

# Toll-like receptors – investigating innate immunity and infection

The BioPark Hertfordshire, Welwyn Garden City, AL7 3AX - 25 September 2007

- 09:00 – 09:45 **Registration - Tea/Coffee**
- 09:45 – 10:00 **Introduction by the Chair:** *Dr Martha Triantafilou/Dr Kathy Triantafilou, University of Sussex, UK*
- 10:00 – 10:30 **The taste of a fungus: recognition of *Candida* by the innate immune system**  
*Professor Neil Gow, University of Aberdeen, UK*  
The outer layer of the cell wall of *Candida albicans* is heavily enriched in glycosylated proteins that play critical roles in cell adherence, and act as major antigens and in the immunoregulation of the host. Analysis of glycosylation mutants demonstrates that the carbohydrate epitopes of mannoproteins play key roles in pathogenesis of *C. albicans* and point to the interactions between O-linked mannans and TLR4 as well as recognition of N-mannan by the mannose receptor and beta glucan by dectin-1. Recent advances in the analysis of the host-fungus PAMP-receptor recognition process will be presented.
- 10:30 – 11:00 **Molecular mechanism and crosstalk in the Toll-like receptor signalling pathways**  
*Dr Nicholas Gay, University of Cambridge, UK*  
TLRs are single pass transmembrane receptors and are activated by a variety of stimuli derived from microbes. The mechanism of signal transduction involves stimulus induced dimerization of two receptor chains. Dimerization appears to involve concerted protein conformational changes and cooperativity which generate a specific cytoplasmic protein scaffold that supports downstream signalling events. I will present recent data about the molecular nature of this signalling process and evidence for complex crosstalk with other signalling pathways such as those of PKC.
- 11:00 – 11:30 **Morning Tea/Coffee and Poster Viewing**
- 11:30 – 12:00 **Analysis of innate immune responses induced via TLR7 and TLR8 activation**  
*Dr Peter Morley, GlaxoSmithKline R&D, Stevenage, UK*  
Toll-like receptors expressed in dendritic cells play a critical role in sensing viral infections and triggering antiviral host responses. Following activation by viral RNA or synthetic immunomodulators, TLR7 has been shown to be responsible for the induction of type I interferons. Plasmacytoid (pDC) are the main type I interferon producing cells in human blood that specifically express TLR7. We isolated pDCs from human blood and analysed the activation pattern of IFN $\alpha$ -subtypes. To further assess the TLR7-induced activation profile of pDC we performed a microarray study to begin to understand the global activation pattern and pDC functions triggered by TLR7.
- 12:00 – 12:30 **Toll-like receptor-mediated viral recognition**  
*Dr Sandra Diebold, Kings College, London, UK*  
The innate immune system has evolved receptors that recognise molecular patterns of pathogens to sense infections. Since viruses make use of the cellular machinery of the host for replication, viral molecular patterns are not fundamentally different from those of the host. Instead of targeting molecular patterns that are unique for viruses, the innate immune system has evolved sensors for detection of viral replication in form of cytoplasmic and endosomal molecules that recognise viral nucleic acids. In specialised endosomal compartments Toll-like receptor 3 (TLR3), TLR7 and TLR9 detect the presence of viral genomic nucleic acids or replication intermediates.
- 12:30 – 13:00 **Group and speakers photo and then Tour of the BioPark**
- 13:00 – 14:00 **Lunch**
- 14:00 – 14:30 **Toll-like receptors in adaptive immunity**  
*Dr Nino Porakishvili, University of Westminster, UK*
- 14:30 – 15:00 **TLRs in non-biomedical research animals – the world beyond**  
*Prof Dirk Werling, Royal Veterinary College, UK*  
Opportunistic infections resulting from intensive husbandry of livestock have become one of the major problems in modern animal production. As bacterial resistance to antibiotics is expected to escalate, novel approaches to disease prevention will need to be established. One approach includes breeding for disease resistance by selecting the 'fittest' innate immune system. The innate immune system recognises pathogens by means of pattern recognition receptors, such as Toll-like receptors (TLRs). These interact with various microbial components and induce a specific innate immune response. Several polymorphisms in TLR genes have been described for bio-medical species that influence the abilities of affected TLRs to recognise pathogen-derived molecules - rendering individuals more or less susceptible to infection. The first nucleotide polymorphisms (SNPs) in ruminant TLRs were characterised in bovine TLRs, with many of them located in the actual ligand binding domains within the leucine-rich repeats. Our data suggest do not only suggest differences in the threshold level of bovine TLR activation, but also a heterogeneity in extracellular regions of TLR genes, which may be advantageous to promote a specific disease resistance, and represent a new approach to select disease resistance
- 15:00 – 15:30 **Afternoon Tea/Coffee**
- 15:30 – 16:00 **SARM as a Negative regulator of TRIF dependent Toll like receptor signalling**  
*Dr Michael Carty, Trinity College Dublin, Ireland*  
Toll-like receptors discriminate between different pathogen-associated molecules and activate signaling cascades that lead to immune responses. The specificity of Toll-like receptor signaling occurs by means of adaptor proteins containing Toll-interleukin 1 receptor (TIR) domains. Activating functions have been assigned to four TIR adaptors: MyD88, Mal, TRIF and TRAM. Here we characterize a fifth TIR adaptor, SARM, as a negative regulator of TRIF-dependent Toll-like receptor signaling. Expression of SARM blocked gene induction 'downstream' of TRIF but not of MyD88. SARM associated with TRIF, and 'knockdown' of endogenous SARM expression by interfering RNA led to enhanced TRIF-dependent cytokine and chemokine induction. Thus, the fifth mammalian TIR adaptor SARM is a negative regulator of Toll-like receptor signaling
- 16:00 – 16:30 **The DNA sugar backbone 2' deoxyribose determine Toll-like receptor 9 activation**  
*Dr Tobias Haas, Institut für Med. Mikrobiologie, Immunologie und Hygiene, Germany*  
Toll-like receptor 9 (TLR9) is believed to recognise CpG-motifs as pathogen derived foreign DNA signature. We show that the DNA sugar backbone 2' deoxyribose determines TLR9 activation and that CpG dependency characterises synthetic phosphorothioate modified DNA.
- 16:30 - 17:00 **Chairman's summing up & close.**