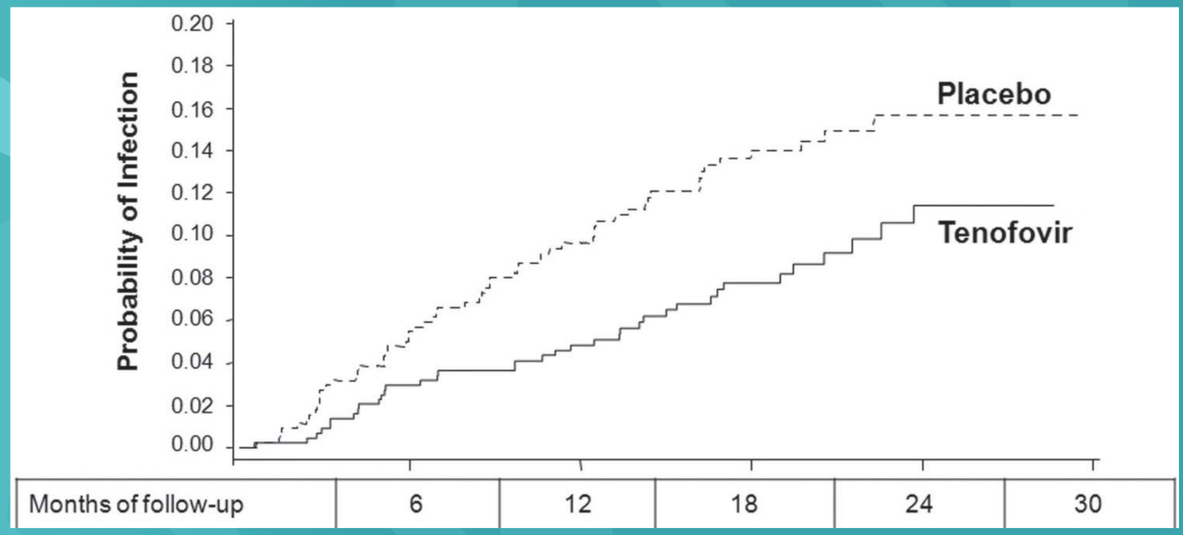
[1] JC Wilt Infectious Diseases Research Center, Public Health Agency of Canada, [2] Department of Medical Microbiology and Infectious Diseases, University of Manitoba, [3] Centre for the AIDS Programme of Research in South Africa, [4] University of Cape Town

1. Purpose

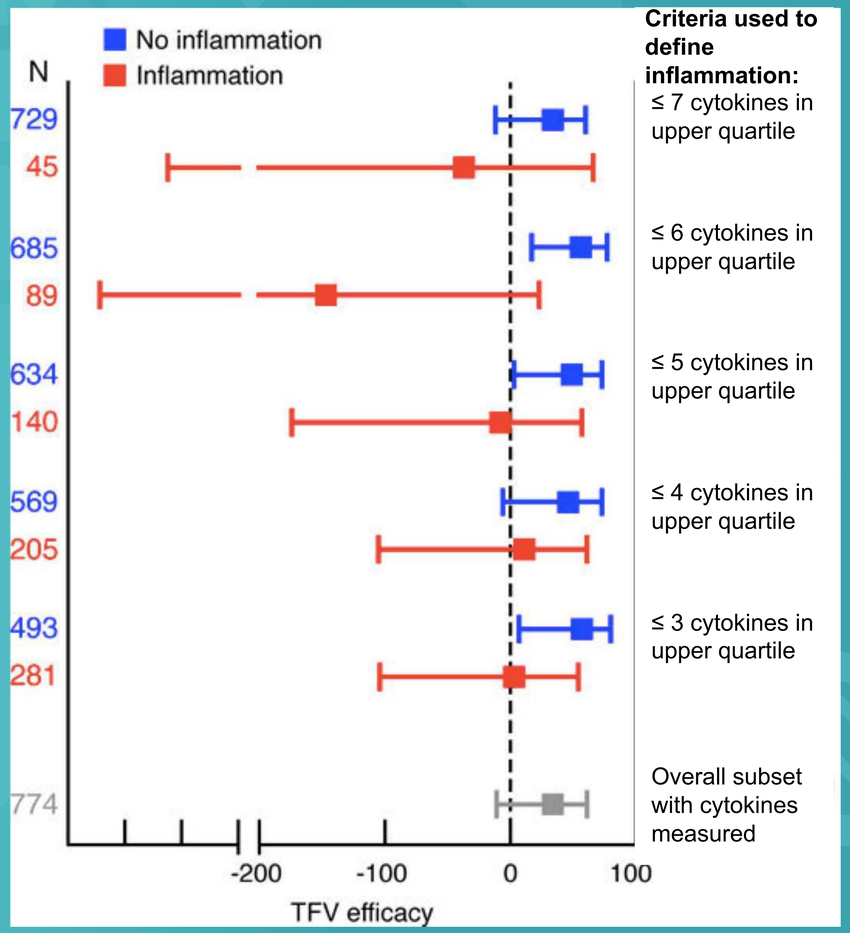
Investigate genetic regulation of differential gene expression in monocytes and protein concentrations of key inflammatory cytokines in plasma. Significant expression quantitative trait loci (eQTL) and protein QTL (pQTL) will be tested for association with HIV acquisition.

