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Infection and Immunity Program

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Monash Biomedicine Discovery Institute

Infection and Immunity Program

Head of Program:

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Immunity is of central importance to all organisms, as their survival is dependent upon the ability to fight infection and disease. To enable this, the immune system is divided into innate and adaptive arms that include an array of cell types with specialised functions. However, while immunity is critical to our survival, immune dysfunction is a major contributor to disease burden in Australia and globally.

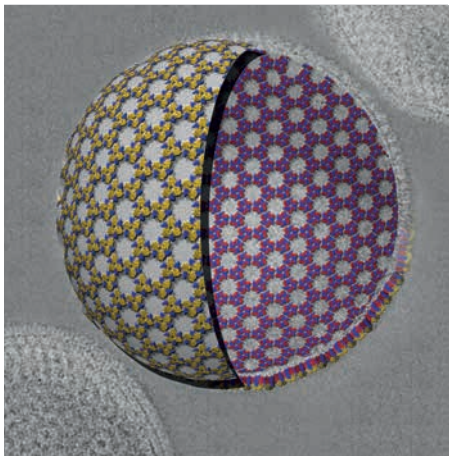
The flip side to immunity, infection, is concerned with how pathogens (viruses, bacteria, parasites and fungi) cause disease. These pathogens have developed, and continually evolve, strategies to overcome the defences of the immune system. Indeed, infection is the cause of half of all illness and death in the world.

The Infection and Immunity Program is geared to bringing a better understanding of how the immune system and microbes function. Led by Professor Jamie Rossjohn, it is the largest Monash BDI Program, bringing together more than 50 group leaders and their research teams. The research covers a breadth of expertise including cellular immunology, cellular microbiology, structural biology, microbial pathogenesis, proteomics and imaging that is supported by state of the art technology platforms.

Our research is funded by fellowships and grants from the NHMRC, ARC, Cancer Council Victoria, international funding agencies, the biotechnology industry and the recently established ARC Centre of Excellence for Advanced Molecular Imaging.

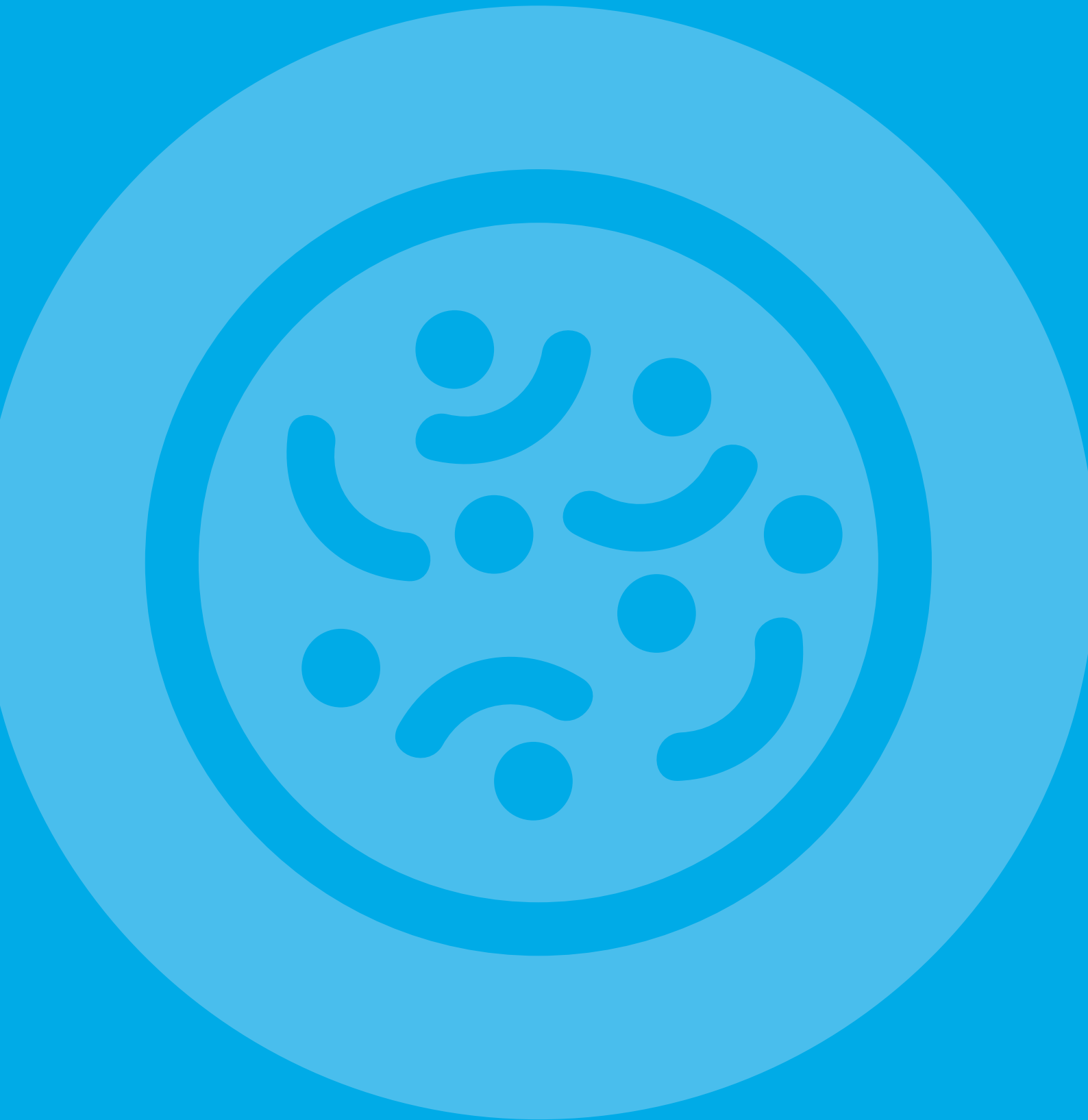
Our research focuses on the following priorities:

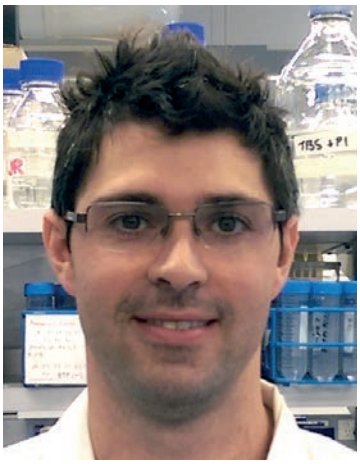
- **Innate and adaptive immunity**
- **Immune dysfunction**
- **Immunotherapy**
- **Macrophage and dendritic cell biology**
- **Molecular aspects of the host-pathogen synapse**
- **Hospital-acquired polymicrobial infections**



- **Molecular mechanisms of fungal infections**
- **Antibiotic resistance and superbugs**
- **Immunity, metabolism and the microbiome**
- **Influenza, other viral infections and disease**
- **Immunology and cancer**
- **Mechanisms of immune evasion**
- **Molecular cell biology of bacterial pathogens**
- **Chemical and structural biology of malaria**

Infection and Immunity Program Group Leaders





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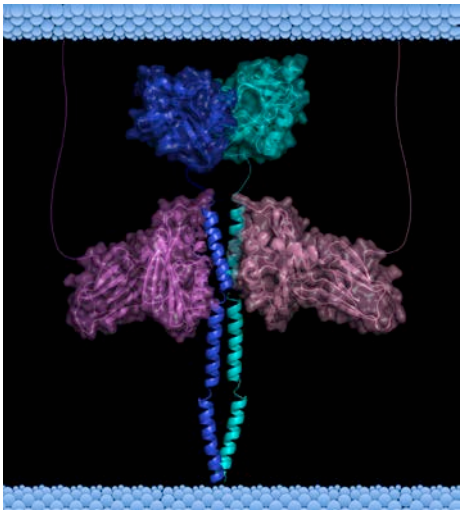
The specificity of the immune system is determined by cell surface receptors that recognise molecules of self- and/or viral origin. Understanding these interactions at the molecular level can provide profound insights into the basic processes underpinning immunity and how these may be modulated to treat infection or disease. My research is focused on two broad areas within this theme;

1. understanding the mechanistic basis of immune receptor triggering, with a particular focus on the T-cell receptor-CD3 signalling apparatus, and
2. investigating how natural killer cell receptors function in both healthy and virally infected organisms.

