NEWS AND EVENTS

The Secrets of Plasminogen Revealed

Prof James Whisstock and colleagues have used the Australian Synchrotron to uncover how the protein ‘plasminogen’ is converted into the enzyme, plasmin. This enzyme removes blood clots and also clears damaged tissue.

Plasminogen - courtesy Prof James Whisstock:
Plasminogen is the proenzyme precursor of the primary fibrinolytic protease plasmin. Fibrinolysis is the process through which mammals remove blood clots and damaged tissue. Accordingly, plasminogen itself is the target of major drugs (plasminogen activators) that are used to remove blood clots following heart attack and stroke. In addition, there is considerable interest in developing molecules that prevent unwanted plasminogen activation and plasmin function in diseases such as cancer.

While the role of plasminogen and plasmin in the fibrinolytic system has been known for over 50 years, the mechanism through which plasminogen is activated to plasmin has long remained elusive. Whisstock, Law and colleagues have recently published the X-ray crystal structure of full length plasminogen. Importantly, the structural studies show how plasminogen is triggered to interact with plasminogen activators and how unwanted plasminogen activation is minimized. These results will help trigger structure guided development of new molecules to modulate plasminogen function in human disease.

Synchrotron Funding

Australian Academy of Science media release 28 March 2012

Synchrotron funding supports Australia’s innovation future

Australian Academy of Science President Professor Suzanne Cory today welcomed news that the immediate future of the Australian Synchrotron has been secured. Under a Memorandum of Understanding to be signed today, the Federal and Victorian Governments have agreed to jointly commit $95 million to running the Synchrotron for the next four years. “It is very important that funding for this world-class facility has been secured so that Australia can continue to produce ground-breaking science for discovery, applied research and industrial purposes,” said Professor Cory. “The Gillard Government and Baillieu Government have both shown vision by committing to this key piece of highly productive scientific infrastructure.”

The Australian Synchrotron has enabled valuable collaborative research to be undertaken by Australian researchers and industry, often with the enthusiastic involvement of international partners. “The Australian Academy of Science last year urged all parties involved in negotiations to resolve funding and administrative arrangements for this key scientific infrastructure,” Professor Cory said. The Synchrotron allows Australian scientists to conduct unique research in an enormous range of fields, including biology, medicine, environmental, agricultural and forensic science, as well as minerals exploration, engineering and advanced materials development.

On behalf of the Department I would like to congratulate James Whisstock on being awarded the MERCK MILLIPORE RESEARCH MEDAL by ASBMB. James will receive his award and present the Merck Millipore Medal Lecture at the 2012 ComBio meeting in Adelaide later this year.

Rod Devenish (Acting Head of Dept)
IUBMB Fellowships Awarded

Two postdoctoral researchers in the Department have been awarded IUBMB Fellowships to participate in the Young Scientists Program associated with the 22nd IUBMB-37th FEBS Congress to take place in Seville, Spain, 4-9 September 2012. These are Richard Berry (Rossjohn Lab) and Gavin Higgins (formerly a member of the Nagley lab and, since 2012, a member of the Mayne lab). They will join about 120 world-wide ECR participants in the Young Scientists Program, which will take place at Costa Ballena, near Cadiz, 1-4 September.

Gavin and Richard were selected as the Australian representatives from a strong pool of applicants from around the world, including many applications from Australia. This will be a great opportunity for Gavin and Richard to present their work to a group of outstanding young researchers in Biochemistry and Molecular Biology.

A Common Fold Mediates Vertebrate Defense and Bacterial Attack and The Structural Basis for Membrane Binding and Pore Formation by Lymphocyte Perforin

**Courtesy: Prof James Whisstock**

In 1896, the Belgium immunologist Jules Bordet discovered that human blood plasma contained a heat labile factor that efficiently destroyed foreign cell types and certain bacteria, a discovery that won him the 1919 Nobel prize in Physiology or Medicine. Paul Ehrlich later used the term “Complement” to describe this non-specific antimicrobial activity, since he argued that it “complemented” the cellular immune response. Later research showed that the lytic activity discovered by Bordet could be ascribed to a pore forming protein called complement component 9 (C9). Furthermore, it was also found that the cellular immunity system used a related pore forming protein, perforin, to destroy targets. Both C9 and perforin present unusual examples of mammalian pore forming proteins, and have the capacity to assemble into giant, membrane inserted pores on the surface of cells.

