

Identifying T Cell Subset Phenotype and Function in Infections

The BioPark Hertfordshire, Welwyn Garden City, AL7 3AX: Thursday, March 10, 2011

"A revolution in the basic understanding of immunology occurred in the late 1980s with the discovery that CD4+ helper T cells were not a homogeneous population but could be divided into Th1 and Th2 subsets based on their cytokine profiles. 20 years later the field of T cell subset phenotype and function remains fast moving with the recently demonstrated existence of T regulatory and Th17 cells adding extra layers of complexity. The meeting will explore current ideas about the roles played by these varied T cells subsets in a variety of parasitic infections with presentations from leaders in the field" Meeting Chair: [Dr Kathryn Else](#), University of Manchester, UK

- 9:00 – 9:45 **Registration**
- 9:45 – 10:00 **Morning Session - Introduction by the Chair:** [Dr Kathryn Else](#), University of Manchester, UK
- 10:00 – 10:30 **Conditional mouse mutants as a tool to analyse Th1, Th2, Th17 and Treg subsets in parasite infection**
Professor Werner Mueller, Manchester, UK
- 10:30 – 11:00 **CD4⁺ T helper subsets in *Helicobacter hepaticus* infection: Th1, Th17, and Treg cells.**
Dr Marika Kullberg, University of York, UK
Inflammatory bowel disease, including Crohn's disease and ulcerative colitis, is a chronic inflammatory disorder of the gastrointestinal tract that is caused in part by an inappropriate immune response to intestinal microbiota. To help our understanding of the process by which bacteria induce inflammation in the gut, our lab is using an experimental model of colitis involving infection with *Helicobacter hepaticus*. This model allows us to examine the early events following bacterial challenge, and to analyze bacterium-specific CD4 T cell responses in disease-susceptible versus disease-resistant hosts. The *H. hepaticus* colitis model also provides a platform by which to elucidate the role of bacterium-specific CD4 T cells and their cytokines in the inflammatory process in the intestine.
- 11:00- 11:05 **Speakers photo**
- 11:05 – 11:30 **Mid-morning break**
- 11:30 – 12:00 **Regulatory T cell populations in human and murine malaria**
Professor Eleanor Riley, London School of Hygiene and Tropical Medicine, UK
Acute, highly virulent infections are accompanied by florid - typically type 1- immune responses which need to be tightly regulated to avoid induction of immune-mediated pathology. In both murine and human malaria infections, immune regulation is mediated by IL-10 and TGF-beta. These cytokines emanate from a variety of cell types including several populations of T lymphocytes. I will present data from murine and human studies on the roles of IL-10, TGF-beta, monocytes, classical (natural or endogenous) regulatory T cells and induced (effector) T cell populations in the regulation of parasite control and immunopathology.
- 12:00 – 12:30 **T helper phenotypes in infectious disease**
Professor Janette Bradley, Nottingham, UK
- 12:30 – 13:30 **Lunch and Poster Viewing**
- 13:30 – 14:30 **Immune responsiveness to schistosome infection**
Dr Adrian P. Mountford, The University of York, UK
- 1430 – 15:00 **Talk title to be confirmed**
Dr Joyce Yeoh, University of Aberdeen, UK
- 15:00 – 15:30 **Afternoon Tea/Coffee and Last Poster Viewing**
- 15:30- 16:00 **The development and interactions of regulatory and effector T cell responses during helminth infections**
Dr Matthew Taylor, University of Edinburgh, UK
Human helminth infections are synonymous with suppression of the host immunity resulting in parasite survival and the maintenance of chronic infections. Using a murine model of filariasis, *Litomosoides sigmodontis* infection

