NEWS AND EVENTS

Rheumatoid arthritis: New piece of the puzzle uncovered

Scientists at Monash University and The University of Queensland (UQ) have advanced our understanding of the high-risk genes involved in rheumatoid arthritis, which, for the first time, allows scientists to directly analyse immune cells responsible for this disorder and test how their behaviour changes following treatment. These findings have been published in the Journal of Experimental Medicine.

Rheumatoid arthritis is an autoimmune disease, which results in chronic inflammation of the joints, and impacts one per cent of the Western population commonly aged 50-75 years. Arthritis Queensland Chair of Rheumatology at UQ Diamantina Institute, Professor Ranjeny Thomas, said people with high-risk genes (HLA) were predisposed to rheumatoid arthritis. “HLA genes influence the way a person’s immune cells respond to an individual’s own body or deal with infections,” Professor Thomas said.

“Some people inherit HLA genes that put them at higher risk of the disease and smoking makes it even more likely for them to develop rheumatoid arthritis-specific antibodies called anti-CCP.”

Anti-CCP antibodies measure a response of the immune system towards a change in the body’s proteins - commonly referred to as antigens. Smoking is known to make these rheumatoid-arthritis specific antibodies more likely.

Professor Jamie Rossjohn, from the Department of Biochemistry and Molecular Biology, and Professor Thomas set out to investigate how high-risk HLA molecules and antigens interact to cause rheumatoid arthritis. They found that antigens involved in the development of this disease fitted into high-risk HLA molecules, like a hand in a glove, but normal self-antigens wouldn’t fit. This means that the immune system of rheumatoid arthritis patients only detects changed proteins and not normal self-antigens in the body. The researchers also found that immune cells in patients with rheumatoid arthritis lacked the usual control mechanisms to prevent runaway inflammation.

Stephen Scally, a PhD student from the Rossjohn lab and Soi Cheng Law, a PhD student from the Thomas lab, worked together to solve the 3-dimensional structure of the key molecules at the Australian Synchrotron and perfected a technique using patient samples to understand what goes wrong with immune cells in rheumatoid arthritis.

“Not only do we have a tool to directly analyse immune cells involved in rheumatoid arthritis and test their behaviour following treatment, these findings pave the way for future immune therapies that specifically target these cells in rheumatoid arthritis patients with high-risk HLA genes,” Stephen Scally said (photo inset). http://www.med.monash.edu.au/sobs/news/2013/rheumatoid-arthritis.html

OVER THE XMAS SHUTDOWN PERIOD:

- Switch off any unused equipment over the university break period.
- Switch off your computer if not in use.
- Ensure your fridges and freezers have been cleaned out and defrosted where possible, and connected to the red power points.
- Time to clean and de-clutter your lab areas.
- Ensure your Scheduled Poisons are LOCKED AT ALL TIMES.
Message from the Head of Department - Professor Roger Daly

Dear colleagues,

As the holiday season fast approaches, it's time to look back over 2013, assess our performance and achievements, and also consider the challenges and opportunities ahead.

The last year saw some fantastic achievements by members of the Department. Amongst these were: the award of the UNSW Eureka Prize for Scientific Research to Professor Jamie Rossjohn and his collaborators Professor James McCluskey and Dr Lars Kjer-Nielsen from the University of Melbourne; the award of Phase II funding through Grand Challenges Explorations, an initiative created by the Bill & Melinda Gates Foundation, to Dr Fasseli Coulibaly; the establishment of the Clive and Vera Ramaciotti Centre for Structural Cryo-EM by Professor James Whisstock in association with Professor Ian Smith and A/Prof Mike Lawrence (WEHI); and the entry of the anti-EphA3 mAb KB004, developed by Professor Martin Lackmann and his collaborators Professor Andrew Boyd (QIMR) and Professor Andrew Scott (Ludwig Institute for Cancer Research), into clinical trials to test its efficacy against acute myeloid leukemia.

