Univ. College Dublin 4 year PhD Programme

Molecular and Cellular Mechanisms underlying Inflammatory Processes

A PhD studentship is available at University College Dublin under the "**Molecular and Cellular Mechanisms underlying Inflammatory Processes**" (MolCellBiol) PhD programme, funded under the Programme for Research in Third-Level Institutions (PRTLI) and co-funded by the European Regional Development Fund. This studentship will join 6 other students who started on the MolCellBiol programme in Sept 2011.

Inflammation is a key process in the development of a wide range of human diseases. To address the need for innovative research into the study of inflammation, this programme contains the research strands of **Infection Biology, Vascular Biology, Neuroscience,** and **Protein Science**. UCD has a critical mass of outstanding researchers in these areas, providing students with a highly collaborative, multidisciplinary environment to train in. This particular studentship is available under the Infection Biology theme.

This 4 year PhD programme will start in January 2012 at the latest. The successful student will receive a stipend of €16,000 and funding to support their research, skills training, and travel. Only the costs of EU student fees are covered by the programme. All students enrolling in this programme will also undertake a Graduate Certificate in Innovation and Entrepreneurship through the UCD-TCD Innovation Academy, providing a unique transferable skill set.

Two projects are available, and the successful candidate will undertake one of these research projects, i.e. either:

1. Prof Steffen Backert and Dr Marguerite Clyne, "Flagellin-independent sensing of bacterial pathogens by TLRs: identification of novel bacterial factors and signal transduction mechanisms"
   Description: Dendritic cells and macrophages are in the first front line of host defences against invading microbial pathogens. When these cells sense infections, they produce cytokines that alert other innate immune cells and also abet adaptive immune responses. Toll-like receptors (TLRs) are the principal signalling molecules through which mammals sense microbes. Each TLR recognizes a restricted subset of microbial molecules and activates immune cells near to and far from the site of infection, mobilizing the comparatively vast immune resources of the host to confine and defeat an invasive organism before it has become widespread. One classical example is bacterial flagellin sensed by TLR5. Remarkably, TLR5 recognizes an evolutionarily conserved motif on flagellin which is required for flagellar filament assembly and motility in many bacterial species. The α– and ε–*Proteobacteria*, including the important human pathogens *Helicobacter pylori*, *Campylobacter jejuni* and *Bartonella bacilliformis*, require flagellar motility to efficiently infect mammalian host species. Interestingly, these bacteria express flagellin proteins that are not recognized by TLR5. However, we could recently show that infection with these bacteria leads to strong upregulation of TLR5 mRNA and protein expression, and TLR5 activation by a yet unknown factor. The aim of this project is to screen generated mutant libraries of *H. pylori* and *C. jejuni* to identify and characterise novel bacterial factor(s) which can stimulate signal transduction through TLR5. For this purpose, we will use human Hek293 cells stably transfected with human TLR5 as an infection model system, and luciferase reporter systems for the pro-inflammatory transcription factor NF-κB.

HEA Higher Education Authority An tÚdarás um Ard-Oideachas
An Roinn Fiontar, Trádála agus Nuálaíochta Department of Enterprise, Trade and Innovation
Ireland's EU Structural Funds Programmes 2007 - 2013
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2. Prof Ulla Knaus and Prof Jeremy Simpson, "Dynamics of mucosal immunity in pathogen recognition and inflammatory disease"
   Description: The mucosal epithelium acts as a primary innate defense system in the lung and intestine. This system maintains an intricate balance with its physiological surroundings while mounting an immune response when encountering pathogenic bacteria. Certain virulence factors and inflammatory tissue injury will lead to altered immune responses. Overall coordination of immune response pathways is provided by the cell cytoskeleton, an intricate network with an essential role in providing structural support and cellular mechanics. When encountering pathogens, the cytoskeleton acts as a signalling platform by spatially and temporally organizing the cellular response. Key molecules orchestrating cytoskeletal remodelling are often disabled or hyperactivated by virulence factors, injury or epithelial junction dissolution. A characteristic feature of the innate immunity is the production of reactive oxygen species (ROS) and changes in redox signaling. Mucosal NADPH oxidase activity, the predominant source for regulated ROS generation, is directly linked to innate immunity by yet unknown mechanisms that rely on the cytoskeletal and microtubule network. Recent data from our laboratory indicate highly specific recruitment of oxidases to the mucosal barrier with implications for chronic inflammatory diseases such as inflammatory bowel disease or ARDS. This project is based on the hypothesis that the cytoskeletal network restricts ROS generation by sequestering NADPH oxidases until an appropriate stimulus is sensed, and that the termination of this cellular response is defective when certain virulence factors are present or persistent inflammation occurs. We will employ high content microscopy combined with a focused siRNA screening approach to identify cytoskeleton-associated genes essential for NADPH oxidase recruitment to sites of host-pathogen interaction. Promising genes will be further evaluated by a multi-facetted approach, including pathogen exposure or sustained inflammation, to unravel the network required for oxidase function. The project will be expanded into analysis in knockout mouse models if appropriate.

Please contact the lead PIs of these two projects for more information. On the application form, please state which of this projects you would be most interested in.

To apply for these positions send a single PDF file to **molcellbiol@ucd.ie** with

- A completed application form (HYPERLINK to form)
- A 1-page personal statement indicating why you are interested in the programme
- A Curriculum Vitae
- TOEFL or IELTS report (if applicable)

Deadline for applications is 18:00 (local time) Friday 28th October 2011.

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