

Cytokines in translational research: bench to bedside

The BioPark Hertfordshire, Welwyn Garden City, AL7 3AX: 8th July 2010

"This meeting will review the importance of efficient cytokine detection in translational medicine from the bench to bedside. From basic research to clinical trials the optimal way to assess cytokine levels will be discussed evaluating relatively low-tech methods such as ELISA to high throughput multiplex platform technologies. The best way to evaluate cytokines as mediators of pathology, as immunotherapeutics and as biomarkers will be addressed" Meeting Chair - Dr Stephen J Thompson, King's College London

This event has CPD accreditation and will have a [troubleshooting panel session](#).

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 Chair:** *Dr Stephen J Thompson*, King's College London
- 10:00 – 10:30 **BiP: an anti-inflammatory mediator which induces a TH2 cytokine profile**
Dr Valerie Corrigan, KCL School of Medicine at Guy's, King's and St Thomas' Hospitals, London, UK
Translational research, from bench to bedside, has many difficulties not least due to the differences that arise following the transfer from in vitro to in vivo systems across species. Our research with BiP has involved human *in vitro*, murine *in vivo* and a human/murine xenogeneic *ex vivo* models. Throughout our investigations we have shown a consistency in the pattern of cytokine production induced by BiP with sustained IL-10 production in conjunction with increased TH2 cytokines, IL-4 and IL-5, and downregulation of pro-inflammatory cytokines such as TNF alpha. This anti-inflammatory cytokine profile is at least partially responsible for the immunomodulatory characteristics of BiP.
- 10:30 – 11:00 **Modulation of Th17 differentiation and function**
Marc Veldhoen, Division of Molecular Immunology, MRC National Institute for Medical Research, Mill Hill, London
Th17 cells are a recent CD4 T cell subset important for the defense against fungal infections and certain extracellular bacteria. Excessive Th17 responses are thought responsible for the initiation of a number of autoimmune diseases. In addition, $\gamma\delta$ T cells are also capable of IL-17 secretion, and genotypically resemble Th17. The transcription factor aryl hydrocarbon receptor (AhR) is selectively expressed in Th17 cells and $\gamma\delta$ T cells. Its activation is important for optimal development of the Th17 cell subset and results in enhanced activation of both Th17 and IL-17 producing $\gamma\delta$ T cells. AhR activation in response to endogenous and exogenous ligands may constitute environmental stimuli that interact with genetic predisposition to certain autoimmune conditions.
- 11:00- 11:10 **Speakers photo**
- 11:10 – 11:30 **Mid-morning break and poster viewing**
- 11:30 – 12:00 **KeyNote Speaker**
From cyto-omics to identifying defective NK cell signaling in systemic onset Juvenile Idiopathic Arthritis
Professor Berent Prakken, University Medical Centre, Utrecht, The Netherlands
Cytokines are crucial effector mediators of the immune system. Though their action is not specific, their importance was shown by the success of blockade of cytokine (receptors) in arthritis and inflammatory bowel disease. In addition cytokines may be useful as prognostic or diagnostic biomarkers in human inflammatory diseases. As cytokines act in concert measurement of a single cytokine is of little value. The multiplex immuno assay allows the simultaneous measurement of multiple cytokines in human biological fluids. We showed how this "cyto-omics" approach has led to the identification of pathogenic mechanistic pathway in a human autoimmune disease, systemic onset Juvenile Idiopathic Arthritis. In this disease a defect in the IL-18 receptor phosphorylation leading to defective IL18-NK cell signaling is the cause of NK cell dysfunction in these patients.
- 12:00 – 12:30 **Talk title to be confirmed**
Mr. Chris Walker, Meso Scale Discovery, USA
- 12:30–13:30 **Lunch and Poster Viewing**
- 13:30 - 14: 30 **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