Despite over a century of intense study, insights into the mechanism of pore formation by C9 and perforin remained frustratingly elusive. In 2007 Whisstock and Dunstone showed through structural studies that perforin-like proteins actually belonged to a famous family of bacterial toxins more usually associated with destruction of mammalian cells - the cholesterol dependent cytolysins (CDCs). The evolutionary implications of this finding are striking and suggest an ancient lineage for these unusual immune proteins. In addition, because CDC’s are structurally and functionally well-characterized, the Monash group were able to propose a CDC-like mechanism for pore formation by perforin and C9.

In a second paper, the Whisstock team, together with Joe Trapani’s group from the Peter Macallum Cancer Centre, determined the high resolution structure of perforin itself. They used this information to interpret a low resolution structure of the perforin pore that had been determined by Helen Saibil’s team at Birkbeck College London. These results provided the first insights into the overall perforin pore structure. The work provided a framework to understand and further develop small molecule perforin-inhibitors to treat immune driven disease.
LATEST MEMBERS OF STAFF

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<th>Lab Head</th>
<th>New Staff Member</th>
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<td>Dr Greg Moseley</td>
<td>Aaron Brice</td>
<td>RA</td>
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<td>Janet Macaulay</td>
<td>Pip Carman</td>
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<td>Ian Smyth</td>
<td>Olga Plotnikova</td>
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<td>Peter Boag</td>
<td>Greta Raymant</td>
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<td>Catherine Itman</td>
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Seminars in April

4 pm on Wednesdays in Building 13A, Lecture Theatre M2

April 4th
Gregory L Blatch (Victoria University)
Regulating protein folding in the cell: the role of molecular chaperones and their co-chaperones in health, disease and infection

April 18th
Carl Walkley (St. Vincent's Institute)
Refining models of human cancer

Please send suggestions for future speakers to committee members:
Travis Beddoe, Melanie Pritchard, Martin Stone, Ana Traven, Catherine Itman, Peter Boag

A list of all seminars for 2012 can be found on the Biochem webpage www.med.monash.edu.au/biochem under “About”

STUDENT SOCIETY

NOT DRS
Necessary Outlets for Tertiary Doctoral Research Students

PhD Oration Program
Joel Selkrig (Lithgow Lab)
4pm Friday, 13th April
M2 lecture theatre

Complimentary pizza provided in the foyer Bld 76/77 afterwards.

To find out more about NOTDRS please visit:

Or find us on facebook:

An image through the base of a hair follicle showing the different cell layers which for the hair shaft.

Photo courtesy Prof Ian Smyth

An image of skin from a model of Harlequin Ichthyosis, a debilitating and often lethal inherited skin disease

Photo courtesy Prof Ian Smyth
LAB HEAD LIMELIGHT: Prof Mark Sleeman

Industry Experience Promotes Collaborative Approach

Professor Mark Sleeman brings a unique wealth of experience to Monash. Mark arrived in July 2011 after 18 years in the United States, with 13 of them at the US biotechnology company, Regeneron Pharmaceuticals Inc. As Head of Metabolic Research, Mark oversaw discovery research and therapeutic development for a variety of metabolic diseases. One of his former team’s lead therapeutics is now in phase two clinical trials, and Mark says it could be a breakthrough for the treatment of high cholesterol in humans. Having returned to where he did his PhD, he is currently assembling the Physiological Genomics Group to research metabolic disease.

Mark says his work at Regeneron gave him the opportunity to generate clinically relevant animal models, do discovery research and quickly make therapeutics that are able to treat the associated human diseases. He hopes to bring this approach to his new team.

“The goal is to bring my expertise in the translation of basic science to therapeutic development and put them into the clinic,” Mark says. “We’re starting to initiate some work on the regulation of food intake, body weight, obesity and lipid disorders, but it’s still in very early stages.

“At the present time one of the biggest issues facing the pharmaceutical industry and biotechnology is that they don’t have enough validated targets. Academics have a greater understanding of the specific disease mechanisms, but few pathways for development of therapeutics and commercialisation. There is a big disconnect. Importantly, I have retained my close affiliation with numerous US based companies that have significant platform technologies that are able to speed the development process up. I want to bridge that gap and bring technology from the US to Australia. One example would be integrate these technologies with the existing facilities to make monoclonal antibodies at Monash, and aid researchers in immune disease, obesity and diabetes in developing human therapeutics. You would then get a closer association between the academics and the commercial arm,” he says.