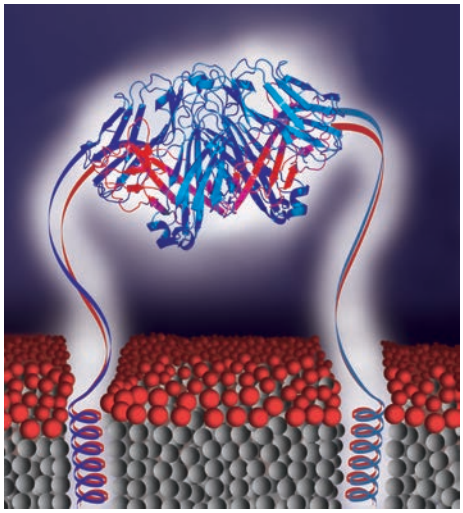
To achieve these aims we use a wide range of structural and biophysical techniques including X-ray crystallography, cryo-EM and small angle X-ray scattering.

Research Projects

1. **The structural basis for signalling via the T-cell receptor-CD3 complex**
2. **Natural Killer cell receptor structure and function**
3. **Subversion of innate immunity by viral immune-evasins**



Representation of the cytomegalovirus encoded m157 immunoevasin (pink) engaging the stalk of the activating Ly49H receptor (blue).



Structure of the pre-T-cell receptor super-dimer.

Selected significant publications:

1. Birnbaum M, **Berry R**, Hsiao Y, Chen Z, Shingu-Vazquez M, Xiaoling Y, Waghrey D, Fischer S, McCluskey J, Rossjohn J, Walz T, Garcia K. 2014. Molecular architecture of the αβ T cell receptor-CD3 complex. *PNAS, USA* 111, 17576-81
2. **Berry R**, Vivian J, Deuss F, Balaji G, Saunders P, Lin J, Littler D, Brooks A, Rossjohn, J. 2014. The structure of the cytomegalovirus encoded m04 glycoprotien, a Prototypical member of the m02 family of immunoevasins. *Journal of Biological Chemistry* 289, 23753-63
3. **Berry R**, Ng N, Saunders P, Vivian J, Lin J, Deuss F, Corbett A, Forbes C, Widjaja J, Sullivan L, McAlister A, Perugini M, Call M, Scalzo A, Degli-Esposti M, Coudert J, Beddoe T, Brooks A, Rossjohn J. 2013. Targeting of a natural killer cell receptor family by a viral immunoevasin. *Nature Immunology* 14: 699-705.
4. Vivian J, Duncan R, **Berry R**, O'Connor G, Reid H, Beddoe T, Gras S, Saunders P, Olshina M, Widjaja J, Harpur C, Lin J, Maloveste S, Price D, Lafont B, McVicar D, Clements C, Brooks A, Rossjohn J. 2011. Killer Immunoglobulin Receptor 3DL1-mediated recognition of Human Leukocyte Antigen B. *Nature* 479: 401-5.
5. Pang S, **Berry R**, Chen Z, Kjer-Nielsen, L, Perugini M, King G, Wang C, Chew S, La Gruta N, Williams N, Beddoe T, Tiganis T, Cowieson N, Godfrey D, Purcell T, Wilce M, McCluskey J, Rossjohn J. 2010. The structural basis for autonomous dimerization of the pre-T-cell antigen receptor. *Nature* 467: 844-848.

Dr Stephen Daley

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The immune system has 2 essential types of thymus-derived (T) cells: i. Conventional T cells (T-conv) promote inflammation to rid the body of pathogens and tumours, and ii. Regulatory T cells (T-reg) suppress inflammation.

Charles Darwin referred to competition between individuals and species as a "struggle for existence". T-conv and T-reg cells also compete against each other for resources. A feature of a safe immune system is that T-reg cells outcompete T-conv cells in the steady state. A key limiting resource is antigen, to which a T cell binds via its unique T-cell receptor (TCR). Self-proteins dominate the body's antigen landscape in the steady state. We aim to understand mechanisms that focus T-reg cells on key self-proteins. We hope that detailed insight into the T-reg/self-protein axis will improve diagnostic accuracy and therapeutic efficacy in autoimmune diseases and cancers.

Research Projects

1. **Defining the B-cell-dependent T-regulatory cell repertoire**

Selected significant publications:

1. Hu DY, Yap JY, Wirasinha RC, Howard DR, Goodnow CC, **Daley SR**. 2015. A timeline demarcating two waves of clonal deletion and Foxp3 up-regulation during thymocyte development. *Immunol Cell Biol.* Oct 29.

2. Altin JA, **Daley SR**, Howitt J, Rickards HJ, Batkin AK, Horikawa K, Prasad SJ, Nelms KA, Kumar S, Wu LC, Tan SS, Cook MC, Goodnow CC. 2014. Ndfip1 mediates peripheral tolerance to self and exogenous antigen by inducing cell cycle exit in responding CD4+ T cells. *Proc Natl Acad Sci USA*. 111, 2067-74.

3. **Daley SR**, Hu DY, Goodnow CC. 2013. Helios marks strongly autoreactive CD4+ T cells in two major waves of thymic deletion distinguished by induction of PD-1 or NF-κB. *J Exp Med.* 210, 269-85.

4. **Daley SR**, Coakley KM, Hu DY, Randall KL, Jenne CN, Limnander A, Myers DR, Polakos NK, Enders A, Roots C, Balakishnan B, Miosge LA, Sjollema G, Bertram EM, Field MA, Shao Y, Andrews TD, Whittle B, Barnes SW, Walker JR, Cyster JG, Goodnow CC, Roose JP. 2013. Rasgrp1 mutation increases naive T-cell CD44 expression and drives mTOR-dependent accumulation of Helios T cells and autoantibodies. *Elife*. Dec 12; 2: e01020.

5. Silva DG*, **Daley SR***, Hogan J, Lee SK, Teh CE, Hu DY, Lam KP, Goodnow CC, Vinuesa CG. 2011. Anti-islet autoantibodies trigger autoimmune diabetes in the presence of an increased frequency of islet-reactive CD4 T cells. *Diabetes*. 60, 2102-11.
*Equal first authors.