2. Background

The Centre for the AIDS Programme of Research in South Africa (CAPRISA) -004 HIV prevention trial demonstrated a 54% reduction in HIV acquisition in high gel adherers in the 1% tenofovir treatment arm compared to the controls[1]. However, a post-hoc analysis considering the impact of vaginal inflammation on the efficacy of the 1 % tenofovir gel found that as women became more inflamed, the efficacy of the 1% tenofovir gel was ablated[2].



1. Karim, Q. A. *et al.* Effectiveness and Safety of Tenofovir Gel, an Antiretroviral Microbicide, for the Prevention of HIV Infection in Women. *Science* **329,** 1168 (2010).



2. McKinnon, L. R. *et al.* Genital inflammation undermines the effectiveness of tenofovir gel in preventing HIV acquisition in women. *Nat. Med.* **24,** 491–496 (2018).

Conflict of Interest Disclosure: I have no conflicts of interest

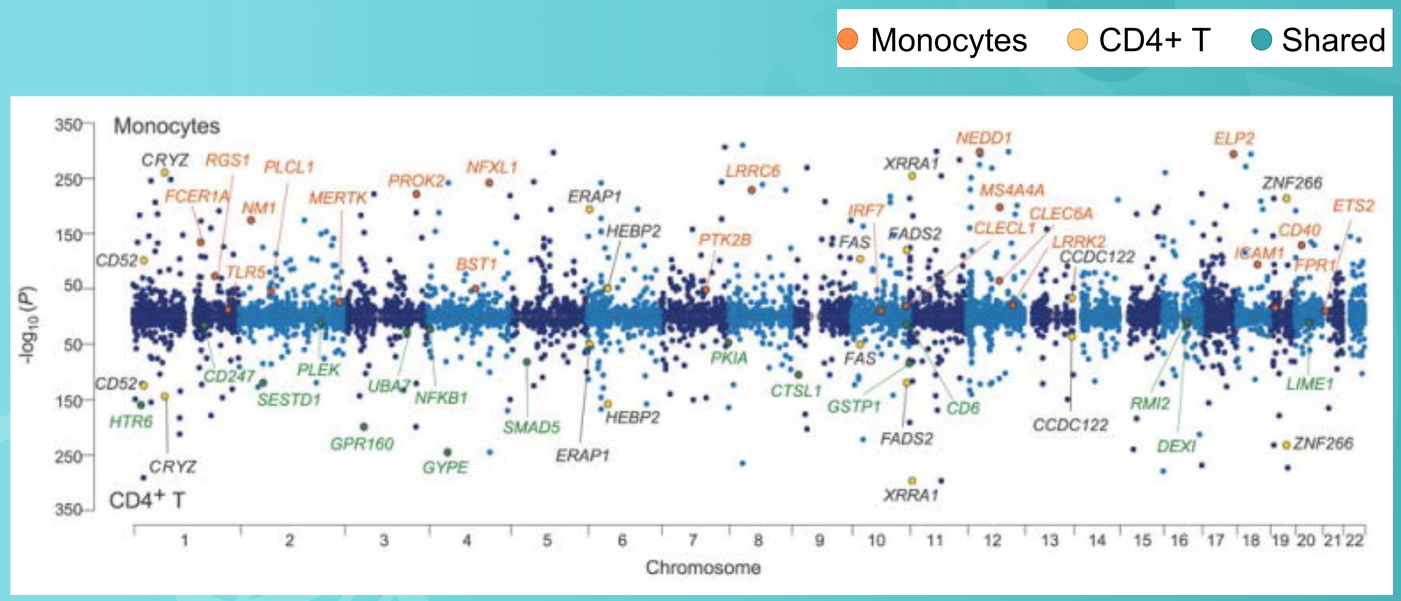
JC Wilt Infectious Diseases Research Center

