

# Inducing and Breaking Tolerogenic Antigen-Presenting Cell Function

The Royal College of Pathologists, Watson & Crick Room, 2 Carlton House Terrace, London

Thursday, 05 July 2012 09:00 - 17:00

Professional antigen-presenting cells (APC) such as dendritic cells (DC) and macrophages play a critical role in the initiation and maintenance of a T cell-mediated immune response. APC are essential for T cell priming, differentiation and activation in lymphoid tissue and at sites of inflammation. Understanding the molecular mechanisms via which APC function can be controlled may give novel insights into how T cell mediated immunity may be induced or blocked. This meeting will highlight current research aimed at inducing APC with tolerogenic function in order to treat inflammatory disease (e.g. rheumatoid arthritis) as well as work aimed at boosting the immunostimulatory function of APC in the context of cancer. The meeting will also highlight recent progress on the suppressive effects of CD4<sup>+</sup> regulatory T cells on APC function, and how these can be overcome.

This event has CPD accreditation and will have a [discussion 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

Meeting chairs: : *Dr Leonie Taams*, Senior Lecturer in Immunology, King's College London Centre for Molecular and Cellular Biology of Inflammation and *Dr Catharien Hilkens*, Reader in Immunotherapy, Newcastle University, UK

9:00 – 9:45 **Registration**

9:45 – 10:00 **Introduction by the Chairs:** *Dr Leonie Taams*, Senior Lecturer in Immunology, King's College London Centre for Molecular and Cellular Biology of Inflammation, *Dr Catharien Hilkens*, Reader in Immunotherapy, Newcastle University, UK

10:00 – 10:30 **Induction and administration of tolerogenic DC in RA**  
*Dr Catharien Hilkens*, Newcastle

10:30 – 11:00 **Selective ERK activation in dendritic cells for the treatment of arthritis**  
*Dr David Escors*, UCL, London

Rheumatoid arthritis is an autoimmune disease characterized by chronic joint inflammation and destruction. However, arthritogenic antigens are unknown and most therapeutic treatments rely on immunosuppressive drugs. We demonstrate that co-delivery of a specific ERK activator with a model antigen induces antigen-specific immune suppression by differentiation of regulatory dendritic cells (DCs) and antigen-specific regulatory T cells (Tregs). Differentiated Tregs strongly proliferate after antigen re-encounter in inflammatory conditions and exhibit antigen-dependent suppressive activities. The suppressive activity of ERK activation depended on secretion of high levels of TGF-beta from mouse and human DCs. In vivo administration of the ERK activator inhibited inflammatory arthritis.

11:00– 11:30 **Mid-morning break, Poster Viewing and Trade Show**

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11:30 – 12:00 **Boosting the immunostimulatory function of dendritic cells in an immunosuppressive tumour environment**  
*Dr Sandra Diebold*, King's College London, London, UK

12:00 – 12:30 **Oral presentations**

12:30 – 13:30 **Lunch, Poster Viewing and Trade Show**

*This is also a good time to fill out your feedback forms*

13:30 - 14:00 **Question and Answer Session and Speakers photo**

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 **Targeting regulatory T cell and dendritic cell interaction in vaccination:CCR4 antagonists as molecular adjuvants**

*Dr Jagadeesh Bayry*, France

CD4+CD25+ regulatory T cells (Tregs) play an indispensable role in maintaining immunological unresponsiveness to self-antigens and in suppressing excessive immune responses deleterious to the host. Since activation state of dendritic cells (DCs) at the time of encounter with antigens determines the outcome of the immune response, limiting the influence of Tregs on DCs at this juncture might lead to an enhanced immune response to poor immunogenic vaccine candidates. Although depletion of Tregs provides a proof of concept for this approach, it is however unlikely that the approach of Treg-depletion per se would be of practical use, since Treg-depletion has been associated with adverse consequences such as localized autoimmune disease. Conversely, we proposed that transient inhibition of Treg function/migration at the time of immunization might be ideal for enhancing immune response to vaccines. We have targeted the interaction between chemokines and their receptors to inhibit transiently the recruitment of Tregs at the site of immunization. Human Tregs express CCR4, a chemokine receptor absent on naive T cells. CCR4 is the receptor for CCL22 and CCL17, the chemotactic agents for Tregs *in vitro* and *in vivo*. Both the chemokines are produced by DC and are crucial in promoting contact between DC and CCR4+ T cells. By *in silico* technique, we identified small molecular weight antagonists to CCR4 that block the migration of CCR4+ Tregs and enhanced DC-mediated human CD4+ T cell proliferation in an *in vitro* immune response model and amplified cellular and humoral immune responses *in vivo* in experimental models when injected in combination with either Modified Vaccinia Ankara expressing Ag85A from Mycobacterium tuberculosis (MVA85A) or recombinant hepatitis B virus surface antigen (rHBsAg) vaccines. In addition, when combined with vaccines, CCR4 antagonists induced antigen-specific CD8+ T cells and tumor immunity against self-antigens. The significant adjuvant activity observed provides good evidence supporting our hypothesis that CCR4 is a viable target for rational adjuvant design.