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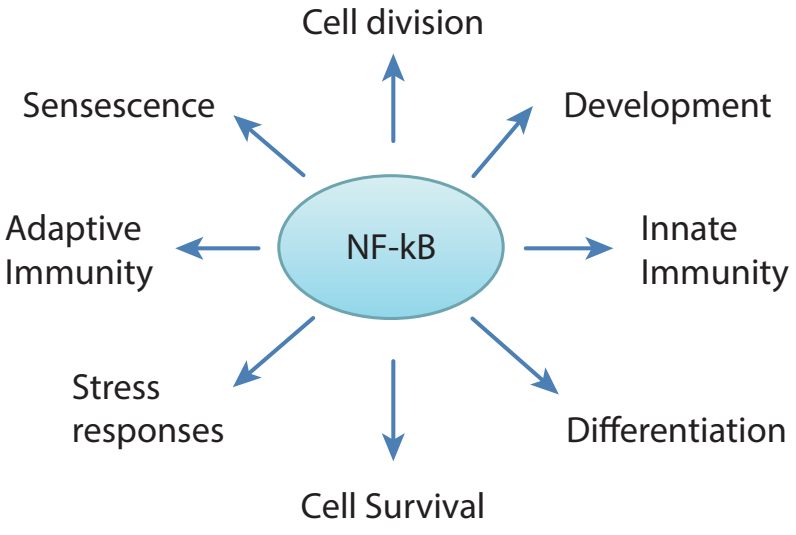
The Nuclear Factor of kappa B (NF-κB) signal transduction pathway plays a key role in the immune system and features prominently in disease-associated pathology. Our group focuses on the use of genetically modified mice to understand how NF-κB regulates normal development, differentiation and cellular functions particularly in the immune system, as well as its roles in autoimmune disease and cancer. The long-term goal of our research is to identify ways of manipulating NF-κB transcription factor activities for therapeutic purposes.

Research Projects

1. **NF-κB signaling, inflammation and aging**
2. **Roles of NF-κB signalling in gastric cancer and B cell malignancies**
3. **NF-κB functions in T cell development and differentiation**
4. **The epigenetics of NF-κB transcription factor function**



NF-kB regulation of cellular functions.

Selected significant publications:

1. **Gerondakis S**, Fulford TS, Messina NL, Grumont RJ. 2014. NF-κB control of T cell development. *Nat Immunol* 15(1): 15-25.
2. Gugasyan R, Horat E, Kinkel SA, Ross F, Grigoriadis G, Gray D, O'Keeffe M, Berzins SP, Belz GT, Grumont RJ, Banerjee A, Strasser A, Godfrey DI, Tsichlis PN, **Gerondakis S**. 2012. The NF- B1 transcription factor prevents the intrathymic development of CD8 T cells with memory properties. *EMBO J* 31(3): 692-706.
3. Isomura I, Palmer S, Grumont RJ, Bunting K, Hoyne G, Wilkinson N, Banerjee A, Proietto A, Gugasyan R, Wu L, McNally A, Steptoe RJ, Thomas R, Shannon MF, **Gerondakis S**. 2009. c-Rel is required for the development of thymic Foxp3+ CD4 regulatory T cells. *J Exp Med.* 206 (13): 3001-14.
4. Grumont R, Lock P,Mollinari M, Shannon FM, Moore A, **Gerondakis S**. 2004. The mitogen induced increase in T cell size involves PKC and NFAT activation of Rel/NF-kappaB-dependent c-myc expression. *Immunity* 21(1): 19-30.
5. Grumont RJ, Strasser A, **Gerondakis S**. 2002. B cell growth is controlled by phosphatidyl-inositol 3-kinase-dependent induction of Rel/NF-kappaB regulated c-myc transcription. *Mol Cell* 10(6): 1283-94.

Dr Stephanie Gras

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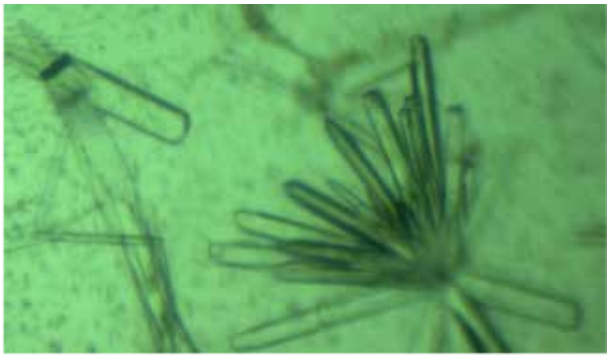
Viruses are part of day-to-day encounters that the immune system needs to deal with. How the immune system "sees", recognises and eliminates viral infection is not fully understood. Indeed, viruses are able to mutate in order to escape the immune system surveillance. If we were to develop better vaccine and drugs, or even vaccine against viruses like HIV, it is essential to understand the mechanism of viral recognition and viral escape prior to this.

Research Projects

1. **Structural investigation into T cell response to Influenza virus**
2. **Structural investigation into T cell response to HIV**



Selected significant publications:

1. Hassan C, Chabrol E, Jahn L, Kester MG, de Ru AH, Drijfhout JW, Rossjohn J, Falkenburg JH, Heemskerk MH, **Gras S**, van Veelen PA. 2015. Naturally processed non-canonical HLA-A*02:01 presented peptides. *Journal of Biological Chemistry* 290: 2593-2603.

2. Liu YC, Chen Z, Burrows SR, Purcell AW, McCluskey J, Rossjohn J, **Gras S**. 2012. The Energetic Basis Underpinning T-cell Receptor Recognition of a Super-bulged Peptide Bound to a Major Histocompatibility Complex Class I molecule. *Journal of Biological Chemistry* 287: 12267-12276.

3. **Gras S**, Chen Z, Miles JJ, Liu YC, Bell MJ, Sullivan LC, Kjer-Nielsen L, Brennan RM, Burrows JM, Neller MA, Purcell AW, Brooks AG, McCluskey J, Rossjohn J, Burrows SR. 2010. Allelic polymorphism in the T cell receptor and its impact on immune responses. *Journal of Experimental Medicine* 207(7): 1555-67.

4. **Gras S**, Kedzierski L, Valkenburg SA, Laurie K, Liu YC, Denholm JT, Richards MJ, Rimmelzwaan GF, Kelso A, Doherty PC, Turner SJ, Rossjohn J, Kedzierska K. 2010. Cross-reactive CD8+ T-cell immunity between the pandemic H1N1-2009 and H1N1-1918 influenza A viruses. PNAS 107(28): 12599-604.

5. **Gras S**, Burrows SR, Kjer-Nielsen L, Clements CS, Liu YC, Sullivan LC, Bell MJ, Brooks AG, Purcell AW, McCluskey J, Rossjohn J. 2009. The shaping of T cell receptor recognition by self-tolerance. *Immunity* 30(2): 193-203.