of susceptible (BALB/c) and resistant (C57BL/6) mice, we have shown that T cell regulation occurs at two levels; through a CD4⁺Foxp3⁺ regulatory T (Treg) cell response and the development of CD4⁺ effector T (Teff) cell hypo-responsiveness. The CD4⁺Foxp3⁺ Treg cell response is initiated by the infective L3 stage rapidly upon contact with the host, with increased CD4⁺Foxp3⁺CD25⁺ Treg cell proliferation *in vivo* resulting in a dominant expansion of CD4⁺Foxp3⁺CD25⁺ T cells. Depletion of CD25⁺ Treg cells prior to infection enhances parasite clearance indicating that the Treg cell response inhibits protective immunity and is mainly recruited from the pre-existing pool of natural CD4⁺Foxp3⁺ Treg cells. The second level of T cell regulation develops as infection establishes and the CD4⁺ Teff become intrinsically hypo-responsive to antigenic stimulation. This is associated with enhanced expression of CTLA-4, GITR, and PD-1. Once established, infection-induced suppression can be overcome by depleting CD25⁺ Tregs, but only if combined with restoring Teff cell responses by providing co-stimulation through GITR, or blocking co-inhibition through CTLA-4. As yet, it is not known what factors drive the initial bias towards a Treg response or the later Teff cell hypo-responsiveness. Our hypothesis is that the balance of co-stimulatory/ inhibitory signals during T cell priming and maintenance determines whether regulatory or effector responses prevail, with a lack of co-stimulation or a bias towards co-inhibition resulting in immune suppression. Initial work shows an important role for GITR in Th2 cell priming as blocking GITRL in resistant C57BL/6 mice ablates the Ag-specific Th2 response (IL-4, IL-13) and results in a Th1 phenotype (increased IFN- γ). Additionally, co-stimulating susceptible BALB/c mice with an agonistic anti-GITR mAb enhances their Ag-specific Th2 response. We are currently investigating whether a bias towards co-inhibition favors a regulatory environment using blocking antibodies against PD-1 and its ligands. To further delineate Th2 responses following infection and treatments, as well as interactions between Treg and Teff cells, we are using BALB/c 4get IL-4gfp mice to track and quantify Th2 cells. Overall we believe that the initial T cell priming to filarial helminths is critical in determining whether the host will succumb to or resist parasite immunomodulation. Co-stimulatory/inhibitory signals play a role in the development of T cell responses against *L. sigmodontis* and therapeutic manipulation of these pathways could be used to enhance immune priming and restore protective immunity.

16:00 – 16:30 **Regulation of infection by gastrointestinal nematodes**
Professor Richard Grencis, University of Manchester, UK

16:30 - 17:00 **Chairman's summing up.**

This meeting was organised by Euroscicon (www.euroscicon.com), a team of dedicated professionals working for the continuous improvement of technical knowledge transfer to all scientists. Euroscicon believe that they can make a positive difference to the quality of science by providing cutting edge information on new technological advancements to the scientific community. This is provided via our exceptional services to individual scientists, research institutions and industry. The event was hosted by 'BioPark' (www.biopark.co.uk), a research and development centre in Welwyn Garden City providing specialist facilities and support for bioscience and health technology businesses to grow, and to develop new products and technologies



About the Chair

Kathryn Else obtained her BSc in Zoology in 1985 at the University of Nottingham and completed her PhD, also at the University of Nottingham, in 1989 focussing on aspects of immunity to intestinal nematode parasites. She continued to pursue her interest in parasite immunology at the University of Manchester, becoming a Wellcome Trust Senior Research Fellow in Basic Biomedical Science in 1995, a position she held for 12 years. She is now a Senior Lecturer at the University of Manchester. Her work has contributed substantially to our knowledge of T cell polarisation and includes the demonstration that the helper T cell response polarises towards either Th1 or Th2 during *Trichuris muris* infection with dramatic consequences for the host in terms of the outcome of infection.

About the Speakers

Professor Eleanor Riley, London School of Hygiene and Tropical Medicine, UK
Eleanor Riley graduated from Bristol University with degrees in Cellular Pathology and Veterinary Science. After an internship in Veterinary Pathology at Cornell University (USA) she studied for a PhD in immunology and parasitology in the Department of Veterinary Pathology at the University of Liverpool. She began working on the immunology of malaria in 1985, as a member of the senior scientific staff at the Medical Research Council Laboratories in The Gambia, West Africa. In 1990, Eleanor moved to the University of Edinburgh as a Wellcome Trust Senior Research Fellow. Eleanor moved to the London School of Hygiene and Tropical Medicine in October 1998 where she is Professor of Infectious Disease Immunology and Head of the Immunology Unit.

Dr Matthew Taylor graduated from the University of Edinburgh with a BSc (Hons) in Immunology. His PhD at the University of Manchester studying immune responses to intestinal nematodes introduced to him to the world of parasitology that has grabbed his attention ever since. His post-doctoral work at the University of Edinburgh continued this interest studying immune subversion by filarial parasites. At the end of 2006 Matthew received a MRC Career Development Award to establish his own group at the university of Edinburgh investigating T cell responses to helminth parasites.

Marika Kullberg obtained her BSc in Chemistry and Microbiology from Stockholm University, Sweden. She went on to do a PhD in Immunology at Stockholm University and at the National Institutes of Health (NIH, USA), focusing on immunoregulation during *Schistosoma mansoni* infection. After a post-doc year at Stockholm University, Marika returned to the NIH in 1997 for a post-doc at the National Institute of Allergy and Infectious Diseases where she spent 8 years as a Visiting Fellow and a Research Fellow. Here, she established a new model of bacterial-induced colitis involving infection with *Helicobacter hepaticus*, and characterized both the pathogenic and the disease-protective arms of the immune response to this bacterium. In 2005, Marika moved to the University of York where she is a Lecturer in Immunology at the Centre for Immunology and Infection and the Hull York Medical School.

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