Mark applies two common ideas in his studies. He first aligns his work with clinical groups that are doing relevant research into disease areas of interest and then uses genetics and genomics to help understand the molecular basis of a disease. One of Mark’s main interests is Type 2 Diabetes.

“The development of insulin resistance is one of the biggest problems facing Type 2 Diabetes, and the therapeutic options for combating that problem are limited. We’ve done a lot on the discovery side of things, looking at proteins within the insulin receptor signalling pathways that potentially mediated insulin resistance. We’ve identified intra-cellular proteins that may be targets for therapeutics, but developing therapies and specific molecules to those targets has been very difficult. So it’s still basic research, but it fits nicely with what a lot of other people are doing at Monash,” Mark says.

Mark’s obesity research has also led him to examine non-alcoholic steatohepatitis (NASH), an inflammatory disease of the liver.

“I am very interested in NASH. It ranges from simply fatty liver but can progress to more severe fibrosis and cirrhosis. It’s associated with obesity, as increased adipose mass leads to inappropriate lipid stores in the liver. We’re looking at the inflammation side of this because it appears to be a significant problem. It’s developing as the population becomes more obese.”

Why Monash?

“IT was always a goal to come back and invest in new talent out of Australia. Australian science has a lot to offer, and I’d like to make a contribution. Monash has a good vision and they’re on a good path.”

Shutdown of Biochem LN2 Facility in 13DG

For those that are unaware, the Biochem Liquid Nitrogen Facility in Building 13DG is being shut down on the 20th April, 2012.

It has come to our attention that a research group with access to this facility is currently using the dewar labelled as “Ralph lab” (~35Lt), but has not left any contact details on the dewar.

Could the owner please come forward immediately and contact either Irene Hatzinisirou or Gavin Higgins ASAP, as arrangements will need to be made to transfer these samples to the vapor Nitrogen Facility in building 77G or elsewhere (at the owner’s discretion, with Oxygen monitoring of course!). The preservation of the samples within this dewar cannot be guaranteed beyond the 20th of April 2012, as the supply of liquid nitrogen to this facility will cease beyond this date.
INTRODUCING: Dr Mary Vail

Background

Having a strong interest in biology and genetics, I undertook a Bachelor of Science in Cellular and Molecular Biology at the University of Washington, in Seattle, Washington. It was during this time I had my first research exposure studying cell cycle genes in yeast. This experience led to my enrolling in the Molecular and Cellular Biology PhD program, also at the University of Washington. I completed my PhD in 2001 under the supervision of Prof. Nelson Fausto studying molecular mechanisms of carcinogenesis and regeneration in the liver using transgenic mice as a model system. I developed a great appreciation for the value of using mouse models to study human disease, in particular cancer, which remains a driving force in my current research in the Lackmann/Protein Interaction and Cancer Research Lab with A/Prof. Martin Lackmann.

In addition to science, I also have a strong interest and passion for education. Upon completing my PhD at the Fred Hutchinson Cancer Research managing the Science Education Partnership program. This unique and valuable program involved bringing secondary science teachers into research labs and teaching them basic molecular biology skills, which they were then able to teach to their students. However, when I moved to Australia in late 2004 I transitioned back to bench science and it was at this time I joined the Lackmann lab.

Projects

A primary draw to the Lackmann lab for me was the translational research focus in understanding the role of the EphA3 receptor in tumourigenesis and applying this knowledge toward the clinical development of an anti-EphA3 monoclonal antibody as a potential anti-cancer therapeutic. Ephs function during tumour growth, invasion, metastasis and neo-vascularisation, where they shape the tumour micro-environment by controlling communication and adhesion between cancer and host cells. In addition to being highly over-expressed on a large proportion of haematopoietic cancers, EphA3 receptor is also found on a large number of human solid tumours, including melanoma, breast, lung, colon, kidney, brain and prostate cancer. We found that in cancer patient samples EphA3 is most prominent on tumour stroma and vasculature - but is absent in normal tissues of these patients, thereby making it an ideal tumour target.

Since joining the lab, I have been involved in evaluating the therapeutic effects of the partially humanized anti-EphA3 (chIIIa4) antibody in nude mouse solid tumour xenograft models in collaboration with our partners at KaloBios Pharmaceuticals and Ludwig Institute for Cancer Research. This has lead to a greater understanding of the function of EphA3 as well as helping to validate the antibody for clinical trials, which have recently commenced for the fully humanized version, KB004.

