

2nd Annual Regulatory Cells in Autoimmunity event: Analysing and moderating function

6th December 2012

The Penridge Suite, 470 Bowes Road, London N11 1NL

A balanced immune response is maintained by a network of regulatory cells including T cells, B cells and iNKT cells. How these cells respond to their environment in order to dampen down inflammation and what goes wrong in autoimmunity, will be the focus of this meeting. Novel insights into positive and negative feedback mechanisms that help balance the immune environment will be discussed. It is only by understanding how immune regulation is maintained in health and what goes wrong during autoimmunity that new targets for therapy can be identified.

We welcome abstract submission for this meeting: selected abstracts will be selected for short oral presentation.

This event has CPD accreditation and will have a discussion panel session.

Meeting Chairs: Dr Elizabeth Jury, UCL, London, Professor Robert Barker, University of Aberdeen

On registration you will be able to submit your questions to the panel that will be asked by the chair on the day of the event

9:00 – 9:45 Registration

9:45 – 10:00 **Introduction by the Chairs:**

10:00 – 10:30 **The induction of antigen-specific regulatory T cells for suppression of autoimmune disease**

Professor David C Wraith, Professor of Experimental Pathology, Department of Cellular and Molecular Medicine, University of Bristol

This talk will compare and contrast different ways of inducing antigen-specific regulatory T cells. Effective control of autoimmunity may involve induction of foxp3 expressing cells or the generation of negative feedback mechanisms involving interleukin 10. Repetitive administration of soluble peptide induces peripheral tolerance. This is characterised by anergic, IL-10 secreting CD4⁺ T-cells with regulatory function. In a model of inflammatory autoimmune disease, IL-10 Treg cells retain the capacity to co-produce interferon gamma and concomitantly express T-bet, demonstrating their Th1 origin. IL-10 Treg cells suppress dendritic cell maturation, prevent Th1 cell differentiation and thereby create a negative feedback loop for Th1 driven immune pathology. Similar negative feedback loops for Th2 and Th17 driven pathologies will be described. The use of peptides for therapy of multiple sclerosis has been tested in a phase I/IIa clinical trial. The results of the trial will be discussed.

10:30 – 11:00 **Talk to be confirmed**

Professor James Brewer, University of Glasgow, Scotland

11:00 – 11:30 **Speakers' photo then mid-morning break and trade show**

11:30 – 12:00 **The role of membrane lipids in the plasticity of T cell responses.**

Dr Elizabeth Jury, UCL, London

Membrane lipid microdomains (lipid rafts) play an important role in T cell function by forming areas of high lipid order that facilitate activation. However, their role in regulating T cell differentiation and function remains controversial. I will reveal that by applying a new approach involving microscopy and flow cytometry, membrane lipid order can be characterized in ex vivo primary human CD4⁺ T cells. Ex vivo CD4⁺ T cells sustain a gradient of plasma membrane lipid order that influences their function in terms of immune synapse formation, proliferation and cytokine production. Importantly, T cell function can be altered by pharmacologically manipulating membrane order. This could represent a new mechanism to control T cell functional plasticity, raising the possibility that therapeutic targeting of membrane lipid order could direct altered immune cell activation in pathology.

12:00 – 13:00 **Lunch and trade show**

13:00 – 14:00 **Question and Answer Session**

Delegates will be asked to submit questions to a panel of experts. Questions can be submitted before the event or on the day

14:00 – 14:30 **The role of soluble CTLA-4 in immune regulation**

Dr Frank Ward, University of Aberdeen, Scotland

It is generally accepted that the CTLA-4 receptor isoform is crucial in regulating effector T cell responses, while alternatively spliced secretable soluble CTLA-4 has rarely been considered in this context. Here I present evidence that sCTLA-4 is actively secreted by T cells during antigen driven immune responses and contributes to extrinsic regulation of these effector responses. To analyse sCTLA-4 function, we developed a monoclonal antibody that selectively binds only the soluble isoform of CTLA-4. Analysis of sCTLA-4 in mice and human effector responses has revealed that functional blockade of sCTLA-4 offers potential for therapy in both cancer and autoimmune disease.

14:30 – 15:00 Afternoon Tea/Coffee and trade show

15:00 – 15:30 **In depth characterization of autoreactive CD8 T cells responses in Type 1 Diabetes – twist of faith.**

Dr Ania Skowera, King's College London, UK

There is considerable evidence that the cytotoxic CD8 T cell response against β -cell peptides has the most direct role in pancreatic β -cell death in Type 1 diabetes. We have identified a highly distinctive HLA A*0201-associated peptide epitope derived from the preproinsulin (PPI) signal peptide 15-24 that exhibits glucose-dependent presentation on the surface of human β -cells in vitro. A CD8 T cell clone specific for PPI₁₅₋₂₄ has a TCR that binds with much lower affinity (>270 μ M) compared to typical virus responses (KD 0.1-10 μ M) hence it is challenging to study such cells in disease. We have made significant progress in all these aspects by utilizing high-end technology to reveal key characteristics of autoreactive T cell clones including a crystal structure specific of the tri-molecular complex, phenotypically characterized the cells from in peripheral blood, started to dissect their clonotypic repertoire and addressed the mechanism via which autoreactive CD8 T cell clones can kill islet cell targets. This work aims to provide novel, in depth insight into autoimmune processes and offers strategies for immune intervention and prevention of the disease.

15:30– 16:00 **Talk to be confirmed**

Dr Milica Vukmanovic-Stejic, UCL Medical School, UK

16:00 – 16:30 Chairman's summing up

Media partners



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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.