14:30 -15:00 **Afternoon Tea/Coffee, Last Poster Viewing and Trade show**

15:00 – 15:30 **CD4+ T cell-monocyte cross-talk and immune regulation of rheumatoid arthritis**

*Leonie Taams*, Kings College London, London, UK

Rheumatoid arthritis (RA) is a painful and debilitating disease affecting 0.5-1% of the Western population. The disease is characterised by chronic inflammation of the synovial lining, leading to damage and destruction of the underlying joint tissue and bone. Immune cells such as CD14+ monocytes and CD4+ T cells are abundantly present at the site of inflammation and are involved in the chronic inflammatory process. Our lab has been interested for many years in the cross-talk between monocytes and CD4+ T cells and how these interactions influence the ensuing immune response. Our previous work has demonstrated that activated monocytes can potently promote a pro-inflammatory Th17 cell response, which may be particularly important in the context of RA (Evans PNAS 2007; Evans PNAS 2009, Gullick PLoSOne 2010). Recent data from our lab indicates that activated monocytes may also influence CD4+CD25+CD127<sup>low</sup> regulatory T cell (Treg) function. We therefore wish to obtain a better understanding of how monocyte activation can be controlled. Data will be discussed demonstrating the mechanisms via which both CD4+ effector and CD4+ regulatory T cells can control monocyte activation. In addition, we will discuss recent data on therapeutic manipulation of monocytes/monocyte-derived factors leading to regulation of the pro-inflammatory Th17 response

15:30 – 16:00 **Inducing and Breaking Tolerogenic Antigen-Presenting Cell Function**

*Dr Steve Cobbold*, University of Oxford, UK

A short treatment with mAbs that block T cell function is able to induce immunological tolerance in mouse models of transplantation and autoimmune disease. Data will be presented to show that this tolerance is induced and maintained by the de novo generation of antigen specific, foxp3+ Treg in the periphery which are required to act continuously to maintain a tolerogenic microenvironment for antigen presentation within the tolerated tissue itself. The molecular mechanisms that constitute this microenvironment, including cytokines, amino acid catabolism, adenosine generation, and infectious tolerance, will be discussed.

16:00 – 16:30 **Chairman's summing up**

Information about the chairs

The main focus of research in **Leonie Taams**, research group is to identify key cellular processes and molecular mechanisms involved in the regulation of inflammation in humans, with a specific interest in the interactions between CD4+ T cells and monocytes. The lab hopes to use this knowledge to identify novel pathways and/or approaches to target inflammation in humans. Research in the Taams laboratory is/has been funded by the Biotechnology and Biological Sciences Research Council (BBSRC), the Medical Research Council (MRC), Arthritis Research UK, the Innovative

Medicines Initiative (IMI), the Department of Health (DoH) via the National Institute for Health Research (NIHR) comprehensive Biomedical Research Centre (BRC) award to Guy's & St Thomas' NHS Foundation Trust (GSTFT) in partnership with King's College London (KCL) and King's College Hospital (KCH) NHS Foundation Trust, and industrial collaborative funding. In addition to her research activities, Leonie is research project module organiser for the MSc Immunology, Chair of the MSc Immunology Exam Board and Deputy Program Director of the MSc Immunology. She is a member of the Higher Education Academy, and serves on a number of (inter)national meeting committees.

**Catharien Hilkens** did her PhD research at the University of Amsterdam, where she worked on regulation of T cell immunity by dendritic cells. She then was awarded an EMBO fellowship to work on understanding how cytokines regulate T cell- and dendritic cell- function at the Imperial Cancer Research Fund (now Cancer Research UK) laboratories in London. In October 2003 she joined Newcastle University, where she runs a research group studying mechanisms underlying immune tolerance, and the development of dendritic cells as an immunotherapeutic tool.

#### About the Speakers

**David Escors** got his PhD from the Autonomous University of Madrid, Spain in molecular virology in 2002. There he got interested in the development of viral vectors for gene therapy. During his first post-doc in the National Centre for Biotechnology, Spain, he was involved in the development of coronavirus-derived gene vectors. In 2005 he joined UCL as a Marie Curie Fellow, and got interested in the manipulation of intracellular signalling pathways in dendritic cells to manipulate immune responses. In 2008 he obtained an Arthritis Research UK Fellowship to manipulate dendritic cells for the treatment of arthritis.

**Steve Cobbold** is currently the Reader in Cellular Immunology at the Sir William Dunn School of Pathology, Oxford working on the mechanisms of immune tolerance with particular focus on regulatory T cells. He studied Biochemistry at Oxford, and developed the first immunosuppressive mAbs during his PhD in Cambridge with Herman Waldmann. As part of the Therapeutic Immunology Group, he contributed to the development of CAMPATH, the first humanized therapeutic antibody. He was a scientific founder of TolerRx Inc., and co-founded BioAnaLab Ltd., which was successfully sold to Millipore in 2009. He has published more than 250 articles and patents.

**Jagadeesh Bayry** is a senior research scientist (Equivalent of Associate Professor) at Institut National de la Santé et de la Recherche Médicale (French National institute of Health and Medical Research) (INSERM). He received his Veterinary Medicine degree with a specialization of Virology and Immunology from the Indian Veterinary Research Institute. He obtained a PhD from the Université Pierre et Marie Curie, Paris in 2003. He later carried out postdoctoral research at the Edward Jenner Institute for Vaccine Research, University of Oxford, UK. In 2006, he was recruited as a scientist by INSERM. His research is aimed at understanding the mechanisms of immune tolerance, the mechanisms of action of intravenous immunoglobulin and the host-pathogen interaction. He has authored more than 130 papers in leading journals. He is an Academic Editor of PLoS ONE and Scientific Reports, editorial board member of several journals, expert member of AERES (French Agency for Evaluation of Research and Higher Education) and expert referee for Panel LS6 "Immunity and Infection" panel of European Research Council.

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**Keywords:** ERK, regulatory T cell, Dendritic cells; tolerance; autoimmunity; cancer; vaccine, Treg, arthritis, RA, Treg, dendritic cells, transplantation tolerance, foxp3, molecular mechanisms, Th17, CD4, RA, rheumatoid arthritis, CD127, CD25

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- 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
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