

Project title: Studies of HIV-1 and herpesvirus co-infection in macrophages and dendritic cells

Laboratory supervisor: Dr Mahdad Noursadeghi and Dr Richard Milne
Clinical supervisor: Dr Mahdad Noursadeghi

The mononuclear phagocytic cell family, comprising monocytes, macrophages and dendritic cells are sentinel cells of innate immunity that initiate host responses to microbial pathogens and contribute to killing of intracellular pathogens¹. We have already established that HIV-1 can cause productive infection of macrophages by evading innate immune cellular activation², and can attenuate specific signalling pathways to subsequent innate immune stimulation³. In this project, we will extend these observations to test the hypothesis that HIV-1 also disrupts host cell responses to clinically relevant co-infecting pathogens. Amongst these, the herpesviruses human cytomegalovirus (HCMV) and herpes simplex virus type 1 (HSV-1) are of particular interest because they also show tropism towards mononuclear phagocytic cells and cause significant morbidity and mortality in HIV-1 infected patients. We will ask whether co-infection of macrophages with HIV-1 and either HCMV or HSV-1, changes the host-pathogen interactions or viral replication in a way that may contribute to the natural history of HIV infection or the pathogenesis of HCMV and HSV-1 diseases in AIDS. Using monocytes, macrophages and dendritic cells, we will study the following basic science questions:

1. The effects of infection and co-infection on host defence responses to each virus
2. The effects of co-infection on the replication dynamics of each virus
3. The effects of infection and co-infection on genome-wide transcriptional profiling of the host cell, validated by appropriate functional assays
4. The molecular determinants of effects on the host cell and on viral replication

In addition we will assess whether these effects are evident in clinical samples from co-infected patients and whether they are associated with clinical disease. This work extends an existing programme of research to study pathogenesis of co-infection associated with HIV-1, and brings together expertise in Dr Noursadeghi's laboratory in HIV-1 infection of mononuclear phagocytic cells and Dr Milne's expertise in herpesviruses. The project will involve the full repertoire of laboratory methodology, including cell culture, molecular virology, immunological assays and expression profiling by PCR and genome-wide microarray technology. It will benefit from broad expertise within the MRC Centre for Virology, within Infection and Immunity at UCL, and from the close links with Clinical HIV services associated with UCLH.

REFERENCE

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2. Tsang, J., B. M. Chain, R. F. Miller, B. L. Webb, W. Barclay, G. J. Towers, D. R. Katz, and M. Noursadeghi. 2009. HIV-1 infection of macrophages is dependent on evasion of innate immune cellular activation. *AIDS*.
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