About the Chairs

Robert Barker holds a personal Chair in Immunology and leads the Immunology and Inflammation Research Programme at the University of Aberdeen. His research has for many years focused on the study of immune-mediated diseases, using red blood cells as model target antigens. The lessons learnt have now been extended to further understand the pathogenesis of a wide range of diseases in which the immune system plays an important role, including autoimmune haemolytic anaemia; haemolytic disease of the newborn; immune-mediated thrombocytopenia; Goodpasture's disease; bullous skin diseases; atopy and asthma; viral and tumour immune evasion. The aim is to be able to control these diseases by manipulating immune regulation, particularly as mediated by regulatory T lymphocytes, and a number of projects are now undergoing commercial development for human trials. Professor Barker is currently a Trustee of the British Society for Immunology, the Groups' Secretary of the British Society for Immunology, and a British Society for Immunology Autoimmunity Affinity Group Committee Member. He also serves as a member of the Research Committee of the Arthritis and Rheumatism Campaign.

Ania Skowera trained in Jagiellonian University in Krakow in Poland, initially obtaining her masters and then moved to London. Her PhD at Kings' College London was on immune activation in Gulf war-related illness. She then began to pursue an interest in autoimmune disease such as Type 1 Diabetes focusing in particular on autoreactive CD8 T cells. She has identified a highly distinctive HLA A*0201-associated peptide epitope derived from the preproinsulin (PPI) signal peptide 15-24. She has Then isolated a first

autoreactive PPI₁₅₋₂₄-specific CD8 T cells clone from a patient that exhibits glucose-dependent killing of human β -cells in vitro. This work was recognized by awarded with Juvenile Diabetes Research Foundation (JDRF) Research Scholar Award.

David Wraith trained as an immunologist: since 1982 he has worked in the field of T cell biology and the role of T lymphocytes in protection from infection and in autoimmunity. His laboratory in Bristol focuses on the mechanism of antigen-specific immune desensitization. They have designed peptides for treatment of multiple sclerosis and conducted clinical trials of their use. His laboratory is currently defining the differentiation pathway of antigen induced Treg cells, focusing on the role of specific genes including IL-10 and CTLA-4.

Recent publications:

- 1) Verhagen, J., Gabrysova, L., Minaee, S., Sabatos, C.A., Anderson, G., Sharpe, A.H. and Wraith, D.C. Enhanced selection of FoxP3⁺ T-regulatory cells protects CTLA-4 deficient mice from CNS autoimmune disease. *Proc. Natl. Acad. Sci. (USA)* (2009) 106: 3306-3311
- 2) Gabrysova, L., Nicolson, K.S., Streeter, H.B., Verhagen, J., Sabatos-Peyton, C.A., Morgan, D.J., and Wraith, D.C. Negative feedback control of the autoimmune response through antigen-induced differentiation of IL-10-secreting Th1 cells. *Journal of Experimental Medicine* (2009) 206: 1755-1767
- 3) Wraith, D.C., Pope, R., Butzkueven, H., Holder, H., Vanderplank, P., Lowrey, P., Day, M.J., Gundlach, A.L., Kilpatrick, T.J., Scolding, N. and Wynick, D. A role for galanin in human and experimental inflammatory demyelination. *Proc. Natl. Acad. Sci. (USA)* (2009) 106: 15466-15471
- 4) Gabrysova, L. and Wraith, D.C. Antigenic strength controls the generation of antigen-specific IL-10-secreting T regulatory cells. *European Journal of Immunology* (2010) 40: 1386-1395
- 5) Sabatos-Peyton, C., Verhagen, J. & Wraith, D.C. Antigen-specific immunotherapy of autoimmune and allergic diseases. *Current Opinion in Immunology* (2010) 22: 609-615

Elizabeth Jury, an Arthritis Research UK Career Development Fellow, has worked at the Centre for Rheumatology Research, UCL since 2000. In this time she has opened up new avenues of research into signaling abnormalities in T and B cells from patients with SLE and RA making significant contributions towards understanding the nature of these abnormalities and how they relate to disease pathogenesis. The main focus of her research is to understand the role of plasma membrane, cellular and serum lipids on immune cell activation with the long-term aim to identify new targets for development of novel therapeutics.

About the Speakers

Prior to an academic career **Dr Frank Ward** spent nine years at ICI Agrochemicals where he operated as part of team that researched and developed fungicide leads. Later, he completed a PhD and worked as a postdoctoral researcher at King's College London, investigating the molecular processes important for immunological tolerance in systemic lupus erythematosus. As a lecturer at the University of Aberdeen, he has focussed on the role that natural soluble CTLA-4 plays in these tolerogenic processes.

Keywords: T cell, co-stimulation, immune regulation, lipid rafts, diabetes, rheumatoid arthritis, NOD, MS, CD4, foxp3, IL-10, T-bet, Th1, Th2, Th17, CTLA-4, TCR, CD8, β -cell, diabetes, HLA, preproinsulin, PPI, islet cell

Registration Web Site: www.regonline.co.uk/autoimmune2012

NOTES ABOUT THIS EUROSCICON EVENT

For your convenience we would like to bring your attention to the following

- You will be issued with a FULL delegate list within 14 days of the event, which will include the email addresses of the delegates (we are sorry that there is this delay in emailing the list, but we need to make sure that it takes into account any late arrivals). You will not be included in this list if you have opted out and you can do this by logging into your registration details. This list will not be sold or ever give out to third parties. Only people attending or sponsoring the event have access to the list
- There may be an independent meeting report published within a few months of this event. If this is published we will send you an email to let you know the reference details
- Notepads and pens are available from the Euroscicon reception desk
- We cannot give out the slides from our speaker's presentations as they are deleted immediately after each event. If you require a particular set of slides please approach the speaker
- Please remember that EuroSciCon is a small independent company with no subsidies from society memberships or academic rates for venues. We try to be as reasonably priced as possible and our delegate rates are substantially lower than comparable commercial meeting organisations
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