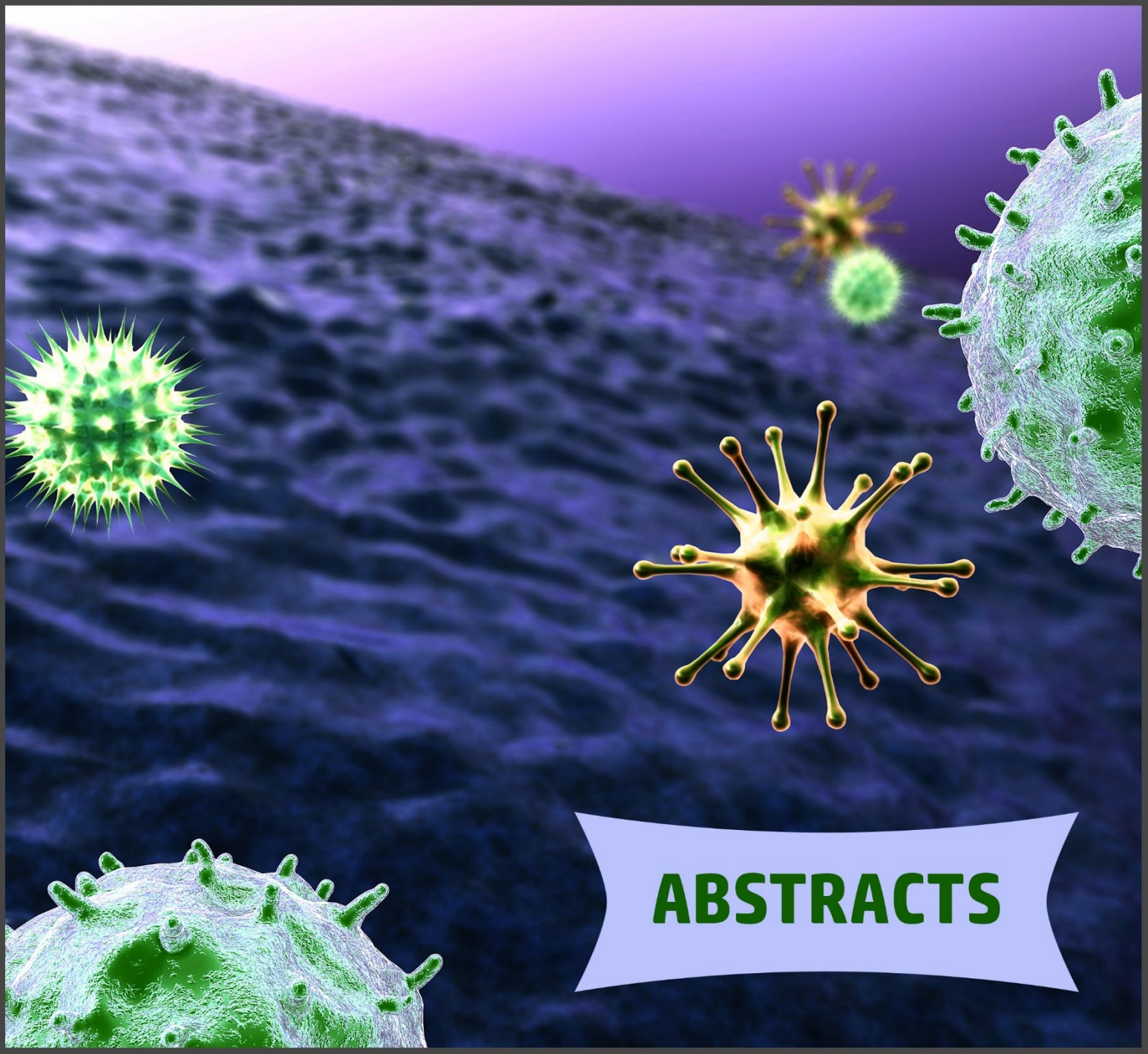
Innate Immunity

The First Line of Defence



ABSTRACTS

15th - 17th November 2016
Location: Online

EuroSciCon

This event will discuss the increasingly appreciated role of the innate immune system in initiating and directing immune responses.

This event has CPD accreditation

This abstract book will be finalised two weeks before the event

www.lifescienceevents.com/innate2016

#InnateESC

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Invited Speakers Abstracts

Innate immune responses to pathogenic mycobacteria

Dr. Antje Blumenthal, The University of Queensland Diamantina Institute, Woolloongabba, Australia

Toll-like receptors (TLRs) are arguably the most studied and best understood pattern recognition receptors. Their contribution to the host response in mycobacterial infection is underpinned by findings in humans and experimental model systems. Radioprotective 105 kDa (RP105; CD180) is an unconventional member of the TLR family that promotes macrophage inflammatory cytokine responses and host resistance in Mycobacterium tuberculosis infection. We discovered that RP105 engages PI3K signalling to direct cytokine trafficking and compartmentalisation of intracellular signalling in mycobacteria-infected macrophages. This identified novel innate immune signalling axis that directs host responses in mycobacterial infection and first insight into the distinct molecular mechanisms by which RP105 shapes macrophage functions.