We have been fortunate to have access to a wide array of state of the art equipment and cutting edge techniques to advance our research. A particular favourite and specialty of mine has been the development and utilization of a number of imaging platforms and strategies throughout, including the use of intravitral multiphoton microscopy to document and monitor in vivo the effects of antibody treatment on tumour vasculature. It is quite exciting to see within the living tumour and work is ongoing to further develop these technologies.

Throughout the course of our research it became evident that the EphA3 expressing cells we were targeting in the tumour were those within the tumour microenvironment. Isolation and characterisation of the antibody-targeted cells revealed a bone marrow-derived mesenchymal stromal cell population that we have been able propagate in and study in culture.

Subsequently we have been using GFP bone marrow transplantation and allograft tumour models to track and further characterize the EphA3 positive cells originating from the bone marrow and transiting to the tumour. Future studies will include targeting the EphA3 expressing bone marrow derived cells with chIIIa4, as well as knocking out Eph3 expression in bone marrow mesenchymal stem cells to

Work within the Lackmann lab is highly collaborative and team-oriented. Animal studies within the lab run in parallel with exciting basic research projects well as those focused on human patient samples. Although distinct projects, ultimately, each informs the other.

Environmental Sustainability At Monash

Anyone concerned with any environmental issues should either contact Leigh Yang (ll.yang@monash.edu) or visit The Office of Environmental Sustainability (TOES) http://www.fsd.monash.edu.au/environmental-sustainability.
POSTGRADUATE MATTERS

PhD Graduate

Kim Yong Loh
Thesis: “Regulation of leptin and insulin signaling by the T cell protein tyrosine phosphatase”
Supervisor: Tony Tiganis

MBio Induction

MBio Induction for all new commencing Masters and PhD students. April 18, students will be emailed details. Compulsory for all new students to attend.
Prof Mibel Aguilar will arrange to meet with them at 9.30 prior to the MBio meeting.

Faculty Supervisors

Faculty Supervisor Accreditation Workshops are to be held June 8 and 15
Register your interest with Phyllis DiPalma (phyllis.dipalma@monash.edu)
Accreditation is necessary to be a main supervisor of Honours, Masters and PhD students.

OHS MATTERS

Message from Prof Rod Devenish, Head of Department

Dear Colleagues,

Following on from the Departmental meeting, I wish to emphasis action be taken on two matters in particular:

1. Chemical Segregation - compliance is required by Victorian State Government Legislation. This has been discussed for some months now and should be completed by Easter 2012.

Our Safety Officers Irene Hatzinisirou and Gavin Higgins are available for consultation, guidance and assistance.

Advise the SOs or HoD if consideration needs to be given to purchase of additional storage cabinets. However, in this context floor groups should give consideration to consolidating stocks.

The SOs will do a quick inspection after Easter (start of May 2012) to ensure that all labs have implemented and are maintaining the segregation, as well to help out with any other related issues that may arise. If the Sos find that NO action has been taken I will be asking the relevant Lab Heads for a please explain and offering the complete removal of the relevant chemicals at the lab’s expense.

2. Leave and After Hours Policy

A. If on “leave” (conference, sick, annual etc) you should not be engaged in laboratory research at Monash as you are not covered for insurance purposes and it is in breach of Workplace legislation.

B. Normal working hours are regarded as 8am-6pm Mon-Fri. If a protocol / procedure is deemed as high risk (such as liquid Nitrogen handling, use of radioisotopes or primary sources of radiation, dangerous chemicals), it should only be carried out if approved by the Supervisor and the Safety Officer with the requirement that a second suitably trained person is available to assist in the case of emergency. Documentation must be kept to support the granting of such approvals.

Thank you for your assistance in meeting our obligations for these important matters.


All queries on Postgraduate matters: Please contact Prof Mibel Aguilar mibel.aguilar@monash.edu

Quick Overview of what to do when an emergency arises:

1. Remain CALM...

2. Yell out for a First Aider (don’t go looking for one yourself, get someone else to go looking)

3. First Aiders: Read MSDS before treating any chemical injury

4. First Aiders: Call Med Centre if necessary ext. 53175

5. First Aiders: Call the Safety Officer and/or Safety Representative as soon as possible
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