

Understanding dendritic cells and their ability to regulate immune responses

The BioPark Hertfordshire, Welwyn Garden City, AL7 3AX: 12th November 2010

This event has CPD accreditation

- 9:00 – 9:45 **Registration**
- 9:45 – 10:00 **Introduction by the Chair:** *Dr Steven Patterson*, Imperial College, London
- 10:00 – 10:40 **Wounding the immune system with its own blade: pathogenic consequences of HIV-mediated pDC activation**
Dr. Adriano Boasso, Imperial College, Dept. Immunology, Chelsea and Westminster Hospital, UK
Human immunodeficiency virus (HIV)-1 infection causes progressive impairment of the immune system in humans, characterized by depletion of CD4 T cells and loss of T cell function. Chronic activation of plasmacytoid dendritic cells (pDC) and subsequent production of type I interferon and indoleamine 2,3-dioxygenase may exert suppressive and cytotoxic effects on T cells. We manipulated HIV in order to reduce its ability to activate pDC and induce immunopathogenesis, while preserving its antigenic potential. More potent T cell memory responses were elicited against non pathogenic HIV, demonstrating that pDC activation may be deleterious rather than beneficial in this setting.
- 10:40 – 11:20 **Talk title to be confirmed**
Dr Siobhan Burns, Institute of Child Health, UK
- 11:20- 11:30 **Speakers photo**
- 11:30– 12:00 **Mid-morning break**
- 12:00 – 12:40 **Talk title to be confirmed**
Professor Stella Knight, Northwick Park and St. Mark's Campus, Imperial College, London, UK
- 12:40 – 13:20 **Human intestinal dendritic cells – the carrot and the shtick.**
Dr Andrew Stagg, Barts and The London School of Medicine and Dentistry, UK airways.
Intestinal dendritic cells (DC) help limit immune recognition of commensal bacteria whilst facilitating the development of appropriate effector responses to pathogens. In the steady-state situation, tissue-specific production of retinoic acid (RA) by subsets of DC and other myeloid antigen presenting cells, links the imprinting of gut tropism on T cells with the generation of regulatory function thereby constraining effector function. We are investigating conditions under which RA availability is regulated to 'uncouple' tissue tropism from regulatory T cell generation leading to the dominant migration of effector populations to the gut mucosa. Such pathways may be desirable during infections to enable effective responses to pathogens to be generated but, unregulated, may contribute to the chronic inflammation of inflammatory bowel disease (IBD).
- 13:20–14:00 **Lunch**
- 14:00 – 14:40 **Talk title to be confirmed**
Professor Giovanna Lombardi - King's College School of Medicine, UK
- 14:40 – 14:55 **Activated Tcell regulates immune response through icos induced icosl down regulation on human dendritic cell**
Amira Fayad, Imperial College London, London, UK
- 14:55 – 15:45 **Human myeloid dendritic cells, different kinds, different properties**
Dr Steven Patterson, Imperial College, London
A number of distinct types of human myeloid dendritic cells (DC) have been identified. These include monocyte derived DC, Langerhans cells, dermal dendritic cells and blood myeloid (BDCA-1) dendritic cells. Much of our present knowledge of human DC biology has been gained from studies of monocyte derived DC and although this has been a highly valuable model it may not reflect the precise biological properties of different DC populations.

Knowledge of the biology of these different DC types is important in the development of vaccines which may target a particular DC population. Aspects of the biology of different types of DC will be presented.

15:45-16:00 **Chairman's summing up.**

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About the Chair:

Steven Patterson was a scientist with the Medical Research Council for 30 years and for most of that time had an interest in viruses and the immune system. In the mid 1980s he investigated interactions between HIV and dendritic cells (DC) and with collaborators at the Clinical Research Centre at Northwick Park showed these cells are targets for HIV infection which are rendered dysfunctional in HIV infection. He has been in the Department of Immunology, Chelsea and Westminster campus of Imperial College since 1999 and has continued investigations into the interactions between HIV and plasmacytoid and myeloid DC. More recently his group has focussed on the biology of DC relevant to HIV vaccines and is principal investigator of a Gates funded consortium developing a CD8 T cell HIV vaccine.

About the Speakers

Stella Knight began studies on "veiled" or "dendritic" cells with Dr. Balfour in 1979. Early observations of the traffic of veiled and dendritic cells (DC) via the afferent lymph formed the backdrop to her first contributions. Localisation of afferent lymph cells in lymph nodes and carriage of contact sensitisers into lymph nodes by veiled cells was described. Stella Knight's original work demonstrated a dual role for DC. She showed not only the stimulatory effects of DC for primary responses to different antigens in syngeneic T-cells but also the capacity of these cells under different environmental conditions to prevent T-cell stimulation. Thus her work showed directly that DC stimulate primary immune responses to contact sensitisers, viruses and bacteria. She showed that DC initiate unwanted immune responses in inflammatory or autoimmune diseases or can prevent immune responses in immunodeficiency diseases such as AIDS. Finally, she identified DC as a target for therapy, providing the first observations of tumour therapy using dendritic cells. Stella Knight is continuing to lead the field in identifying mechanisms by which DC perform the dual roles of either initiating or blocking the development of immunity. Over the last 10 years she has established her Immunopathology laboratory of the Antigen Presentation Research Group as a major research facility for St. Mark's Hospital and Institute of Colorectal Diseases. She now works on human Mucosal Immunity and Nutrition and Immunity.

