

## 8) How do PTPN22 genetic variants predispose to autoimmune disease *in vivo*?

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Activation and differentiation of T and B lymphocytes underpin the adaptive immune response. These processes need to be tightly regulated in order to provide optimal host defence to foreign pathogens, while at the same time preventing autoimmune and inflammatory responses directed at host tissues. Regulation of lymphocyte activation following engagement of the antigen T cell receptor (TCR) is maintained at least in part through the opposing action of kinases and phosphatases. Lyp, encoded by the *PTPN22* gene, is a tyrosine phosphatase expressed in haematopoietic cells which, like its mouse orthologue PEP, functions in a complex with the kinase Csk to downregulate the activity of src kinases Lck and Fyn in human and mouse T cells. The importance of *PTPN22* in human immunobiology has become appreciated since the discovery that a non-synonymous mutation 1858T (R620W), identified in whole genome association studies, is associated with rheumatoid arthritis, systemic lupus erythematosus, type I diabetes and autoimmune thyroiditis, among other autoimmune syndromes. Functional analysis of the disease associated variant suggested initially that mutant R620WLyp failed to associate with Csk leading to loss of inhibitory effects of the Lyp/Csk complex. This variant would be predicted to augment T cell receptor (TCR) signalling, providing a plausible explanation for its association with autoimmunity. This region in Lyp is identical in sequence to PEP, apart from a single substitution, and mutating the corresponding residue in PEP, Arg619 to Ala, abolishes binding of PEP to Csk. Therefore, an R619W variant of mouse PEP is predicted to phenocopy the human R620W mutation.

Since these initial reports, studies have suggested that R620WLyp is in fact a gain of function variant, leading to increased phosphatase activity and attenuation of T cell activation. Peripheral blood T cells from *PTPN22* 1858T carriers were shown to make less IL-2 and IL-10, but comparable TNF $\alpha$  and IFN $\gamma$ , in response to TCR stimulation. Interestingly, the number of memory CD4<sup>+</sup> T cells was expanded, a finding also documented in PEP deficient mice, and possibly as a consequence of enhanced self-reactivity *in vivo*. Therefore, while impaired recruitment of the Lyp R620W appears to decrease T cell responsiveness, there exist paradoxical features of sustained T cell activation in human peripheral blood. The precise mechanisms whereby *PTPN22* variants promote autoimmunity are therefore far from clear. This project seeks to reconcile these experimental observations through the use of novel *in vivo* models for exploring the functional genomics of *PTPN22*. This project will provide broad training in *in vivo* models of inflammatory arthritis and will address, at the molecular and cellular level, fundamental questions relating to how perturbations of T cell activation promote autoimmune disease.