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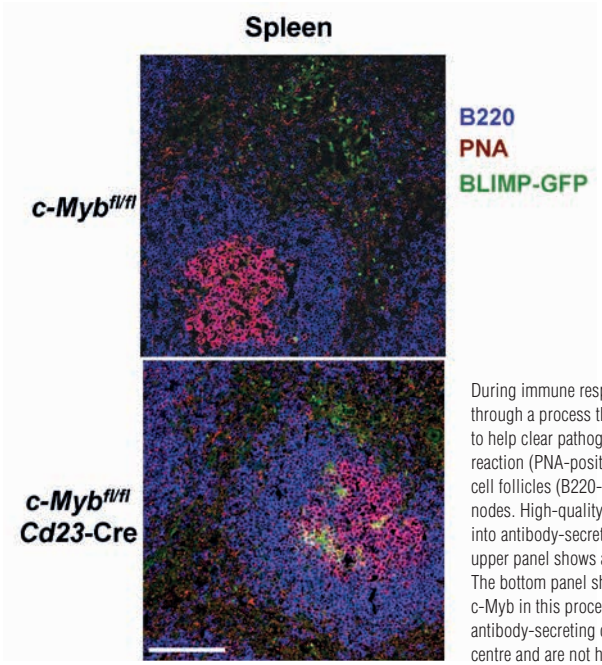
Human health and longevity is dependent on the ability of the immune system to clear the multitude of different foreign pathogens encountered over the life of the host. Our research studies the ability of the immune system to clear pathogens and form immunity through production of antibody and B cell memory. These projects will use both immunological assays and molecular biology techniques to study how the immune system forms long-lived immunity.

Research Projects

1. **Transcriptional regulation of antibody diversity**
2. **Epigenetic regulation of immune memory**
3. **Chronic infectious diseases**



During immune responses to pathogens, B cells go through a process that improves the quality of antibody to help clear pathogen. This is called the germinal centre reaction (PNA-positive cells in images) that occur in B cell follicles (B220-positive) of the spleen and lymph nodes. High-quality B cells are selected to differentiate into antibody-secreting cells (Blimp-GFP-positive). The upper panel shows a typical germinal centre response. The bottom panel shows the critical role of the gene c-Myb in this process. When c-Myb is not present, antibody-secreting cells form early within the germinal centre and are not high quality.

Selected significant publications:

1. **Good-Jacobson KL**, O'Donnell K, Belz GT, Nutt SL, Tarlinton DM. 2015. c-Myb is required for plasma cell migration to bone marrow after immunization or infection. *Journal of Experimental Medicine* 212(7): 1001-9.
2. **Good-Jacobson KL**, Chen Y, Voss AK, Smyth GK, Thomas T, Tarlinton D. 2014. Regulation of germinal center responses and B-cell memory by the chromatin modifier MOZ. *Proceedings of the National Academy of Sciences* 111(26): 9585-90.
3. Tarlinton D, **Good-Jacobson KL**. 2013. Diversity among memory B cells: origin, consequences, and utility. *Science* 341(6151): 1205-11.
4. **Good-Jacobson KL**, Szumilas CG. Chen L, Sharpe AH, Tomayko MM, Shlomchik MJ. 2010. PD-1 regulates germinal center B cell survival and the formation and affinity of long-lived plasma cells. *Nature Immunology* 11(6): 455-543.
5. **Good KL**, Tangye SG. 2007. Decreased expression of Krüppel-like factors in memory B cells induces the accelerated response typical of secondary antibody responses. *Proceedings of the National Academy of Sciences* 104: 13420-13425.

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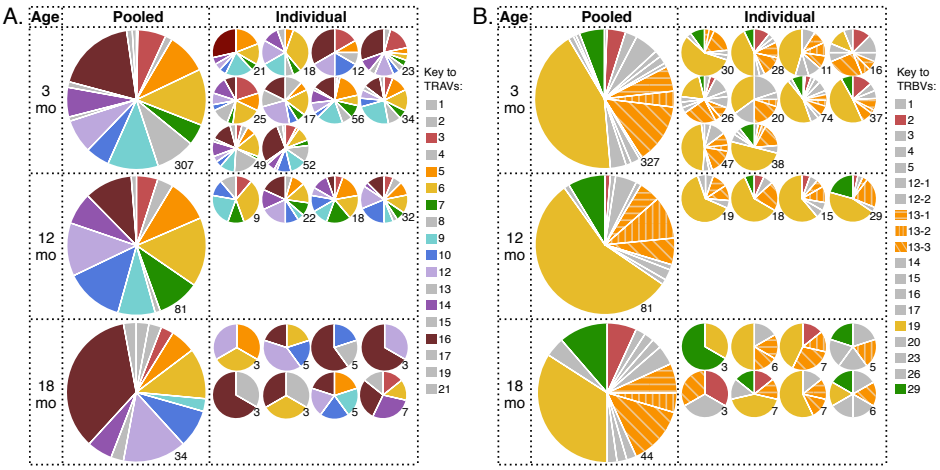
CD8+ T cell immunity is critical for the effective elimination of viruses. Our research utilizes advanced cellular and molecular approaches to interrogate the key determinants of effective CD8+ T cell responses to virus infection; namely those controlling CD8+ T cell recognition of virus, anti-viral CD8+ T cell magnitude, and T cell effector function. Understanding these determinants confer optimal immunity also allows us to perform targeted analyses of CD8+ T cell dysfunction, such as that observed with advanced age.

Research Projects

1. **Cellular and molecular analysis of ageing in CD8+ T cells**
2. **The influence of thymic selection on virus-specific CD8+ T cell populations**
3. **Unravelling antiviral CTL response determinants**



Selected significant publications:

1. Quinn KM, Zaloumis SG, Cukalac T, Kan WT, Sng XY, Mirams M, Watson KA, McCaw JM, Doherty PC, Thomas PG, Handel A, **La Gruta NL**. 2016. 1. Heightened self-reactivity associated with selective survival, but not expansion, of naïve virus-specific CD8+ T cells in aged mice. *Proc Natl Acad Sci* 113(5):1333-8.
2. Tscharke DC, Croft NP, Doherty PC, **La Gruta NL**. 2015. Sizing up the key determinants of the CD8 (+) T cell response. *Nat Rev Immunol* 15(11):705-16.
3. Cukalac T, Kan WT, Dash P, Guan J, Quinn KM, Gras S, Thomas PG, **La Gruta NL**. 2015. Paired TCRαβ analysis of virus-specific CD8(+) T cells exposes diversity in a previously defined 'narrow' repertoire. *Immunol Cell Biol* 93(9):804-14.
4. Cukalac T, Chadderton J, Zeng W, Cullen JG, Kan WT, Doherty PC, Jackson DC, Turner SJ, **La Gruta NL**. 2014. The influenza virus-specific CTL immunodominance hierarchy in mice is determined by the relative frequency of high-avidity T cells. *J Immunol* 192(9):4061-8.
5. **La Gruta NL**, Rothwell WT, Cukalac T, Swan NG, Valkenburg SA, Kedzierska K, Thomas PG, Doherty PC, Turner SJ. 2010. Primary CTL response magnitude in mice is determined by the extent of naive T cell recruitment and subsequent clonal expansion. *J Clin Invest* 120(6):1885-94.

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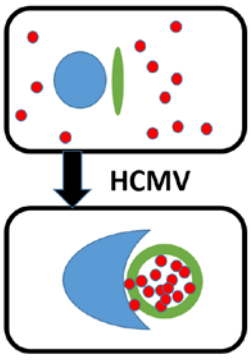
HCMV is a β-herpesvirus that infects over 60% of the adult population. HCMV is a significant cause of morbidity and mortality in immuno-compromised individuals such as organ transplant recipients. However, the largest burden of disease occurs from intrauterine HCMV transmission during pregnancy. Occurring in 1% of pregnancies worldwide, HCMV can cause permanent hearing loss, vision impairment, and mental retardation. There is no vaccine currently available, and discovery of new antivirals is urgently required. Importantly, the process by which infectious virus is packaged and released is not well understood, and this presents a novel molecular loci to develop antiviral therapeutics.

