

# Understanding dendritic cells and their ability to regulate immune responses

The BioPark Hertfordshire, Welwyn Garden City , AL7 3AX

16 November 2007

- 09:00 – 09:45 **Registration - Tea/Coffee**
- 09:45 – 10:00 **Introduction by the Chair:** *Dr Catherine Derry*, Science Communicator
- 10:00 – 10:30 **Human mucosal immunology: dendritic cells, adipose tissue and immunoregulation**  
*Professor Stella Knight*, Imperial College, London, UK  
Lymph nodes in mammals are embedded within discrete pads of adipose tissue. This perinodal adipose tissue (PAT) has site-specific properties distinguishing it from adipose tissue at other locations; it is high in polyunsaturated fatty acids, is sensitive to effects of cytokines on immune sensitization and contains large numbers of dendritic antigen presenting cells. These properties of mesenteric PAT are altered in Crohn's disease. The specialised properties of PAT mean that this tissue may provision immune activation within lymph nodes and also provide key cellular, fatty acid and adipokine immunoregulatory materials that have an impact both on local immunity and adiposity.
- 10:30 – 11:00 **Immune regulatory properties of mucosal CD103+ dendritic cells**  
*Dr Janine Coombes*, Sir William Dunn School of Pathology, University of Oxford South Parks Road, Oxford
- 11:00 – 11:10 **Group photo**
- 11:10 – 11:30 **Morning Tea/Coffee and Poster Viewing**
- 11:30 – 12:00 **Negative vaccination with Dendritic Cell subsets**  
*Dr Giovanna Lombardi*, King's College School of Medicine, UK  
A different subset of DCs, plasmacytoid dendritic cells (pDCs) are emerging as playing a critical role in autoimmunity and tolerance, alongside their more classically recognised role in the innate immune response and anti-viral immunity. Recent research has identified that pDCs are responsible for the induction of transplant tolerance in a murine heart transplantation model and that the removal of pDCs prior to transplantation can significantly abrogate the acceptance of the transplanted tissue. We are investigating their potential as alternative "tolerogenic" DCs and have data showing that they are inefficient in activating T cells both in vitro and in vivo. We are currently comparing the tolerogenic capacity of pDCs to mDCs as an adoptive cell transfer therapy in a skin allograft model and have some evidence of their potential to prolong graft survival. This work is being extended to assessing their ability to prevent the induction of indirect-specific allo-responses in both heart and skin transplant models.
- 12:00 – 12:30 **Dendritic cells, HIV and vaccines**  
*Dr Steve Patterson*, Imperial College School of Medicine, London, UK  
In HIV infection there is a progressive loss and dysfunction of blood myeloid and plasmacytoid dendritic cells (DC). The BDCA-1 population of blood myeloid DC is considered to be the precursor of immature tissue myeloid DC that capture invading pathogens and subsequently stimulate pathogen-specific CD4 and CD8 T cell responses. In healthy individuals we observed that freshly isolated blood myeloid DC differentiate into two distinct cell populations in culture. The major population is phenotypically similar to immature monocyte-derived DC and express DC-SIGN, CD1a and CD11b. A smaller population representing 20-30% of the cells is mature, expressing high levels of MHC class II and co-stimulatory molecules and is negative for DC-SIGN, CD1a and CD11b. Both populations stimulate allogeneic T cell proliferation. In HIV infected patients differentiation into these two populations is severely impaired and this may partly explain why these cells are dysfunctional. Monocyte-derived DC (mdDC) have been used as therapeutic vaccine vehicles to stimulate HIV responses. We have analysed these cells generated from healthy controls, HIV infected anti-retroviral-treated and untreated patients. Although similar yields of mdDC were derived from all groups, the mdDC generated from infected patients were impaired in their ability to stimulate T cells and produce cytokines. This may limit the use of these cells in immunotherapy. The skin is an attractive target for vaccines as it is rich in DC. There are two main populations of skin DC, the superficial Langerhans cells in the epidermis and the deeper dermal type DC. As toll receptor ligands are increasingly being considered as vaccine adjuvants we have analysed expression TLR receptors on CD34 derived Langerhans and dermal type DC. These two DC populations show differences in TLR profile and in TLR ligand-induced cytokine responses which may be relevant to vaccine development.
- 12:30 – 13:00 **Tour of the BioPark**