- 14:30 – 15:00 **Flow cytometry to analyse T cell subsets in tissue & Th17 cells**
Dr Alistair Noble, King's College London
 Direct ex vivo analysis of T cell subsets in inflamed peripheral tissues by intracellular cytokine staining can be hampered by high background staining and low percentages of cytokine-positive cells. We have analysed T cell cytokine phenotypes in allergic airway disease and obtained cytokine profiles of T cell subsets during the acute and chronic stages of inflammation. Despite low levels of secreted IL-17 in lavage fluid at the acute stage we demonstrated the predominance of the CD4 Th17 subset in inflamed lung tissue and in the airways. Collaboration between Th17 and Th2 cells in the lung may regulate the progression of asthmatic disease via remodelling of the airways.
- 15:00 – 15:30 **Cytokine secretion for the isolation of antigen specific T cells - from rare cell analysis to cellular therapeutics**
Dr John Campbell – Miltenyi Biotec Ltd, Surrey, UK
 Antigen-specific T cells secrete cytokines in response to stimulation with their cognate antigen. Using the cytokine capture system, we can harness this to examine and isolate antigen specific T cells even at very low frequencies from complex mixtures. The ultimate application of this is in the clinical-grade isolation of antigen-specific T cells for therapeutic use. Here I will discuss the applications of this technology in both the diagnostic and therapeutic settings.
- 15:30 – 16:00 **Afternoon Tea/Coffee**
- 16:00 – 16:30 **Cytokine-based strategies for diagnostics and therapeutics in autoimmune disease**
Professor Mark Peakman, Kings College, London
 Type 1 diabetes arises when the immune system becomes poorly regulated and destroys the beta cells in the pancreas, which make insulin, a hormone that controls blood glucose levels and is therefore vital to life. The immune attack is the result of a genetic predisposition, and is probably triggered by a common environmental insult. Our research focuses on the role of autoreactive T cells in this process and in recent years we have unravelled elements of the pathways to disease using cytokine-based approaches.
- 16:30 – 17:00 **T regulatory cells in autoimmune CNS inflammation - good or bad?**
Professor Steve Anderton, University of Edinburgh, Scotland
 Experimental autoimmune encephalomyelitis (EAE) remains the primary preclinical murine model for multiple sclerosis. Although EAE is well defined as a CD4+ T cell driven disease, remarkably, the precise factors (cytokines and otherwise) that determine pathogenicity and resolution of disease are poorly defined. This talk will describe the identification of Foxp3+ Treg within the inflamed CNS and their roles in the natural resolution of EAE. Therapeutic utility and stability of function (cytokine production) of Treg in this model will also be discussed. These will be set in the context of the translation to the clinic.
- 17:00 **Chairman's summing up.**

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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. 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:

Stephen Thompson received his B.Sc. in Cellular Pathology from the University of Bristol in 1984. He received his PhD in 1989 for studies characterising the role of House Dust Mite allergens in children with asthma and eczema. After these studies he began working on murine models of inflammatory arthritis, most notably pristane-induced arthritis, where he and his group were one of the first to characterise the immunopathology of this disease. Through the award of Arthritis Research Campaign post-doctoral fellowships (both in the UK and at the Southwestern Medical Center in Dallas, USA) he developed his interests in the role of stress proteins as inducers or targets of regulatory T cells and their potential use as anti-inflammatory immune modulators. He is currently based at Kings College London, Department of Rheumatology at Guys Hospital where he and his colleagues continue translational research to evaluate novel immunotherapeutic strategies for the treatment of rheumatoid arthritis

About the Speakers

Following a degree in Bacteriology from Edinburgh University Valerie Corrigall gained her PhD in Immunology from London University. Since then she has had a specific interest in T cells in inflammation biology and in particular their role in rheumatoid arthritis. Valerie is now senior lecturer in the Academic Department of Rheumatology on the Guy's Hospital Campus of KCL School of Medicine. Recently she was instrumental in isolating and identifying the stress protein BiP as a novel autoantibody in rheumatoid arthritis. Her subsequent work has generated data showing BiP has powerful anti-inflammatory and immunoregulatory properties. A clinical trial for BiP as a novel immunotherapy for rheumatoid arthritis is to be started later this year.

Berent Prakken is professor of paediatric immunology at the University Medical Centre Utrecht, the Netherlands. Since 2000 he is heading a research group that studies the regulation of inflammation in chronic inflammatory diseases. The main focus of his research is on the role of regulatory cells in the control of inflammation; the development of immune therapy for arthritis; and the role of heat shock proteins as targets for specific immune regulation (1-3). Prakken is scientific director of the Eureka Institute for Translational medicine (www.eurekainstitute.org) and co-director of He Center for Molecular and Cellular Interventions (CMCI).

Mark Peakman trained in medicine at University College Hospital and pursued postgraduate training in clinical immunology. After he received his PhD in immunology of type 1 diabetes he held a senior clinical research fellowship at University of Pittsburgh. He subsequently returned to the UK and now oversees a research group at King's College London in the Department of Immunobiology. The main focus of the research is the cause of the autoimmune disease, type 1 diabetes (T1D). T1D is the third commonest autoimmune disease in the UK after thyroid autoimmunity and rheumatoid arthritis. Through defining critical targets for the immune response in diabetes the group has been able to examine how the immune system recognizes beta cells, and thus unravel disease mechanisms. More recently, this knowledge has been used to conduct the first clinical trial in T1D of a novel approach, called peptide immunotherapy. Going forward, a better understanding of the role of the immune response in T1D will promote the development of novel therapeutic strategies.