In 2013 we maintained our strong performance in terms of publications: our projected output will be ~ 250 papers with an average impact factor (IF) of ~ 6.3. This provides an excellent platform for us to build on. My directive as we move forward is that we should focus on quality rather than quantity, with research excellence being our primary goal. Unfortunately, we fared less well in terms of NHMRC Project and ARC Discovery grants than in recent years. Given these results it's critical that our grant applications in 2014 are of the highest quality, and an encouraging sign in this regard is that we're seeing a much higher proportion of chief investigators use our internal peer-review system to develop and polish their grants prior to submission. Despite these results, a positive outcome for 2013 was the number of our researchers receiving Early Career Fellowships/Awards, and we've taken the opportunity to highlight these successes in this newsletter.

An important event in terms of the future development of the Department was the Strategic Planning Retreat, held in mid-November. This provided us with a unique opportunity to assess and discuss the Department’s performance and international standing, and develop a shared vision for its future strategic development. Of course, it’s critical that recommendations from the retreat are translated into real outcomes. To this end, a draft strategic planning document has been prepared, and this will be discussed and then ratified by the Departmental Executive in January. This will result in an action plan for implementation in 2014 and over the next 5 years.

Finally, I’d like to thank everyone in the Department for their hard work, dedication and support throughout 2013. I’d also like to thank those who have taken the time during 2013 to explain the inner workings of Monash to me, particularly members of the Departmental Executive, A/Professor Martin Stone, Professors John Carroll and Christina Mitchell, as well as Doug McGregor and Alan Hunter. Wishing you and your families a happy and relaxing holiday season,

All the best,

Roger

Discovery Early Career Researcher Award (DECRA) Recipient:

Jiyoti Verma-Gaur

Jiyoti completed her PhD at the Indian Institute of Science in Bangalore in the field of eukaryotic gene transcription. As a postdoctoral fellow, Jiyoti worked at Umeå University (Sweden) with Prof. Thomas Grundström, a leader in the field of oncogene, and then at the Scripps Research Institute (USA) with Prof. Ann Feeney, who leads one of the best labs in the field of B and T cell receptor recombination. At the Scripps, Jiyoti discovered novel regulatory mechanisms of recombination in antigen receptors in B and T lymphocytes. This work resulted in several top publications, including two first author papers in PNAS.

During her career, Jiyoti had opportunities to collaborate across disciplines, to unravel the biology and the evolution of gene expression in a model eukaryote, yeast, and in mice. She joined Dr. Ana Traven’s lab in October 2012, driven by a desire to combine her expertise in cutting-edge transcriptomics and genomics, with her interest in gene regulation to study post-transcriptional regulation by RNA binding proteins. Ana’s lab uses comparative analysis in model and pathogenic yeasts to understand fundamental aspects of eukaryotic biology.

With the DECRA fellowship, Jiyoti aims to understand a core question in biology: how do distinct phenotypes evolve between closely related species? It is known that a key driving force for evolutionary change is re-wiring of transcriptional gene networks. How post-transcriptional mRNA regulation contributes to the evolution of gene expression is very poorly understood. Jiyoti will tackle this question by studying mRNA networks coordinated by RNA binding proteins, their regulation and their evolution. A further major aim is to develop new technology in the fungus Candida albicans, using cutting edge “omics” approaches, e.g. RIP-sequencing to study RNA-protein interactions on a global scale, quantitative proteomics, and innovative methods to analyse subcellular mRNA localization. Because the project focuses on an important human pathogen (C. albicans), and studies a key virulence attribute (hyphal growth), the outcomes will also provide the knowledge base for understanding fungal pathogenesis, and a foundation for future studies in public health and hospital acquired infections. Regulation of RNA is the new frontier in gene regulation, and this project at Monash is an ideal spring-board for launching her independent career.
Patricia Illing