Research in our laboratory uses cutting-edge proteomics together with virology, molecular biology, microscopy, and bioinformatics to investigate the molecular mechanisms used by viruses to replicate and assemble infectious virions.

Research Projects

1. **Dissecting the viral assembly complex induced by Human Cytomegalovirus**
2. **Investigating hijacking of exosomes and secretion pathways for Human Cytomegalovirus egress**
3. **Exploring the biological functions of the novel lipoamidase $SIRT_4$**



HCMV induces profound host organelle remodelling to create the viral assembly complex (vAC).

Uninfected cells contain dispersed endosomes (red), and Golgi stacks (green) in close proximity to the nucleus (blue)

HCMV induces the vAC containing endosomes clustered within Golgi-derived vesicles, juxtaposed to the enlarged kidney bean shaped nucleus.

Selected significant publications:

1. Gopal SK, Greening DW, Zhu HJ, Simpson RJ, **Mathias RA**. 2016. Transformed MDCK cells secrete elevated MMP1 that generates LAMA5 fragments promoting endothelial cell angiogenesis. ***Sci Rep.*** doi: 10.1038/srep28321
2. Gopal SK, Greening DW, Hanssen EG, Zhu HJ, Simpson RJ, **Mathias RA**. 2016. Oncogenic epithelial cell-derived exosomes containing Rac1 and PAK2 induce angiogenesis in recipient endothelial cells. *Oncotarget*. In Press, doi: 10.18632/oncotarget.7573
3. **Mathias RA**, Greco TM, Oberstein A, Budayeva HG, Chakrabarti R, Rowland EA, Kang Y, Shenk T, Cristea IM. 2014. Sirtuin 4 is a lipoamidase regulating pyruvate dehydrogenase complex activity. *Cell*. 159, 1615-25
4. Tauro BJ*, **Mathias RA***, Greening DW, Gopal SK, Ji H, Kapp EA, Coleman BM, Hill AF, Kusebauch U, Hallows JL, Shteynberg D, Moritz RL, Zhu HJ, Simpson RJ. 2013. Oncogenic H-ras reprograms Madin-Darby canine kidney (MDCK) cell-derived exosomal proteins following epithelial-mesenchymal transition. *Mol Cell Proteomics*. 12, 2148-59 (* Co-first author)
5. Chen YS*, **Mathias RA***, Mathivanan S, Kapp EA, Moritz RL, Zhu HJ, Simpson RJ. 2011. Proteomics profiling of Madin-Darby canine kidney plasma membranes reveals Wnt-5a involvement during oncogenic H-Ras/TGF-beta-mediated epithelial-mesenchymal transition. *Mol Cell Proteomics*. 10, M110.001131 (* Co-first author)

A/Professor Meredith O'Keeffe

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OTHER PROGRAM AFFILIATIONS

Cancer

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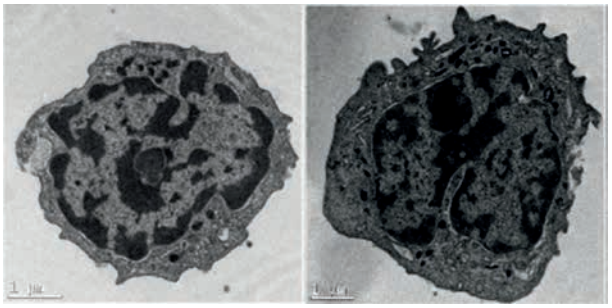
Dendritic cells are sentinels of the immune system that produce cytokines and interferons upon sensing danger. They are also professional antigen presenting cells, thereby connecting the innate and adaptive immune systems. Our laboratory investigates how pathogens and their products and/or or self-nucleic acids activate dendritic cells. We aim to decipher how this activation influences the function of dendritic cells. We investigate how this process may differ in different body locations, at different ages and in different disease settings. Major aims are to understand the role of dendritic cells in bone marrow malignancies and in autoimmune diseases such as Lupus.

Research Projects

1. **The role of checkpoint inhibitors in dendritic cell activation**
2. **The role of bone marrow dendritic cells in the transition of myelodysplasia to leukemia**
3. **The contribution of interferon-lambda to disease in lupus**
4. **The response of dendritic cells to antibiotic-resistant strains of Staphylococcus aureus**
5. **The interaction of dendritic cells with malaria parasites**



Electron micrographs of the major anti-viral type I interferon-producing dendritic cells of the bone marrow.

Selected significant publications:

1. Luber CA, Cox J, Lauterbach H, Fancke B, Selbach M, Tschopp J, Akira S, Wiegand M, Hochrein H, **O'Keeffe M***, Mann M* .2010. Quantitative proteomics reveals subset-specific viral recognition in dendritic cells. *Immunity*. 32:279-89. **Equal contributors*
2. Lauterbach H, Bathke B, Gilles S, Traidl-Hoffmann C, Luber CA, Fejer G, Freudenberg MA, Davey GM, Vremec D, Kallies A, Wu L, Shortman K, Chaplin P, Suter M, **O'Keeffe M**, Hochrein H. 2010. Mouse CD8alpha+ DCs and human BDCA3+ DCs are major producers of IFN-lambda in response to poly IC. *J Exp Med.* 207:2703-17.
3. Fancke B, Suter M, Hochrein H, **O'Keeffe M**. 2008. M-CSF: a novel plasmacytoid and conventional dendritic cell poietin. *Blood*. 111:150-9.
4. Naik SH, Metcalf D, van Nieuwenhuijze A, Wicks I, Wu L, **O'Keeffe M**, Shortman K. 2006. Intrasplenic steady-state dendritic cell precursors that are distinct from monocytes. *Nat Immunol.* 7:663-71.
5. **O'Keeffe M**, Hochrein H, Vremec D, Caminschi I, Miller JL, Anders EM, Wu L, Lahoud MH, Henri S, Scott B, Hertzog P, Tatarczuch L, Shortman K. 2002. Mouse plasmacytoid cells: long-lived cells, heterogeneous in surface phenotype and function, that differentiate into CD8(+) dendritic cells only after microbial stimulus. *J Exp Med.* 196:1307-19.