2. Background Continued

Inflammation Contributors
- Sexually transmitted infections
- Bacterial vaginosis
- Age
- Physical damage
- Genetics?

Genetic regulation of gene expression has been investigated in inflammatory cell populations in a cohort of multiethnic healthy individuals[3].

Key findings in monocytes:
- eQTLs present in two key inflammatory diseases, Alzheimer's and Parkinson's disease[3]
- Population specific eQTLs[3]



3. Raj T, Rothamel K, Mostafavi S, et al. Polarization of the Effects of Autoimmune and Neurodegenerative Risk Alleles in Leukocytes. Science (80-). 2014;344(6183):519-523. doi:10.1126/science.1249547

QTL studies have found approximately 25 – 40% of cis-eQTLs mediating pQTLs[4].

eQTLs can be used in combination with pQTLs to help elucidate pathways for drug targets for the prevention and treatment of HIV.

4. Folkersen, L., et al. Genomic evaluation of circulating proteins for drug target characterisation and precision medecine. BioRxiv. 2020. doi: https://doi.org/10.1101/2020.04.03.023804

3. Hypothesis

1. Differential gene expression in inflammatory cell populations is associated with the establishment of inflammation

2. Differential gene expression is controlled by genetic variants whose frequency differs in the HIV infected verses uninfected