Patricia began her research into adverse drug reactions (ADR) associated with the Human Leukocyte Antigen (HLA) molecules in 2008 during her Honour's year in the laboratory of Prof. Jim McCluskey in Department of Microbiology and Immunology at the University of Melbourne. She continued this research during her PhD, focussing on Abacavir hypersensitivity syndrome (AHS), a potentially fatal ADR that occurs exclusively in individuals possessing the HLA variant HLA-B*57:01. During this time, Patricia formed part of a collaboration with the laboratories of Prof. Anthony Purcell (then at the University of Melbourne) and Prof. Jamie Rossjohn (Monash University) that unravelled the mechanism behind this association. They showed that abacavir interacted with HLA-B*57:01, but not other closely related HLA, causing a change in the way HLA-B*57:01 presented self-peptides to the immune system and stimulating an autoimmune response. This research was published in Nature in 2012.

Patricia now moves to the laboratory of Prof. Anthony Purcell, where she will form part of a team investigating the interaction of small molecules such as drugs and cellular metabolites with HLA molecules. It is hoped that this research will expand our knowledge of small molecule interactions with the HLA, assisting prediction and avoidance of immunogenic interactions between drugs and the HLA, as well as shed light on a potential role for endogenous small molecule metabolites in HLA-associated autoimmunity.

Kwok Wun

Wun has recently returned from the laboratory of Prof. E. Yvonne Jones at the University of Oxford to join the department in Prof. Jamie Rossjohn's laboratory. Through his NHMRC Early Career Fellowship (ECF), Wun will be extending his interest in the innate and adaptive immunity by studying CD1c, a member of the CD1 family of lipid-antigen presenting molecules.

Wun’s primary interest is on the molecular basis of lipid-mediated immunity, which includes the innate and adaptive arms of the protective immune response to pathogens. The CD1 family of antigen-presenting molecules fascinates him as they present lipid-based antigens for T Cell recognition compared to the conventional MHC molecules that present peptide antigens. Mycobacterium tuberculosis is the causative agent that causes tuberculosis and is one of the major causes of microbial infection death in the human population. Mannosyl beta-phosphomycoketide (MPM) is a cell wall component of M. tuberculosis that has been shown to bind and be presented by CD1c for T cell recognition and activation. Despite its emergence as a possible form of treatment and prevention for tuberculosis, structural information of the TCR-CD1c-MPM interaction is currently unknown.

Wun’s interest in immunity is coupled by the use of X-ray crystallography and Surface Plasmon Resonance to gain a structural and biophysical understanding of the TCR-CD1c-antigen complex. He intends to build on previous data of CD1d-antigen studies and utilise a cross-disciplinary structural and functional approach to elucidate the molecular basis of T cell recognition of CD1c-tuberculosis related lipid antigens. This vital knowledge will not only provide necessary advancement into the field of T cell-CD1-lipid interaction but will also aid in the future development of immunology based tuberculosis diagnostic and treatment.

“I will like to take the opportunity to acknowledge Jamie, Jenny and members of the Monash Research Office for their assistance during the application process. I look forward to a fruitful research experience at Monash!”

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Satellite Conference- Viruses - Pathogenic Nanomachines

This upcoming satellite meeting to the 39th Lorne Proteins conference brings together researchers using molecular virology, structural biology and high-resolution imaging in order to understand the virulence, replication and structure of viruses.

7th February 2014
Monash Biomedical Imaging Centre
62-772 Blackburn Rd, Clayton VIC 3168

Registration and abstract submission deadline:
Monday 8 December 2013 available on the Lorne Protein conference website: http://www.lorneproteins.org/viruses-pathogenic-nanomachines-satellite
or directly through Kristie McHutchison - kristie@asnevents.net.au if registering for the satellite only.

Please see flyer on website for further details and list of presenters:
Mitophagy under the Microscope

It is vital that eukaryotic cells maintain a healthy population of mitochondria. Failure to eliminate accumulated defective mitochondria may have severe health implications, and plays a role in cancer, neurodegenerative diseases, and aging.