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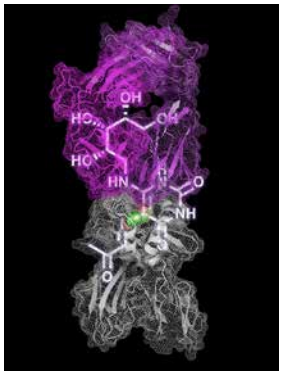
The academic research program within this laboratory is concerned with understanding the processes that control infection and immunity, specifically host recognition, responses developed by the pathogen and therapeutic development to modulate and/or counteract these events. The laboratory's research in adaptive and innate immunity has provided an understanding of the basis of peptide and lipid presentation, T-cell triggering, aberrant T-cell reactivity, monomorphic and polymorphic Natural Killer (NK) receptor recognition. The team's research on anti-viral immunity has provided an understanding of the factors that shape MHC-restriction (e.g. Immunity, 2003; Nature Immunology, 2005). Moreover, we have demonstrated how the pre-TCR, a receptor crucial for T-cell development, functions by autonomous dimerization (Nature, 2010). In relation to aberrant T-cell reactivity, our team has provided insight into alloreactivity (Immunity, 2009), Celiac Disease (Immunity, 2012) and HLA-linked drug hypersensitivities (Nature, 2012). Regarding innate and innate-like recognition, the team has shed light into how Natural Killer cell receptors (Nature, 2011) interact with their cognate ligands. Further, we have provided fundamental insight into how the Natural Killer T-cell TCR recognizes lipid-based antigens – which markedly contrasted that of TCR-pMHC recognition - and this has implications for glycolipid-based vaccine development (e.g. Nature, 2007). Most recently, our team identified the long sought after ligand for MAIT cells, namely showing that MAIT cells are activated by metabolites of vitamin B (Nature 2012, 2014 –see image). Our research program uses numerous biochemical and biophysical techniques including protein expression and purification, surface plasmon resonance and three-dimensional structure determination with the use of the Australian Synchrotron. Further, cellular immunology techniques are taught within the laboratories of the collaborators of the Rossjohn laboratory.



Research Projects

1. **MHC-restricted protective immunity**
2. **T-cell autoimmunity and alloreactivity**
3. **HLA-linked drug hypersensitivities**
4. **Lipid-mediated immunity**
5. **Metabolite-mediated immunity**
6. **NK cell recognition**
7. **T-cell signaling machinery**

Selected significant publications:

1. Kjer-Nielsen L, Patel O, Corbett AJ, Le Nours J, Meehan B, Liu L, Bhati M, Chen Z, Kostenko L, Reantragoon R, Williamson NA, Purcell AW, Dudek NL, McConville MJ, O'Hair RA, Khairallah GN, Godfrey DI, Fairlie DP, **Rossjohn# J** & McCluskey# J. 2012. MR1 presents microbial vitamin B metabolites to MAIT cells. *Nature*. 491, 717-723.

2. Illing PT, Vivian JP, Dudek NL, Kostenko L, Chen Z, Bharadwaj M, Miles JJ, Kjer-Nielsen L, Gras S, Williamson NA, Burrows SR, Purcell AW#, **Rossjohn# J** & McCluskey# J. 2012. Immune self-reactivity triggered by drug-modified Human Leukocyte Antigen peptide repertoire. *Nature*. 486, 554-558.

3. Vivian JP, Duncan RC, Berry R, O'Connor GM, Reid HH, Beddoe T, Gras S, Saunders PM, Olshina MA, Widjaja JML, Harpur CM, Lin J, Maloveste SM, Price DA, Lafont BAP, McVicar DW, Clements CS, Brooks# AG & **Rossjohn# J**. 2011. Killer cell immunoglobulin-like receptor 3DL1-mediated recognition of human leukocyte antigen B. *Nature*. 479, 401-405.

4. Pang SS, Berry R, Chen Z, Kjer-Nielsen L, Perugini MA, King GF, Wang C, Chew SH, La Gruta LN, Williams NK, Beddoe T, Tiganis T, Cowieson NP, Godfrey DI, Purcell AW, Wilce MCJ, McCluskey# J & **Rossjohn# J**. 2010. The structural basis for autonomous dimerization of the pre T-cell antigen receptor. *Nature*. 467, 844-848.

5. Borg NA, Wun KS, Kjer-Nielsen L, Wilce MC, Pellicci DG, Koh R, Besra GS, Bharadwaj M, Godfrey DI, McCluskey# J & **Rossjohn# J**. 2007. CD1d-lipid-antigen recognition by the semi-invariant NKT T-cell receptor. *Nature*. 448, 44-49.

# denotes joint senior author

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NHRMC Principal Research Fellow

Head, T Cell Transcriptional Regulation and Epigenetic Regulation

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Infection and Immunity Program

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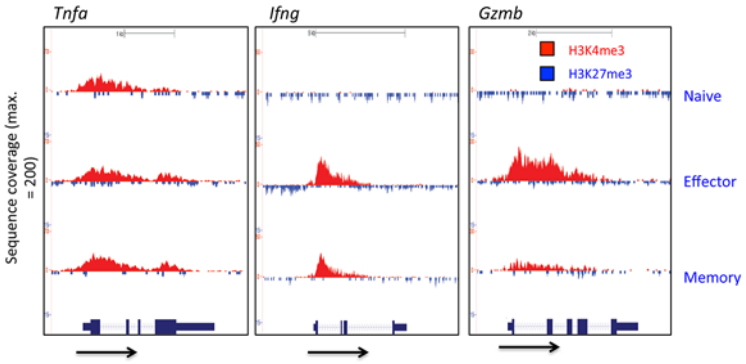
Our laboratory aims to identify novel transcriptional and epigenetic pathways and regulatory elements that regulate virus-specific killer T cell differentiation, function and the establishment of immunological memory. Such analysis will lead to the identification of molecular immune correlates of protective immunity that will serve to better understand how optimal immunity is generated. Further, this information will contribute to improvement of immunotherapies for infection (vaccines), autoimmune disease and cancer therapy. We use a multidisciplinary approach that includes the application of multiple next generation sequencing applications (RNA-seq, ChiP-seq, ATAC-seq, and HiC), small molecule inhibitor treatment of epigenetic and transcriptional regulators, novel transgenic and gene deficient mouse models, viral models of immunity and advanced bioinformatics.

Research Projects

1. **The role of chromatin remodellers in determining chromatin architecture during virus-specific T cell responses**
2. **Mapping genome wide targets and mechanisms of action of killer T cell specific transcription factors**



Mapping genome wide deposition of histone protein modifications during virus-specific T cell differentiation.
Shown is mapped ChIP-seq data for two histone modifications, H3K4me3 (red) and H3K27me3 (blue).

Selected significant publications:

1. Nguyen MLT, Hatton L, Li J, Olshansky M, Russ BE and **Turner SJ**. 2016. Dynamic regulation of permissive histone modifications and GATA3 underpin acquisition of Granzyme A expression by activated CD8+ T cells. *Eur J Immunol*. 46:307-318.
2. Harland KL, Day EB, Russ BE, Apte SH, Doherty PC, **Turner SJ** and Kelso A. 2014. Unique epigenetic signatures are associated with induction, silencing and re-expression of CD8 during T cell development and activation. *Nat Comm*, 5:3547.
3. Russ BE, Olshansky M, Li J, Smallwood HS, Denton AE, Prier JE, Stock AT, Nguyen MLT, Rowe S, Olson MR, Finkelstein DB, Kelso A, Thomas PG, Speed TP, Rao S and **Turner SJ**. 2014. Mapping histone methylation dynamics during virus-specific CD8+ T cell differentiation in response to infection. *Immunity*. 41:853-865.
4. Denton AE, Russ BE, Doherty PC, Rao S, **Turner SJ**. 2011. Differentiation-dependent functional and epigenetic landscapes for cytokine genes in virus-specific CD8+ T cells. *Proc Natl Acad Sci USA*. 108:15306-15311.
5. Day EB, Guillonneau C, Gras S, La Gruta NL, Vignali DA, Doherty PC, Purcell AW, Rossjohn J, **Turner SJ**. 2011. Structural basis for enabling T-cell receptor diversity within biased virus-specific CD8+ T-cell responses. *Proc Natl Acad Sci USA*. 108:9536-9541.