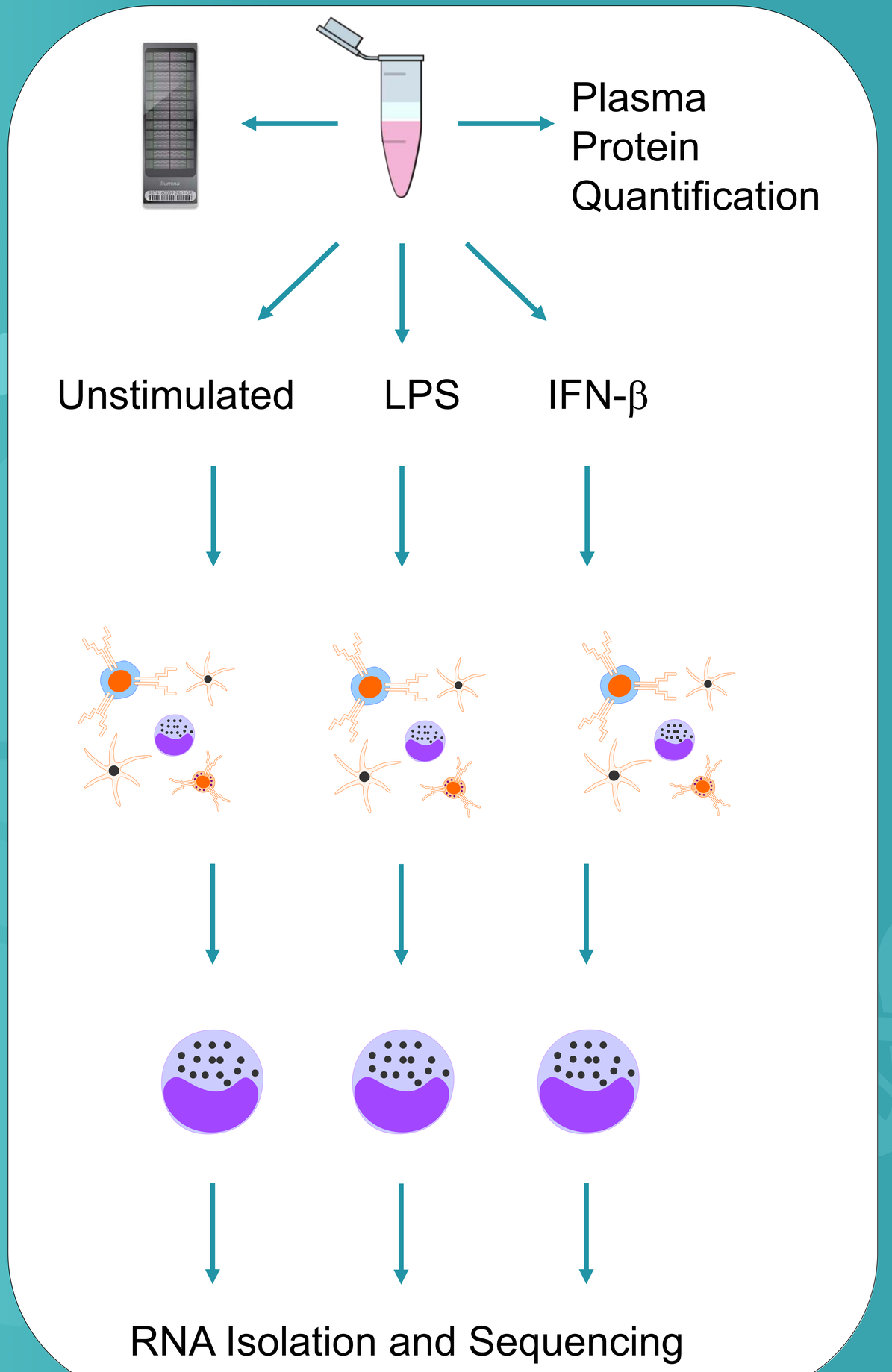
3. Key inflammatory proteins within the plasma are genetically regulated either independently or in association with eQTL

4. Objectives

1. Define genes differentially expressed between populations via transcriptional profiling of monocytes
2. Identify genetic variants impact on expression of associated genes
3. Test association between significant eQTLs and pQTLs with HIV

5. Methods

Individuals from the CAPRISA-004 cohort have been genotyped (n=782), plasma protein levels have been measured for key inflammatory cytokines (n=833), and peripheral blood mononuclear cells have been split into three stimulation conditions (unstimulated, LPS, IFN-b) before being sorted into pure inflammatory cell fractions for RNA isolation and sequencing of monocytes (n=180). Differential gene expression will be assessed between groups (cases and controls, inflamed and not inflamed, and stimulated and not stimulated) ang genes that differ at least 2.5 fold will be tested for genetic regulation. eQTLs identified will be tested for co-localization with significant pQTLs.



6. Summary

1. Quantify differential gene expression in monocytes between cases and controls across stimulation conditions
2. Determine associations between significant genes and HIV acquisition
3. Determine associations between significant proteins and HIV acquisition
4. Investigate genetic regulation of genes and proteins significantly associated with HIV acquisition
5. Determine co-localization between significant eQTLs and pQTLs

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9. Contact Information

Shanelle N. Gingras
PhD Student
Medical Microbiology and Infectious Diseases
University of Manitoba
Email: gingrass@myumanitoba.ca

McLaren Lab
https://mclarenlab.wixsite.com/mclaren-lab/about-the-team