Impact of microbiota on ocular immunity

Professor Mihaela Gadjeva, Brigham and Women's Hospital, Boston, United States

The existence of the ocular microbiota has been reported but functional analyses to evaluate its significance in regulating ocular immunity are currently lacking. We compared the relative contribution of eye and gut commensals in regulating the ocular susceptibility to Pseudomonas aeruginosa–induced keratitis. We find that in health, the presence of microbiota strengthened the ocular innate immune barrier by significantly increasing the concentrations of immune effectors in the tear film and the type of immune response to gram-negative pathogens. Cumulatively, these data underline a previously unappreciated role for microbiota in regulating susceptibility to ocular keratitis.

Peptidoglycan and You: Perfect Together?

Assistant Professor Catherine Leimkuhler Grimes, Department of Chemistry, University of Delaware, USA

All bacterial cells are surround by a polymer called peptidoglcyan. Small fragements of this polymer have long been known to activate an immune response in humans. In order to gain a deeper understanding of how this polymer is processed and sensed by the mammailian immune system, we have developed multiple probes: synthethic bacterial cell wall fragments, bioenginnered E. coli bacterial cell wall and chemoenzymatic peptidoglcyan builidng blocks. In addition, we have learned how to express and purify the innate immune receptors which sense these fragements, developed binding assays and cell based activation systmes. Here we will report on the developement of these probes and how they have been used to advance the field of innate immunology.

Influence of the tumor suppressor p53 on human innate immune responses

Dr. Daniel Menendez, National Institute of Environmental Health Sciences (NIEHS), Durham, United States

The commonly held view of the tumor suppressor p53 as a regulator of cell proliferation, apoptosis and senescence has expanded greatly in recent years to cover many biological processes as well as external and internal stress responses. Since the discovery over 30 years ago there has been an intertwining of p53 activities with immune-related processes, especially as relates to cancer. Here I will discuss examples of interactions between the genome guardian p53 and the immune system at transcriptional level, particularly in response to DNA metabolic and environmental stressors.

Molecular dynamics insights into NOD1-RIP2 interaction

Mr Jitendra Maharana, Orissa University of Agriculture and Technology, Bhubaneswar, Odisha, India

The nucleotide-binding and oligomerization domain (NOD)-containing protein 1 (NOD1) plays pivotal role in host-pathogen interface of innate immunity. Following to the recognition of iE-DAP, NOD1

self-oligomerizes in an ATP-dependent fashion and interacts with adaptor molecule RIP2 for the propagation of innate immune signalling. This interaction (NOD1-RIP2) transmits the downstream signals for the activation of NF-κB signalling pathway, has been arbitrated by respective CARDs. The so-called CARD-CARD interaction (mediated by NOD1 and RIP2 CARDs) is still remained contradictory due to inconsistent results. Henceforth, to understand the interaction mode, a combinational approach of docking and molecular dynamics simulation was employed. The results revealed that NOD1CARD uses multiple surfaces for RIP2-mediated CARD-CARD interaction.

A parasite-derived suppressor of IL-33 release

Dr. Henry McSorley, University of Edinburgh, Edinburgh, United Kingdom

The IL-33 pathway is strongly implicated in the development of allergic diseases such as asthma, while parasitic infection correlates with reduced rates of asthma. We previously showed the the products of Heligmosomoides polygyrus, a murine parasitic helminth, abrogated lung pathology in the Alternaria mouse model of allergic asthma, through suppression of IL-33 release. We recently identified HpARI (H. polygyrus Alarmin Release Inhibitor), a single recombinant protein which abrogates the release of IL-33, ILC2 and eosinophilc responses to Alternaria allergen. We are presently investigating the mechanism of action of HpARI and translating its effects to human cells.

Investigating the role of STIM1-mediated calcium signalling and ER-membrane contact sites in dendritic cell biology

Dr. Paula Nunes, University of Geneva, Geneva, Switzerland

Dendritic cells (DCs) can both neutralize pathogens through phagocytosis, as well as present the ingested antigents to T cells, thereby playing essential roles in both innate and adaptive immunity. The molecular mechanisms underlying cross-presentation, a specialized DC functions that leads to cytotoxic T cell activation, are still poorly understood but are known to involve ER proteins. STIM1 is an ER protein and master regulator of store-operated calcium entry. Our recent data show that STIM1 regulates phagosome maturation and antigen cross-presentation in DCs, and suggests that it may do so by bridging the ER to phagosomes through membrane contact sites.