Dr Julian Vivian

Research Fellow

Head, Vivian Research Group

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Infection and Immunity Program

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Our work is principally focused on events central to infection and immunity. Specifically we work on deducing the structural arrangement of Killer-Cell Immunoglobulin-like Receptors (KIR) and their ligands and detail the molecular mode of interaction generating their complexes. This has important implications in disease and transplant outcomes. We also investigate immune reactions to specific drugs. This work is intended to lead to the better design and screening of new therapeutics.

Research Projects

1. **Structural and functional investigation of KIR receptors**
2. **What causes drug hypersensitivity?**

Selected significant publications:

1. Moradi S, Berry R, Pymm P, Hitchen C, Beckham SA, Wilce MC, Walpole NG, Clements CS, Reid HH, Perugini MA, Brooks AG, Rossjohn J, **Vivian JP**. 2015. The structure of the atypical killer cell immunoglobulin-like receptor, KIR2DL4. *J Biol Chem*. 290(16):10460-71.
2. **Vivian JP**, Saunders PM, Baschuk N, Beddoe T, Widjaja J, O'Connor GM, Hitchen C, Pymm P, Andrews DM, Gras S, McVicar DW, Rossjohn J, Brooks AG. 2015. The interaction of KIR3DL1*001 with HLA class I molecules is dependent upon molecular microarchitecture within the Bw4 epitope. *J Immunol.* 194(2):781-9.
3. de Weerd NA, **Vivian JP**, Nguyen TK, Mangan NE, Gould JA, Braniff SJ, Zaker-Tabrizi L, Fung KY, Forster SC, Beddoe T, Reid HH, Rossjohn J, Hertzog PJ. 2013. Structural basis of a unique interferon-signaling axis mediated via the receptor IFNAR1. *Nat Immunol* 14(9):901-7.
4. Illing PT, **Vivian JP**, Dudek NL, Kostenko L, Chen Z, Bharadwaj M, Miles JJ, Kjer-Nielsen L, Gras S, Williamson NA, Burrows SR, Purcell AW, Rossjohn J, McCluskey J. 2012. Immune self-reactivity triggered by drug-modified HLA-peptide repertoire. *Nature*. 486(7404):554-8.
5. **Vivian JP**, Duncan RC, Berry R, O'Connor GM, Reid HH, Beddoe T, Gras S, Saunders PM, Olshina MA, Widjaja JM, Harpur CM, Lin J, Maloveste SM, Price DA, Lafont BA, McVicar DW, Clements CS, Brooks AG, Rossjohn J. 2011. Killer cell immunoglobulin-like receptor 3DL1-mediated recognition of human leukocyte antigen B. *Nature.* 479(7373):401-5.

Why choose us?

The scope and scale of our research

Research that finds solutions to complex global biomedical challenges requires scale. We bring together more than 700 of Australia's most creative and innovative minds, with expertise spanning a range of biomedical and related research areas.

An international outlook

We are expanding our international footprint. Recently, more than 20 research teams have joined us from countries including Germany, Canada, the US and Denmark.

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Our experts from different fields work together in collaborative multi- and cross-disciplinary teams. This approach ensures each scientific problem can be examined from a range of perspectives and each research program benefits from a diversity of expertise.

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Monash University has invested significantly in high-quality research infrastructure and expertise to establish our platforms. The platform network brings together leading researchers from different fields to engage with local, national, and global, academic and commercial research sectors. Coupled with certification from the International Organization for Standardization (ISO), these platforms are a game-changer for academic and industry collaboration.

Established industry partnerships

These valuable partnerships boost research excellence and deliver solutions to current industry challenges. We are committed to working with industry, business, government, and the community sector to find innovative solutions to today's global health problems.

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These networks accelerate the translation of our discoveries into health outcomes and enable clinical imperatives to inform our innovative research agenda. Our work begins in the laboratory with fundamental discovery research and ends with impactful treatments.

Contact us

Whether you want to research, invest, study or partner with us, we'd be delighted to hear from you.

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Centre for Inflammatory Diseases, Monash University, Monash Medical Centre

Director: Professor Richard Kitching

Research in the Monash University Centre for Inflammatory Diseases (CID) spans basic experimental biology, clinical research and clinical practice in inflammatory diseases. We use both clinical and laboratory based experimental techniques to explore the mechanisms of inflammatory injury in important human diseases - and then relate these to unmet needs in patient treatment and management.

Monash Health Departments of Nephrology, Rheumatology, Gastroenterology and Hepatology, and Infectious Diseases are prominently represented in the Centre, with strong links between patient care and research. We train scientists and clinician-scientists at a high level, with many having gone on to work as independent and successful researchers.

There are more than 80 research students and staff in the Centre, sustaining a track record of important publications in journals including Nature Medicine, PNAS USA, Journal of the American Society of Nephrology, Arthritis and Rheumatology, Blood, The Lancet, Hepatology and The Journal of Clinical Investigation, with over 200 scientific papers published in the last five years. The Centre has had NHMRC and other competitively acquired grant funding over many years and holds over 30 grants totalling $3.5 million.

Website:
http://www.med.monash.edu.au/scs/medicine/cid/

School of Clinical Sciences Honours Coordinator: Dr Paul King

Contact details: Phone: (03) 8572 2602
paul.king@monash.edu

Website for prospective students:
http://www.med.monash.edu.au/scs/students/prospective/

Description of key research areas

Research in the Monash University Centre for Inflammatory Diseases (CID) spans basic experimental biology, clinical research and clinical practice in inflammatory diseases. Our main areas of interest (and Research Group Head) are:

- Vascular biology (Prof Alex Bobik, Prof Ban Hock-Toh, Prof Peter Tipping)
- Autoimmune kidney disease and vasculitis (Prof Richard Kitching)
- Chronic kidney disease and transplantation (Prof David Nikolic-Paterson / Dr Greg Tesch)
- Inflammatory respiratory disease (Dr Paul King)
- Actions of leukocytes in inflammatory disease (Prof Michael Hickey)
- Liver/Gut inflammation and fibrosis (Prof William Sievert)
- Lupus and arthritis (Prof Eric Morand)
- Infectious diseases (Dr Tony Korman)
- Neuroinflammation (Dr Connie Wong)

Centre for Inflammatory Diseases

Autoimmune Kidney Disease and Vasculitis Research Group

Laboratory Head: Professor Richard Kitching
Centre for Inflammatory Diseases
School of Clinical Sciences
Level 5, Block E
246 Clayton Road, Clayton
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Overview:

White blood cells are central to the development of severe forms of human glomerular inflammation. They are also increasingly recognised as important in acute kidney (renal) injury, a common complication of hospital stays that increases the chance of a poor clinical outcome. Studies of human kidney biopsies and immune cells, as well as relevant animal models, help define the critical molecular steps in the induction of these types of injury and provide novel therapeutic targets for new and less toxic therapies.