Marc Veldhoen trained in Medical Biology at the Faculty of Medicine, Utrecht University, and continued his scientific career at the Division of Molecular Immunology at the National Institute for Medical Research in Mill Hill, London. He was the first to describe the de novo differentiation of the new Th17 as well as the Th9 subsets of T helper cells. He went on to show the importance of Th17 cells in the initiation of autoimmune responses and, via the identification of the Aryl Hydrocarbon Receptor in Th17, established a link between environmental toxins and auto-immunity.

Steve Anderton is Professor of Therapeutic Immunology at the University of Edinburgh, where he leads on the theme of Modulation and Resolution of Inflammation within the MRC Centre for Inflammation Research. He received his PhD from the University of Newcastle and held positions at Utrecht, Cambridge and Bristol before moving to Edinburgh in 2000. He held a MRC Senior Research Fellowship and a Research Councils UK Fellowship in Translational Medicine. Steve's main research focus is on the signals that lead to the activation of T cells that cause CNS autoimmune disease. Recent work has focused on the roles of B cells and of foxp3+ regulatory T cells in the natural resolution of disease, how these cells interact with pathogenic effector T cells, and how these interactions can be manipulated to therapeutic benefit.

John Campbell joined Miltenyi Biotec Germany in 2001 as project leader in T cell immune therapy, formerly lecturer in tumour Immunology at Glasgow University. Director of Clinical Immunology 2005-2006 USA. Now managing all aspects of clinical trials and applied immunology for MB UK. Long standing interest in flow cytometry, particularly rare cell analysis; use of MHC-Antigen complexes; measurement of cytokine production; analysis of patient samples; isolation of cells from complex mixtures

Alistair Noble started his career in cellular immunology research with a PhD at Guy's Hospital Medical School, investigating regulation of the allergic immune response. After postdoctoral studies in immune regulation at Harvard Medical School he returned to the UK to join King's College London in 1996. His research group investigates the regulation of T cell subsets and inflammatory processes in allergy and asthma.

No quantitative changes in the systemic immune response during pregnancy despite changes in cytokine production and composition of leucocytes.

Lisa E.E.L.O. Lashley*, Marie-Louise P. van der Hoorn*, Barbara J. van der Mast*,

Tamara Tilburgs*, Nadine van der Lee*, Carin Kleijburg*, Dave L. Roelen**, Frans H.J. Claas**, Sicco A. Scherjon*

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During pregnancy the immune system of the mother is modulated in order to allow tolerance to the fetus and at the same time retain protective properties against infectious organisms.

It is known that the clinical severity of some T-cell mediated autoimmune diseases such as rheumatoid arthritis decline during pregnancy while type 2 related, humoral autoimmune diseases flare-up. This suggests a decreased adaptive immune system and a compensating expanded innate immune system during pregnancy.

Analyses on the maternal immune response so far have focussed on complicated pregnancies like recurrent spontaneous abortions and pre-eclampsia. The differences in immune response in normal pregnancy and non-pregnant controls have insufficiently been elucidated.

In this study we analyzed peripheral blood from women at term pregnancy (mPBMC) for leukocyte composition, *in vitro* proliferative responses and cytokine production after non-specific and fetus-specific stimulation. mPBMC were stimulated with umbilical cord blood (UCB) of the own child, 3rd-party UCB, the non-specific mitogen PHA and the T cell stimulus anti-CD3 antibody. As a control group we studied non-pregnant age-matched healthy females (cPBMC). All tested allogeneic combinations were HLA-DR haplo-identical.

The response of mPBMC upon specific stimulation with fetal antigens was similar to that of cPBMC. Also no differences were found when comparing the maternal response upon stimulation to her own child with stimulation to a control child. Non-specific stimulation with PHA and anti-CD3 Ab did not reveal a difference in proliferation rate between maternal and control PBMC. However, mPBMC contained a higher percentage of CD14⁺ cells and activated T cells (CD25^{dim}), but a lower percentage uterine NK cells. mPBMC produced more IL-6, IL-10 and IL-17 compared to controls.

In conclusion, we found differences in lymphocyte composition and cytokine production between mPBMC and cPBMC. However, these differences did not result in quantitative changes in proliferative responses during pregnancy compared to non-pregnant controls. This confirms the concept that maternal immunomodulation upon pregnancy is a local process which takes primarily place at the fetal- maternal interface.

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