The role of the human DEAD-box protein DDX3 in innate immunity

Dr Martina Schroeder, National University of Ireland Maynooth, Maynooth, Ireland

The human DDX3 protein is a DEAD-box RNA helicase with conventional functions in RNA remodelling and the regulation of gene expression. We have identified a role for DDX3 in innate immune signalling pathways leading to type I IFN induction and dissected the molecular mechanisms by which it regulates the activity of other pathway components.

Inflammasomes in non-immune cells: not just a cytokine story

Dr. Melanie Scott, University of Pittsburgh, Pittsburgh, United States

Inflammasomes and caspase-1 are activated in non-immune, parenchymal cells similarly to immune cells. However, the function of activated inflammasomes and caspase-1 in these cells may not be to produce mature/activated IL1b or IL-18. Our work shows that caspase-1 plays an important protective role in hepatocytes (an epithelial cell type) under conditions of redox stress by regulating autophagy and removal of damaged mitochondria. We also show that this response is initiated through activation of AIM2-inflammasome by endogenous release of DNA into the cytosol, and inflammasome activation is regulated by redox changes in an inflamamsome accessory molecule, HMGB1.

Species-specific regulation of innate immunity by hormonal vitamin D

Dr. John H. White, McGill University, Montreal, Canada

Vitamin D has emerged as an important regulator of innate immunity in humans. Vitamin D signaling lies upstream and downstream of pattern recognition receptor function, and the hormonal form of vitamin D regulates the expression of genes encoding several aspects of innate immune responses. Intriguingly, regulation of menay of these genes appears to be human/primate specific.

Structural Basis of Cell Surface Positioning and Activation of Macrophage-secreted Metalloproteases

Professor Steven R. Van Doren, University of Missouri, Columbia, United States

Matrix metalloproteinases-7 and -12 are secreted by macrophages and play antimicrobial roles. Though both MMPs are water-soluble and can diffuse in the extracellular matrix (ECM), we find both proteases to have dual modes of binding bilayers, using NMR and fluorescence. Both MMPs are quickly internalized via membranes, with MMP-12 consistently entering the nucleus. We find that proMMP-7 binding of glycosaminoglycans (GAGs from cell surfaces and ECM) activates this protease by assembling it, along with allostery. We located binding sites for GAG fragments in the catalytic and pro-domains of MMP-7. Part of the binding sites might be suitable for theranostic targeting.

The Inflammasome and Intestinal Homeostasis

Dr. Hasan Zaki, UT Southwestern Medical Center, Dallas, United States

The inflammasome, which induces pyroptotic cell death and activates proinflamamtory cytokines IL-1b and IL-18, is a multiprotein complex formed by an activated cytosolic pattern recognition receptor in association with caspase-1 and/or caspase-11 via the adapter ASC. Recent studies underscore critical function of inflammasomes in host defense against intestinal inflammation, infections and tumorigenesis. This presentation will discuss how the inflammasome contributes to the protection against intestinal disorders.

Oral Presentation Abstracts

Oral presentations will be added after the submission deadline

Day 1:

Day 2:

Day 3:

TARGETING THE CONVERGENCE OF INTRACELLULAR INNATE IMMUNE PATHWAYS AS AN AGNOSTIC THERAPY FOR INFECTIOUS DISEASE AND TISSUE DAMAGE

O. Donini, PhD and R. Straube, MD

Soligenix, Inc., 29 Emmons Drive, Suite C-10, Princeton, NJ, USA, 08540

Dusquetide, a novel, first in class Innate Defense Regulator (IDR), interacts with the p62 (sequestosome-1) protein at a key convergence point in the MyD88 and TRIF signalling pathways downstream of most innate immune receptors. Unlike other innate immune modulators, which target individual inputs or outputs of the innate immune system, IDRs alter the downstream signalling cascade and cellular recruitment to sites of tissue damage and/or infection after the innate immune system is activated. Dusquetide has been demonstrated to be safe in a 84-subject Phase

1study and has also demonstrated efficacy in a Phase 2 clinical study in head and neck cancer patients at risk for development of severe oral mucositis, a debilitating and life-threatening side effect of cancer therapy. Oral mucositis is both initiated and driven by the innate inflammatory response to chemotherapy and/or radiation induced damage. Treatment with dusquetide not only reduced the duration of severe oral mucositis, but also decreased the incidence of non-fungal (bacterial) infection. These results are consistent with preclinical studies in which dusquetide has demonstrated an ability to reduce the duration of both chemotherapy and radiation induced mucositis as well as prophylactically and therapeutically treat bacterial infection, whether caused by antibiotic sensitive or antibiotic resistant bacteria, as either a stand alone agent or in conjunction with antibiotics. Dusquetide demonstrates the power and broad-spectrum applicability of therapies targeting the innate immune system across many important clinical indications, including emerging and/or antibiotic resistant infectious disease as well as inflammatory indications (oral mucositis, collitis, etc.).

Poster Presentation Abstracts

Poster abstracts will be finalised weeks before the event

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