- 13:00 – 14:00 **Lunch and Poster Viewing**
- 14:00 – 14:30 **Particle nanoengineering for interstitial injections**  
Dr Moein Moghimi, University of Brighton, UK  
Interstitially injected vesicular and polymeric nanoparticles are drained into the initial lymphatic system through patent junctions in the lymphatic capillaries and are then conveyed to the regional lymph nodes via afferent lymph. Within the lymph nodes the drained nanoparticles are susceptible to extraction by macrophages of the medullary sinuses and paracortex. At the injection site nanoparticles may also interact with phagocytic and dendritic cells and act as adjuvants, and subsequently reach the lymph node via cellular migration. Such means of nanoparticle transportation from interstitial sites and retention in the regional lymph nodes has numerous medical applications to include lymphoscintigraphic tracing, lymph node mapping, antimicrobial and antigen delivery, and immune modulation. However, the kinetics of nanoparticle drainage through the ground substance of the interstitium into the initial lymphatic systems and subsequent interaction with macrophages and antigen-presenting cells are controlled by a complex array of physicochemical factors to include particle size, morphology, and surface characteristics (electric charge, hydrophilicity/hydrophobicity, and ligand expression and density). These nanoengineering aspects will be discussed with particular reference for design of advanced lymphatic nanomedicines and nanoplatforms as well as particulate adjuvants
- 14:30 – 15:00 **NOD2 signalling in human dendritic cells**  
Dr Alison Simmons, John Radcliffe Hospital, Oxford, UK  
NOD2 is an intracellular pattern recognition receptor (PRR) mutated in a significant number of Crohn's disease (CD) patients. NOD2 recognises Muramyl-dipeptide (MDP), an abundant component of commensal bacterial flora, and is expressed in key immune cells such as dendritic cells (DCs), that dictate the nature of our immune response. In normal individuals several PRRs act in concert to recognise different components of commensal bacteria, triggering a tolerogenic immune response characteristic of self-antigen recognition. In CD this recognition is imbalanced leading to an inappropriate inflammatory response. We have investigated the basis of this aberrant recognition using genomic and proteomic techniques. The large-scale gene expression profiles of NOD2 and Toll-like receptor-2 (TLR2) activated DCs were compared, and computational and biological methods used to unravel the transcriptional regulatory elements controlling NOD2 signalling. In addition a phosphoproteome analysis was undertaken that revealed components of the intracellular machinery required to transmit NOD2 signalling. Specific immune modulators were induced following NOD2 activation that likely control normal immune handling of gut microbes. How the situation changes following CD mutant NOD2 expression is being compared.
- 15:00 – 15:20 **Afternoon Tea/Coffee and Last Poster Viewing**
- 15:20 – 15:50 **Regulation of human dendritic cell functions by CD4<sup>+</sup>CD25<sup>+</sup> regulatory T cells**  
Dr Jagadeesh Bayry, Centre de Recherche des Cordeliers, France  
Interactions between dendritic cells (DC) and T cells are known to involve the delivery of signals in both directions. We show that culture of human DC with CD25<sup>high</sup> CD4<sup>+</sup> regulatory T cells (Tregs) produce DC with a mixed phenotype. By many criteria, Tregs inhibit DC maturation and function. However, DC exposed to Tregs also show some changes typically associated with DC maturation. Both soluble factors and cell-associated molecules are involved in Treg modulation of DC, with LAG-3 playing a predominant role in driving maturation-associated changes. The data show that Tregs induce the generation of semi-mature DC with the potential to migrate into lymphoid organs, suggesting a possible mechanism by which Tregs down-modulate immune responses.
- 15:50 – 16:20 **Regulation of dendritic cell migration by WASP**  
Dr Yolanda Calle, Kings College London, UK
- 16:20 - 16:50 **The split personality of Myeloid-Derived Suppressor Cells**  
Dr Sonia Quarantino, University of Southampton, UK
- 16:50 – 17:00 **Chairman's summing up & close**