Giovanna Lombardi obtained her degrees (BSc and PhD) in Rome working on the regulation of human T cell responses to *Candida albicans*. In 1987 she moved to London. During the first few years she elucidated the molecular basis of allorecognition of MHC molecules. In more recent years she has focused on the understanding of the mechanisms involved in peripheral tolerance. Recently, she was involved in the discovery of CD4⁺CD25⁺ Tregs in the human. Two years ago she moved to KCL from Imperial College and is now studying the phenotype and function of Tregs and the use of alloantigen-specific Tregs for immunotherapy in transplantation. Recently she has also developed an interest in the differentiation, function and manipulation of human dendritic cells.

Adriano Boasso received his PhD from the University of Milan, Italy. He then completed five years of post-doctoral training at the Experimental Immunology Branch of the National Cancer Institute in Bethesda, Maryland, USA. In 2009 he joined Imperial College in the Department of Immunology at Chelsea and Westminster Hospital, first as recipient of a Wellcome Trust VIP award then taking his current post as holder of a Wellcome Trust Career Development Fellowship

Andy Stagg conducted his PhD studies on T cell responses to *Mycobacterium leprae* at the National Institute for Medical Research, London. His interest in dendritic cells developed during a post-doc in the laboratory of Prof. Stella Knight at the MRC Clinical Research Centre in Harrow where his research focused on the role of these cells in inflammatory joint disease. Dr Stagg spent time at the University of Texas Southwestern Medical Center in Dallas, where he explored the role of dendritic cells in a transgenic model of HLA-B27 spondyloarthritis. Upon his return to Imperial College London, Dr Stagg's interests developed into the area mucosal immunology, focusing initially on the genital tract and subsequently on the intestine. As part of these studies he discovered that DC are

able to control the homing properties of T cells by imprinting expression of specific homing receptors. In 2007 Dr Stagg moved to the Blizard Institute of Cell & Molecular Science, at Queen Mary University of London, where his Lab continues to explore the role DC in regulating immune responses in the human intestine.

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POSTERS

ACTIVATED T CELL REGULATES IMMUNE RESPONSE THROUGH ICOS INDUCED ICOSL DOWN REGULATION ON HUMAN DENDRITIC CELL

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Background: Immune homeostasis entails the continuous regulation of the expression of cell molecules to maintain an effective balance between immune stimulation and inhibition. The ICOS-ICOSL costimulatory pathway is important for effective T cell function, and dysregulation of this pathway enhances or induces autoimmune responses. ICOS is induced on naive T cells following TCR stimulation, and binds selectively to ICOSL. ICOSL is expressed at low levels on resting APCs, B cells, monocytes, and non-lymphoid cells, and can be induced upon cytokine-stimulation. Kinetic expression of ICOSL on DC surface is specifically regulated, however the exact regulatory mechanisms, and the significance of controlling the expression levels are unknown.

Aim of the study To analyse the kinetics of ICOSL expression by DC in different maturation stages, and identify the role of T cells in regulating ICOSL expression. Also to identify the possible molecular mechanisms that regulate ICOSL expression in human DCs.

Methods: DCs were generated from CD14⁺ monocytes using GM-CSF and IL-4, and matured using IFN- γ and TNF- α . Expression of ICOSL, CD80, C86 and MHC class II were analyzed by flow cytometry. The effect of blocking the ICOS:ICOSL pathway on T cell function was assessed in mixed lymphocytic reaction with and without anti-ICOSL blocking Ab. T cell proliferation was assessed by [³H]-thymidine incorporation and the cytokine proliferative changes was analysed by ELISA. ICOS induced ICOSL down regulation was assessed in human DCs and CHO cells expressing ICOSL following co-culture with activated T cells using protease inhibitor, and ICOSL expression was analysed by flow cytometry. ICOSL protein and mRNA expression was assessed by western blotting and RT-PCR respectively.

Results: Immature DCs have high ICOSL expression level that was down regulated on maturation. ICOSL surface expression was down regulated on DC and ICOSL CHO following co-culture with activated T cells or their supernatant. ICOSL down regulation was mediated through a dependent cell to cell contact pathway following binding to ICOS on T cells, and an independent cell to cell contact following incubation with supernatant of activated T cells. In the cell to cell contact dependent pathway, down regulation of ICOSL probably occurs through shedding of the extracellular domain after binding to ICOS receptor on activated T cells, as ICOSL down regulation was inhibited by a cocktail of protease inhibitors. There were no significant changes in mRNA levels encoding ICOSL, following incubation of DC with supernatants of activated T cells, suggesting that down regulation was at the post transcriptional level. Unexpectedly ICOSL mRNA was down regulated in ICOSL CHO following incubation with activated T cell at the early hours of incubation and returned back to nearly baseline level in 48 hours. Western blotting of cell lysates following co culture detected the full ICOSL band and a smaller band which may correspond to the remaining extracellular domain after ICOSL cleavage.

Conclusion: ICOSL down regulation is a negative feedback loop that regulates the immune response, as T cells are activated, they up-regulate ICOS receptor that binds to ICOSL on APC. This is followed by down regulation of ICOSL expression causing modulation of the immune response. The kinetic changes of ICOSL expression by DC are related to the maturation state of the DC, which reflect

the correlation between the level of ICOSL expression and the stage of immune response. It was shown that ICOS induced ICOSL down regulation could be a novel regulatory mechanism in human DC.