Immune cell dynamics & control of persistent virus infection

Lies Boelen[1], Bisrat Debebe[1], Marcos Silveira[1,2], Arafa Salam[3], Julia Makinde[4], Chrissy h. Roberts[5], Eddie C.Y. Wang[6], John Frater[7,8], Jill Gilmour[4], Katie Twigger[1], Kristin Ladell[6], Kelly L. Miners[6], Jyothi Jayaraman[9], James A. Traherne[9], David A. Price[6], Ying Qi[10], Maureen P. Martin[10], Derek C. Macallan[3], Chloe Thio[11], Jacquie Astemborski[11], Gregory Kirk[11], Sharyne M. Donfield[12], Susan Buchbinder[13], Salim I. Khakoo[14], James J. Goedert[15], John Trowsdale[9], Mary Carrington[10,16], Simon Kollnberger[6], Becca Asquith[1]

[1]Department of Medicine, Imperial College London, London, UK. [2]Faculty of Engineering, São Paulo State University - UNESP, Brazil. [3]Institute for Infection and Immunity, St. George's Hospital, University of London, UK. [4]International AIDS Vaccine Initiative Human Immunology Laboratory, London, UK. [5]Clinical Research Department, London School of Hygiene and Tropical Medicine, London, UK. [6]Division of Infection and Immunity, Cardiff University School of Medicine, Cardiff, UK. [7]Nuffield Department of Medicine, University of Oxford, Oxford, UK. [8]Oxford NIHR Biomedical Research Centre, Oxford, UK. [9]Immunology Division, Department of Pathology, University of Cambridge, Cambridge, UK. [10]Cancer and Inflammation Program, Leidos Biomedical Research Inc., Frederick National Laboratory for Cancer Research, Frederick, Maryland, USA. [11]Johns Hopkins University, Baltimore, Maryland, USA. [12]Rho, Chapel Hill, North Carolina, USA. [13]San Francisco Department of Public Health, San Francisco, California, USA. [14]Faculty of Medicine, University of Southampton, Southampton, UK. [15]Division of Cancer Epidemiology and Genetics, National Cancer Institute, Bethesda, Maryland,

Chronic viral infections such as human immunodeficiency virus (HIV-1), hepatitis C virus (HCV) and human T cell leukemia virus (HTLV-1) are marked by huge between-individual variation in outcome. Some people infected with HIV-1 will develop AIDS in less than 5 years others will remain healthy for 10 years or more. In HCV infection, some individuals spontaneously clear the virus others develop persistent infection and subsequent risk of liver failure. Similarly in HTLV-1 infection, some individuals remain lifelong healthy carriers of the virus whilst others will develop an aggressive, rapidly fatal leukemia.

We are coupling analysis of genetic data from large patient cohorts with mechanistic mathematical modelling and in vitro and in vivo T cell dynamics experiments to gain insight into what determines the clinical outcome of viral infection. We have found that receptors called KIRs alter immune CD8+ T cell dynamics in vitro, we hypothesise that this tips the host-pathogen balance and strengthens control of chronic virus infection. Our data suggest that engagement of KIRs enhances the CD8+ T cell response against HIV-1, HCV and HTLV-1 and is a significant determinant of clinical outcome in all three viral infections[1,2]. We are now extending this work by quantifying the relationship between KIR genotype and immune cell dynamics in humans in vivo.

1. Boelen et al. Inhibitory killer cell immunoglobulin-like receptors strengthen CD8+ T cell-mediated control of HIV-1, HCV, and HTLV-1. ***Science Immunol*** 3(2018).
2. Seich Al Basatena NK et al KIR2DL2 enhances protective and detrimental HLA class I-mediated immunity in chronic viral infection. ***PLoS Pathog*** 7, e1002270 (2011).