

Project title

**The impact of B cell depletion on abnormal regulatory T cell biology in patients with systemic lupus erythematosus.**

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Clinical supervisor: Professor David Isenberg

Our research group focusses on translational research in patients with autoimmune rheumatic disease. We have been studying regulatory (immune suppressing) T cells (Treg) in an effort to harness/manipulate these lymphocytes to treat patients more effectively. One approach we have been taking is to use novel biologic therapies as a tool to understand the aberrant immune responses found in patients with autoimmunity (1). We have so far focussed our efforts on patients with rheumatoid arthritis and demonstrated that Treg are defective in this disease. We have identified a potential molecular explanation for this defect (2), which could represent a novel therapeutic target. In addition, after anti-TNF therapy we have observed the induction of an “adaptive” Treg population, which suppresses via different mechanisms to the “natural” Treg found in healthy individuals (3).

Systemic lupus erythematosus (SLE) is an autoimmune rheumatic disease, which affects young women and is associated with significant morbidity and mortality. We have established that there are abnormalities in Treg number and function in patients with SLE. The aim of the PhD will be to investigate the relevance of these findings to disease pathogenesis. A special focus of the proposed experiments will be to study regulatory T cell number and function before and after B cell depletion. One of the most exciting recent developments in the treatment of SLE is the introduction of B cell depletion (rituximab) (4). However, its mechanism of action is poorly understood. **We hypothesise that the abnormal B cells present in patients with SLE are interfering with Treg function.** Our eventual goal is restore tolerance in patients with SLE through manipulation of regulatory T cells or the pathogenic B cells that modulate their function.

The experiments proposed will examine Treg function and how they are influenced not only by direct interaction with B cells through surface molecules (e.g CTLA-4), but also the cytokines they produce, such as IL-10 and TGF beta which are known to induce Treg. The function of other cytokines, which have been separately implicated in the pathogenesis of SLE and in modulating Treg function, will also be studied. The proposal will not only shed light on the mechanism of action of B cell depletion but also elucidate the interaction between B cells and Treg in the pathogenesis of SLE.

The PhD student will join a successful group of scientists and clinical investigators with an outstanding publication track record, working to understand pathogenesis and develop novel therapies for patients with autoimmune disease. The laboratory has expertise in a wide array of techniques focussed on cellular and molecular immunology.

References:

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3. Nadkarni, S., C. Mauri, and M.R. Ehrenstein. 2007. Anti-TNF- $\alpha$  therapy induces a distinct regulatory T cell population in patients with rheumatoid arthritis via TGF- $\beta$ . *J Exp Med* 204:33-39.
4. Leandro, M.J., J.C. Edwards, G. Cambridge, M.R. Ehrenstein, and D.A. Isenberg. 2002. An open study of B lymphocyte depletion in systemic lupus erythematosus. *Arthritis Rheum* 46:2673-2677.