In research published in the special November issue of Autophagy (IF 12.0) dedicated to Mitophagy, a team led by Dr Georg Ramm and Dr Mark Prescott have investigated the fate of mammalian and yeast mitochondria whose function has been disrupted. They reveal that the mechanisms for mitochondrial degradation used by yeast and mammalian cells are more conserved than previously recognised.

Mitochondria are targeted to the lysosome for degradation by a selective autophagic process called mitophagy. Parkin-induced mitophagy is the most commonly used model to investigate the process in mammalian cells. In this model, mitophagic clearance of all mitochondria in the cell is triggered in Parkin-expressing cells by treatment with CCCP, a protonophore that inhibits mitochondrial function by collapsing the mitochondrial membrane potential. This pathway for triggering mitophagy does not seem to exist in yeast cells.

Using an advanced imaging technique called live cell correlative light and electron microscopy, PhD student Ben Padman showed that contrary to published models, mitochondrial remnants persist in mammalian cells indicating that mitochondria are not completely destroyed. Importantly, this new research shows that the Parkin-model of mitophagy is actually performed under conditions which block rather than induce mitophagy. An alternative proteasomal pathway for mitochondrial degradation is activated.

The paper also shows that the commonly used MitoTracker series of dyes can be mistargeted to lysosomes in the presence of the protonophore CCCP. This finding has important mechanistic implications, and indicates that caution should be exercised when using fluorescent dyes to identify cellular compartments.

Figure 1: Correlative light and electron microscopy shows that contrary to the published Parkin-model of mitophagy, mitochondria (labelled with dsRed-Mito) are not completely destroyed.

Figure 2: Mitochondrial markers such as DiOC6 (green) do not label mitochondria (dsRed-Mito, red), but lysosomes (LTR, red) in the presence of the protonophore CCCP.

OHS MATTERS

AFTER HOURS = UNIVERSITY HOLIDAY PERIODS & WEEKENDS & HOURS BETWEEN 6pm-8am
Always refer to your protocol/procedure & Risk Assessment if you can carry out the specified work during After Hours.
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BREATHING APPARATUS Trained PERSONNEL
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From the last SOBS OHS meeting for 2013, the following changes have now been implemented. All breathing apparatus personnel will now be looked after by SOBS management for keeping personnel up to date with training and also will be responsible for organising to have the gas cylinders from the breathing apparatuses topped up after using.

POSTGRADUATE MATTERS

PhD Graduates
Hui Ting Ho
Supervisor: Gui-Ying Nie

All queries on Postgraduate matters:
Please contact Prof Mibel Aguilar
mibel.aguilar@monash.edu
Laboratory Head Profile: Professor Robert Pike

I started my scientific life as a young Honours student in the Department of Biochemistry at the University of Natal in Pietermaritzburg, South Africa. I had done a degree in Agriculture initially and then fallen in love with column chromatography of proteins during a third year biochemistry subject. In my Honours year, I was charged with developing a new protein fractionation technique and amazed both my supervisor and myself by getting highly publishable results: the level of surprise was due to the lack of correlation between my interesting results and my rather low marks for undergraduate Biochemistry! So, somewhat to my surprise, I embarked on a Masters course and got further good results on the family of enzymes, proteases, which unbeknownst to me were to become the focus of my life’s work. I then converted to PhD studies and was one of the first PhD graduates in my Department for quite some time.

I hadn’t realised how just independent I had become over the course of these studies until I accepted a post-doctoral fellowship at the University of Georgia in Athens, USA, but overall I found being a “post-doc” easy due to the independence I had had to cultivate as a PhD student with a supervisor with a relatively immense teaching load. In Georgia, I studied a group of proteases from a bacterium that causes periodontal (gum) disease, Porphyromonas gingivalis. Looking back now, I realise this was probably the most fun period of my research life. I worked with an outstanding team of fellow scientists and an amazing boss (Jim Travis) to achieve some fantastic results in understanding the enzymes and how they interacted with the host system molecules to fulfil the goal of the bacterium in colonising the host. I am still very proud of my first paper from this period, which has been cited well over 200 times and almost certainly helped me to establish a scientific career. The only downside to my time in this laboratory was that growing the bacterium, which was immensely smelly, was done under very crude conditions and so to this day I have little sense of smell!