In our bid to identify potential therapeutic targets, the overall aim of our group's research is to further our understanding of:

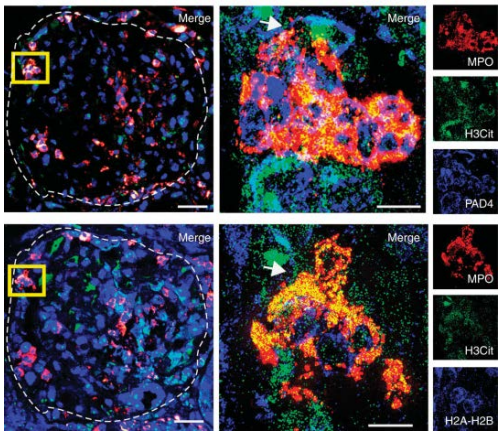
- Key events in the generation of nephritogenic immune responses
- Autoimmunity as it pertains to the kidney
- Effector responses in the kidney.

The *Autoimmune Kidney Disease and Vasculitis Research Group* has the following project available for Honours and PhD students:

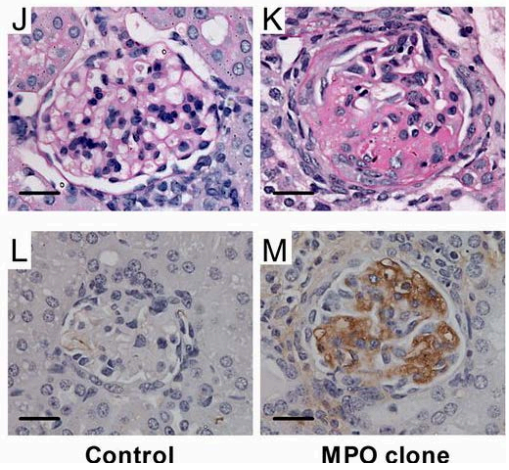
Aging and autoimmune vasculitis

Supervisors: Prof Richard Kitching and Dr Joshua Ooi

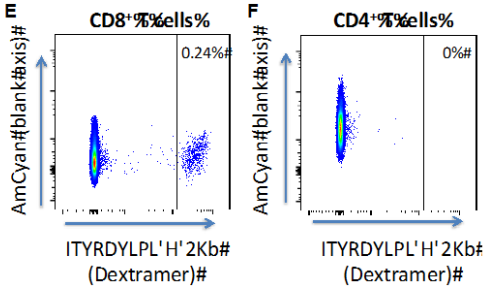
Age is a risk factor for the development of autoimmune vasculitis. However, it is not known how age affects the development of pro-inflammatory autoimmune responses. This Hons. project will determine the effect of age by comparing mice aged 2 months with mice aged 18 months. This project will involve the use of MHC class I and class II tetramers to phenotype autoantigen specific T cells and the use of mouse models of vasculitis.



Deposition of the target autoantigen, myeloperoxidase (MPO) within the glomerulus by netting neutrophils.
O'Sullivan KM et al, Kidney Int, 2015.



Transfer of MPO specific T cell clones causes glomerular segmental necrosis (top) and fibrin deposition (bottom).
Ooi JD et al, Proc Natl Acad Sci USA, 2012.



Identification of MPO specific CD8+ T cells using MHC class I dextramers.
Chang J et al, J Am Soc Nephrol, 2016.

Dr Joshua Ooi

Kitching/Holdsworth Laboratory Group

Centre for Inflammatory Diseases

Leukocyte Trafficking Research Group

Laboratory Head: Professor Michael Hickey
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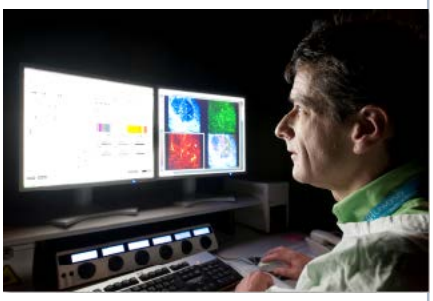
Overview:

Leukocytes play critical roles in protective responses to infection and injury. However, these same cells are also major contributors to inappropriate, injurious responses in inflammatory diseases. Our laboratory studies the actions of leukocytes in models of inflammatory disease, using state of the art imaging systems to directly visualise leukocytes in vivo during their recruitment from the bloodstream, and subsequent to their entry into tissues.

The recruitment of leukocytes to tissues, via leukocyte interactions with the endothelial vascular lining cells, is a key contributor to tissue injury in most inflammatory diseases. Studying these processes in real time in living tissues allows mechanisms of injury to be defined and new therapies developed.



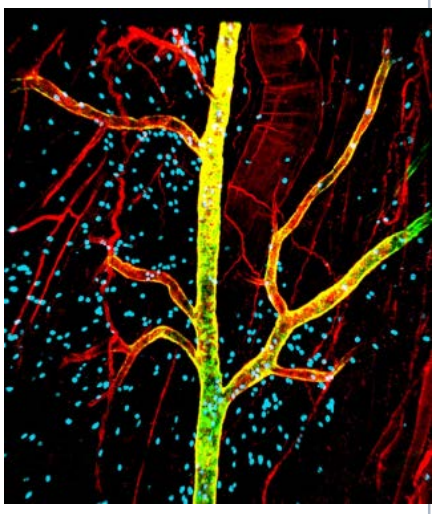
Using the multiphoton microscope

The *Leukocyte Trafficking Research Group* has the following project available for Honours and PhD students:

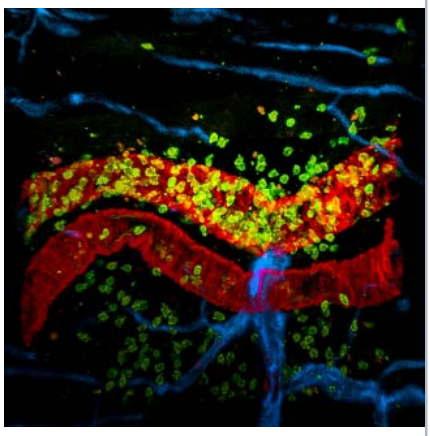
Control of Regulatory T cell recruitment and migration in inflamed skin

Supervisors: Prof Michael Hickey and Dr Sarah Snelgrove

The regulatory CD4+ T cell (or 'Treg') is an anti-inflammatory immune cell with a critical role in preventing inappropriate inflammation in the skin. This is demonstrated by the observation that patients with dysfunctional Tregs are commonly affected by spontaneous skin inflammation. However, the mechanisms whereby Tregs prevent skin inflammation remain unclear. Our laboratory has been using advanced in vivo imaging to investigate regulatory T cell behaviour in the skin in a model of T cell-mediated inflammation. This work has revealed that the skin contains a resident Treg population under resting conditions, but during inflammation, the number of Tregs in the skin increases dramatically. Whether this involves recruitment from the bloodstream or local proliferation is yet to be determined. In addition, many Tregs become highly migratory at the peak of inflammation, suggesting that this behaviour is critical for control of inflammation, although this hypothesis has not been tested. Therefore the aims of this project will be to investigate the mechanisms underlying the increase in Treg numbers during skin inflammation and to examine the role of intradermal Treg migration in controlling skin inflammation. This project will use state of the art in vivo microscopy techniques, including multiphoton and spinning disk confocal microscopy, in combination with Treg reporter (Foxp3-GFP) mice to enable direct visualization of Tregs in the skin. It will involve intricate surgical procedures for preparation of the inflamed skin for microscopy procedures. This work will lead to an increased understanding of the molecular basis whereby Tregs control inflammation in the skin.



'Tree of Life'
Dr Michaela Finsterbusch



'Immune cells at work'
Dr Michaela Finsterbusch

Dr Sarah Snelgrove

Leukocyte Trafficking Laboratory Group