Project Title: Novel strategies to promote immune regulation in autoimmune diabetes

Primary Supervisor: Prof Lucy Walker (moving to UCL in January 2013)
Secondary/Clinical Supervisor: Prof Hans Stauss

The UK is facing a huge increase in the number of people with diabetes: since 1996 the number of people diagnosed with diabetes has increased from 1.4 million to 2.9 million. The incidence of autoimmune or Type 1 Diabetes, in which the immune system attacks and destroys the insulin-producing cells in the pancreas, is increasing by around 3% per year. The Walker lab is trying to unravel what triggers the immune system to become dysregulated leading to the development of this condition.

The lab has developed a novel transgenic mouse model of diabetes in which the T cells responsible for causing pathology can be tracked and studied(1). By using adoptive transfer to selectively introduce pathogenic or regulatory T cell populations into recipient mice, we have a unique opportunity to ask defined questions about which genes are required in each of these populations for their full function. For example we have been able to show that regulatory T cells require the inhibitory protein CTLA-4 in order to effectively suppress diabetes *in vivo*(2, 3).

Our work to date has revealed that effective immune regulation relies not only on the presence of sufficient numbers of Treg, but also on having an environment that is permissive of their function. In this regard, we have found that the cytokine IL-21 can potently counteract Treg suppression(1). Recent exciting developments have revealed that IL-21 can work by altering the availability of IL-2, a key survival factor for Treg(4). The current project seeks to utilize this insight to develop new strategies to promote immune regulation in the setting of autoimmune diabetes. The candidate will use a variety of approaches to modulate the cytokine environment *in vivo* and will assess the effect on Treg homeostasis and suppressive function. Use of mouse models allows us to monitor immune regulation at several stages including analysis of T cell phenotype (multi-parameter flow cytometry), T cell tissue infiltration (confocal microscopy of pancreas sections) and diabetes onset (blood glucose measurement). The student will also have the opportunity to work with T cells isolated from patients with Type 1 Diabetes to verify our findings from the mouse model in the human setting. The combination of working with transgenic mouse models and clinical samples will allow the student to acquire broad-based expertise in translational immunology over the course of the PhD.

The candidate will join a successful and well-funded research group with a strong track record in immune regulation and autoimmune diabetes. The project will be hosted in the new Institute for Immunity, Infection & Transplantation at the Royal Free hospital campus of UCL Medical School. The second supervisor brings to the project key strengths in analysis and genetic modification of regulatory T cell populations and the work will also benefit from close interaction with Dr Miranda Rosenthal, the clinical lead for Type 1 Diabetes at the Royal Free hospital.

References

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