After this successful time, I was attracted back to South Africa under a fellowship scheme and returned to my alma mater in Pietermaritzburg, where I worked on proteases from the organism that causes African sleeping sickness, Trypanosoma brucei. The parasites were difficult to grow and we got tiny amounts of material to work with, but somehow we managed to purify a new protease and characterise its activity. This was a very interesting time in South Africa’s history, as I arrived home shortly after the first post-Apartheid elections, but I was only to spend two short years there before moving to the University of Cambridge in the UK.

In Cambridge, I worked on the serpin, antithrombin. Once again, I was able to work with a talented group of scientists and it was there that I met James Whisstock and Steve Bottomley, who were to become long term collaborators and friends. I also met an Australian scientist called Stuart Stone, whom I bugged to distraction in order to learn how to do stopped flow kinetics so that I could measure the effects of clinically relevant mutations on antithrombin’s ability to bind its cofactor, heparin. The work was really successful and somewhere along the line all of my persistent bugging of Stuart must have “paid off”, because he asked whether I might be interested in moving to Australia as part of his group when he took up the position as Head of the Department of Biochemistry & Molecular Biology at Monash University. Since I was rather tired of moving continents, I asked whether there was any chance of getting an academic position and indeed there was, so after Phillip Nagley had checked me out in an interview in Cambridge, I was offered a position as Lecturer in the Department. Unfortunately, as has been well documented, Stuart died of a heart attack after only 6 months in the job and I only arrived after his death.

When I first arrived in the department in 1997, myself, Steve Bottomley and James Whisstock survived initially on funding that Stuart had obtained from the NHMRC, ARC and Heart Foundation. We established collaborations and got going with our work on proteases and serpins, with the strong support of our new Head, Christina Mitchell, who actively promoted all of our careers. I have now been here for over 16 years and have worked on a number of new and old projects. My interest remains in the area of proteases and how these molecules function as pathogenic agents in bacteria and parasites, as well as how these same molecules and their inhibitors and receptors are used by the host system to defend against pathogens. My major interest at present is the complement system, which uses proteases within a cascade of events to target pathogens and alert the immune system to their presence. I remain fascinated by the intricate control mechanisms that are built into the various molecules and how these affect their activity. The lab has recently identified an entirely new regulatory site in one of the complement proteases and worked out how this is affected when the enzyme transitions from an inactive to active form. The major “next” challenge is to use these same mechanisms to control the molecules in the context of a number of inflammatory diseases.

I consider that I have had a fortunate career that has taken place on four continents. Each of my moves was punctuated by a great deal of agonising, as I had always been offered a position in situ that was quite attractive as well. Each time I took the more challenging path of moving: I believe it has paid dividends in terms of personal growth and the development of my career. My major piece of advice to young scientists is therefore to challenge yourself and make use of the fact that our careers ARE indeed played out on the international stage.

OHS MATTERS

PC2/1 LAB ESSENTIALS DURING WARMER MONTHS

• You still need to wear:
  • CLOSED SHOES (no holes/gaps, non-absorbent, fully closed from the front and back of the shoe)
  • Your lab coat
  • Your Personal Safety Glasses
  • Do you need to wear a face mask? If yes WEAR IT!

Link to MBio e-bulletin:

MBio Graduates
making a world of difference

November/December 2013, Issue 40 Department of Biochemistry and Molecular Biology
OHS MATTERS

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Emergency Contact Details:
1. FIRST dial 000 for all Emergencies requiring an ambulance,
2. Call Security 333 to guide the ambulance to your location.
3. Do not leave the patient till either a First Aider or the Ambulance arrives.
4. First Aiders: Call Med Centre if necessary ext. 53175. First Aiders: Read MSDS before treating any chemical injury
5. First Aiders: Call the Safety Officer and/or Safety Representative as soon as possible

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