Characterisation of TRIM21 and intracellular viral neutralisation.

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We are interested in the mechanisms and innate immune consequences of intracellular viral neutralisation mediated by TRIM21. The immune system protects our body against primary viral infection using a rapid and broad specificity innate immune system, which instructs cells to produce restriction factors that inhibit the virus, and educates adaptive immunity to form immunological memory of the viral pathogen. Antibodies represent an important aspect of immunological memory. The best-characterised function of viral neutralising antibodies is to prevent them from entering cells. We are investigating a novel mechanism of virus neutralisation whereby antibody-coated viruses still enter cells but are destroyed once inside by proteasomal degradation. The intracellular neutralising activity is mediated by the Tripartite-Motif containing protein, TRIM21 (1). The C terminal B30.2 domain of TRIM21 recruits the antibodies attached to the virus and its N-terminal RING and B-box domains are required for ubiquitination and proteasomal targeting.

We are investigating whether TRIM21 triggers innate immune responses when engaged by virus. This exciting possibility will demonstrate that antibodies not only act during the secondary, adaptive immune response, but also function as co-factors for innate immune detection of viral pathogens. We will characterise the nature of the innate signalling pathways triggered by intracellular virus neutralisation and the molecular mechanisms that facilitate innate immune receptor recognition of cytosolic virus-antibody complexes. The ubiquitination pathways required for TRIM21 activity will also be investigated. Characterising TRIM21 function is important because antibodies against TRIM21 protein are a major biomarker in autoimmune diseases such as systemic lupus erythematosus and Sjögren's syndrome. We hypothesise that the novel intracellular neutralisation function of TRIM21 plays a role in these diseases. We aim to apply our knowledge of TRIM21 intracellular viral neutralisation to study the TRIM21 related autoimmune diseases. This study will resolve the underlying molecular mechanisms contributing to the aetiology of poorly understood autoimmune diseases. This project is built on our long-standing interest in Tripartite-Motif containing proteins (2), ubiquitin pathways (3), and innate immune recognition of viruses. This project will be co-supervised by Professor Michael Ehrenstein, of the UCL Centre of Rheumatology. PhD candidate working on this project will be trained in the state-of-art molecular virology, cell biology and immunological techniques. This project offers the opportunity to translate novel *in vitro* findings into clinical applications that will be of immediate benefit to the diagnosis and treatment of autoimmune diseases.

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2. **Wilson, S. J., B. L. J. Webb, L. M. J. Ylinen, E. Verschoor, J. L. Heeney, and G. J. Towers.** 2008. Independent evolution of an antiviral TRIMCyp in rhesus macaques. Proc Natl Acad Sci USA **105:**3557-3562.
3. **Pardieu, C., R. Vigan, S. J. Wilson, A. Calvi, T. Zang, P. Bieniasz, P. Kellam, G. J. Towers, and S. J. D. Neil.** 2010. The RING-CH ligase K5 antagonizes restriction of KSHV and HIV-1 particle release by mediating ubiquitin-dependent endosomal degradation of tetherin. PLoS Pathog **6:**e1000843.