A new lab is seeking excellent and highly motivated MSc and PhD students

**Cell**

**RIPK1 Regulates RIPK3-MLKL-Driven Systemic Inflammation and Emergency Hematopoiesis**

James A. Richard, 1,3,4,5 Joanne A. O'Donnell, 1,6,7 Joseph M. Evans, 6,7 Rejana Ledain, 1,8 Ashleigh R. Poh, 1,9 Tethali Rogers, 1,10 James E. Vinoski, 1,11 Kate E. Lawlor, 1,12 Robert L. Nemo, 1,13 Holly Anderson, 1,14 Catherine Hall, 1,15 Shankara A. Srirao, 1,16 Toby J. Phares, 1,17 Helen E. Allan, 1,18 Louise H. Goggin, 1,19 Jason Corbin, 1,20 Sandra Mitrou, 1,21 Ludmila DiFagio, 1,22 Donald Naulty, 1,22 Matthias Enz, 1,23 Grant Denson, 1,24 Andrew W. Roberts, 1,25 Warren S. Alexander, 1,25 James M. Murphy, 1,25 Paul G. Evett, 1,25 Seth L. Masters, 1,26 David L. Viscic, 1,26 Ben A. Criner, 1,26,27 Motti Gerlic, 1,26,27,28 and John Silke 1,22,29,30

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If you are interested in studying the inflammatory and innate immune response, in particular the inflammasome and non-apoptotic cell death mechanisms during infection, please contact:

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**Immunity**

**NLRP1 Inflammasome Activation Induces Pyroptosis of Hematopoietic Progenitor Cells**

Seth L. Masters, 1,2,3 Motti Gerlic, 1,2,3,4,5 Donald McGett, 1,6 Simon Preston, 1,6 Marc Pollock, 1,6 Joanne A. O'Donnell, 1,6 Kate McArthur, 1,7 Tracey M. Baldwin, 1,8 Stephanie Cheader, 1,9 Cameron J. Nowell, 1,6 Lozzer H. Geng, 1,8 Kehya J. Henley, 1,8 Janelle C. Collins, 1,8 Daniel L. Kustner, 1,6 Le-definition, 1,6 Douglas J. Hilton, 1,6,7 Warren S. Alexander, 1,2,3,4,5 Benjamin T. Kul, 1,2,3,4 and Ben A. Criner 1,2,3,4

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Project title:

*Necroptosis and Pyroptosis in immune response, molecular mechanisms and physiological relevance.*

- **Project type**
  - MSc and/or PhD
- **Research theme**
  - Infectious diseases
  - Immune disorders
- **Scientific discipline**
  - Infectious disease
  - Inflammation
  - Immunology
  - Cell death
  - Molecular biology

**Supervisor**

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**Details of project**

Cell death is an essential cellular process during development, but also facilitates the removal of damaged or infected cells, and is required for the resolution of innate and adaptive immune responses. Apoptosis, programmed cell death, was first described as a form of death associated with membrane blebbing, where the cell breaks into membrane-wrapped vesicles (apoptotic bodies) and are phagocytosed.\(^1\) This process is hypothesized to be immunologically ‘silent’, as the contents of the cell are contained, preventing recognition of the contents by cells of the immune system.\(^2\) However, this process relies on the clearance of apoptotic bodies by macrophages to prevent the necrosis of cellular apoptotic bodies.\(^3,\,4\)

Recently, two new forms of cell death were identified: 1) Pyroptosis - a Caspase-1-dependent cell death,\(^5\) and; 2) Necroptosis, a RIPK3/MLKL-dependent caspase independent cell death.\(^6,\,7\) Pyroptosis can be beneficial to eliminate infected cells, as suggested in our recent publication,\(^8\) and necroptosis was suggested to eliminate infected cells when apoptosis is suppressed.\(^9\) However, the immunological and haematological consequences of activating these death pathways are not fully understood.\(^5,\,7\) This project will continue the studies on these two new cell death pathways, pyroptosis and necroptosis, during infection and inflammation. We will use different infection models, which will include viral, bacterial and parasites, together with genetic and biochemical tools we have in the laboratory.
Project references
Research interests

Our research focus is the understanding of the inflammatory response, with particular emphasis on novel NLRs (Nucleotide-binding domain and Leucine-rich repeat containing Receptors), and of apoptotic and non-apoptotic forms of cell death during infection. In particular we are interested in how pathogens (viruses and bacteria) are recognized by the innate immune system to facilitate these signals and how some pathogens evolve to target these mechanisms and prevent the host inflammatory response.

Recently, we discovered a physiological role for NLRP1 in driving a lethal, systemic inflammatory disease that is triggered by Caspase-1 activation and IL-1β production. Remarkably, active NLRP1 triggered a Caspase-1-dependent form of cell death, known as pyroptosis. This cell death affected hematopoietic stem and progenitor cells (HSPC), resulting in leukopenia at steady state, and cytopenia, bone marrow hypoplasia and immunosuppression, during periods of hematopoietic stress induced by chemotherapy or viral infection.1 Our recent research into how pathogens modulate complexes such as the NLRP1 and NLRP3 inflammasomes has defined two mechanisms by which viruses target inflammasomes: firstly, translation inhibition of the NLRP3 protein by the EBV microRNA, BART15;2 and secondly, direct inhibition of the NLRP1 inflammasome by the Vaccinia Virus protein, F1L.3 These findings reveal novel mechanisms for viruses to evade host innate immune responses. Furthermore, we recently changed the thinking of necroptosis, which was thought to be RIPK1-dependent. We found the opposite, namely, that RIPK1 acts as a negative regulator of necroptosis, and loss of RIPK1 results in a lethal multi-organ systemic inflammatory response.4

Selected publications


