

**Project title: Interferon inducible restriction of HIV-1 in humans**

Laboratory supervisors: Professor Greg Towers & Dr Mahdad Noursadeghi  
Clinical supervisor: Dr Mahdad Noursadeghi

We study the role of innate immune responses to HIV-1 and host cell factors that can restrict HIV-1 infection. A number of HIV restriction factors have been identified that are induced by innate immune interferon responses, including TRIM5 $\alpha$ , APOBEC3G and tetherin. For each of these factors, there is evidence for evolution of viral evasion mechanisms and counteracting host evolution<sup>1-4</sup>. We aim to identify and characterise the repertoire of antiviral restriction mechanisms that may provide novel therapeutic opportunities and increase our understanding of HIV-1 immune evasion.

We have recently established that HIV-1 infection of macrophages is dependent on evasion of innate immune cellular activation, which would otherwise induce interferon responses that effectively restrict the virus, despite the full repertoire of virus evasion mechanisms<sup>5,6</sup>. Genome-wide transcriptional profiling reveals interferon induced upregulation of >800 genes that may mediate this effect, many of which have not been characterised. We aim to identify host antiviral restriction factors in this model by cloning interferon-induced cDNA from macrophages into lentiviral vectors and then screening the cDNA library for HIV-1 restriction in otherwise permissive cells. We aim to clone and characterise novel restriction factors and establish the mechanism and specificity of their antiviral effects.

In addition we aim to investigate whether known, or novel factors identified here, contribute to HIV-1 control *in vivo*. We will undertake a cross-sectional study of restriction factor gene expression levels in peripheral blood of asymptomatic antiretroviral naïve HIV-1 infected patients. We will test the hypothesis that gene expression levels of these restriction factors exhibit a reciprocal correlation with HIV-1 viral load. We will explore the molecular associations of successful HIV-1 restriction in patients with low viral load in contrast to HIV-1 escape in patients with high viral load. Finally, host genomes will be analysed for polymorphisms associated with altered restriction factor activity. The functional importance of molecular associations discovered in this clinical context will be tested by cloning selected variants of viral and host factors for expression in established *in vitro* cell culture assays of restriction.

This project aims to translate exciting discoveries in molecular virology to novel clinical research methodology and in turn to take advantage of clinical samples that reflect biologically important host-pathogen relationships for further basic science research. It encompasses a comprehensive range of laboratory techniques with particular emphasis on molecular biology, virology and cell culture. All the equipment and expertise required for this project are available locally.

## Reference List:

1. Price, A. J., F. Marzetta, M. Lammers, L. M. Ylinen, T. Schaller, S. J. Wilson, G. J. Towers, and L. C. James. 2009. Active site remodeling switches HIV specificity of antiretroviral TRIMCyp. *Nat Struct. Mol Biol.*
2. Gupta, R. K., S. Hue, T. Schaller, E. Verschoor, D. Pillay, and G. J. Towers. 2009. Mutation of a single residue renders human tetherin resistant to HIV-1 Vpu-mediated depletion. *PLoS Pathog* 5:e1000443.
3. Huthoff, H., and G. J. Towers. 2008. Restriction of retroviral replication by APOBEC3G/F and TRIM5alpha. *Trends Microbiol.* 16:612.
4. Wilson, S. J., B. L. Webb, L. M. Ylinen, E. Verschoor, J. L. Heeney, and G. J. Towers. 2008. Independent evolution of an antiviral TRIMCyp in rhesus macaques. *Proc. Natl. Acad. Sci. U. S. A* 105:3557.
5. 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.*
6. Noursadeghi, M., J. Tsang, R. F. Miller, S. Straschewski, P. Kellam, B. M. Chain, and D. R. Katz. 2009. Genome-wide innate immune responses in HIV-1-infected macrophages are preserved despite attenuation of the NF-kappa B activation pathway. *J Immunol* 182:319.

