New ways to treat solid tumours with monoclonal antibodies

An international team of scientists from Monash University and Ludwig Institute for Cancer Research, in Australia, and KaloBios Pharmaceuticals, in the US, has shown that an antibody against the protein EphA3, found in the micro-environment of solid cancers, has anti-tumour effects.

As EphA3 is present in normal organs only during embryonic development but is expressed in blood cancers and in solid tumours, this antibody-based approach may be a suitable candidate treatment for solid tumours.

These research findings have recently been published in the journal *Cancer Research*.

The team, led jointly by the late Professor Martin Lackmann, from the Department of Biochemistry and Molecular Biology, and Professor Andrew Scott, from Ludwig Institute for Cancer Research, has found that even if tumour cells do not have this molecule they can thrive by recruiting and taking advantage of supporting EphA3-containing cells in the tumour micro-environment.

“The tumour cells send out signals to the surrounding area and say: ‘We need a blood supply and a foundation upon which to spread,’” explained first author Dr Mary Vail, from the Monash Department of Biochemistry and Molecular Biology.

“We have shown that EphA3 expressing stromal stem cells, which are produced by the bone marrow, form cells that support and create blood vessels in tumours.”

Professor Andrew Scott’s team at the Ludwig introduced human prostate cancer cells into a mouse model to mimic disease progression in humans. EphA3 was found in stromal cells and blood vessels surrounding the tumour.

They also observed that treatment with an antibody against EphA3 (chIIIA4) significantly slowed tumour growth. The antibody damaged tumour blood vessels and disrupted the stromal micro-environment, and cancer cells died because their ‘life-support’ was compromised.

““In addition, we screened various tumours from patient biopsies - sarcomas, melanomas as well as prostate, colon, breast, brain and lung cancers - and confirmed EphA3 expression on stromal cells and newly forming blood vessels,” Professor Scott said.

“Our research findings indicate that the tumour micro-environment is important, and monoclonal antibodies against EphA3 are one way to target and kill a variety of solid tumours as well as blood cancers.”

Currently, KaloBios Pharmaceuticals is testing the anti-EphA3 antibody KB004 in a multi-centre Phase I/II clinical trial in Melbourne and the US in patients with EphA3 expressing blood malignancies: AML, MDS and myelofibrosis.

This research represents Martin Lackmann’s life work said Dr Vail, who collaborated with her former mentor on the project for 10 years.

“Martin was dedicated to helping people, and believed that KB004 was a promising therapeutic approach. He rightly anticipated that it would be well-tolerated in cancer patients, and through this collaborative project, his pioneering research has progressed to clinical trials and potentially new treatments for cancer patients.”

The research study was funded by ARC, NHMRC and KaloBios Pharmaceuticals.
Monash researchers who have received DTRA funding. From left to right: Professor Jonathan Baell, Dr Kylie Wagstaff and Professor David Jans.

Message from the Head of Department- Professor Roger Daly

Dear colleagues,

The last few months have seen us enter an exciting phase of the Department’s development. Several new laboratory heads have joined us, while others will be relocating to our Department in the very near future. This recruitment activity will greatly enhance our expertise and critical mass in high priority areas, and open up new opportunities for research collaboration and synergy. In order to keep everyone abreast of these changes and to maximize research interaction I’ve taken this opportunity to provide some background on these new additions to the Department.

First, Professor Mike Ryan has recently joined us from La Trobe University. Mike’s research focuses on mitochondrial diseases, dynamics and proteomics, and he brings major expertise in protein biochemistry, cellular imaging and state-of-the-art gene targeting strategies. Mike’s group are situated on Level 2 of Building 77, and later this month Drs Hans and Dominika Elmlund will also be establishing a new laboratory on this floor. Hans and Dominika, who join us from Stanford University, are both experts in cryo-Electron Microscopy (EM) and they will provide leadership and expertise in EM as applied to structural biology. Both Hans and Dominika have led the development of exciting new computational approaches for determining protein structures from EM data, and together with Georg Ramm they will help bring the high-end FEI Titan Krios online when it arrives later this month. They will also have close links to researchers within the ARC Centre of Excellence in Advanced Molecular Imaging.

In addition to cellular and molecular imaging, an additional focus area for recruitment is cellular immunology, and we have made significant progress in this regard. First, two laboratory heads have recently joined us from Clayton Immunology. Dr Di Yu will lead the Molecular Immunomodulation Laboratory. Di’s research interests include IL21 therapy for anti-infection and anti-tumour immunity and the function of follicular helper T cells. In addition, Dr Eliana Marino will establish a new Diabetes, Diet and Inflammation Laboratory that will focus on T cells and antigen presentation by B cells in the context of Type I Diabetes. Second, in December, Professor Steve Gerondakis will join us from the Alfred Medical Research and Education Precinct. Steve’s research interest is NFkappaB signaling, and he will head the Immune and Cancer Cell Signalling Laboratory.

A recommendation from our strategic planning retreat last year was the establishment of a new Biochemistry Fellows Scheme, aimed at recruiting outstanding postdoctoral scientists into ‘Lab Head Track’ positions. The first appointment to this scheme will be Dr Antonella Papa, who has recently completed a highly successful postdoc in the laboratory of Pier Paulo Pandolfi at Harvard University, she will join us at the start of October. Anto’s research interest is the signaling mechanism and function of the PTEN phosphatase in human cancer, and her group will be situated alongside the Mitchell Laboratory on Level 1 of Building 77.

Further information regarding these new laboratories is, or will be, available from the corresponding Web pages. In addition, we’ll hold a reception towards the end of the year for our new researchers in order to welcome them to their new home and toast future research collaboration and success.

All the best,
Roger.

International funding to tackle deadly virus

Australian and American scientists will receive up to $1.5 million USD of funding from the US Defense Threat Reduction Agency (DTRA), to identify candidate drugs to treat a virus called VEEV. Venezuelan Equine Encephalitis Virus (VEEV) is a mosquito-borne virus that can cause large-scale outbreaks in animals such as horses, donkeys and humans in South and Central America, as well as the US. While horses show progressive central nervous system disorders as a result of brain inflammation, infected humans develop flu-like symptoms, become severely ill or die from encephalitis. Currently, there are no antiviral drugs to treat this disease.

A team of researchers from the Monash Department of Biochemistry and Molecular Biology and Monash Institute of Pharmaceutical Sciences led by Professor David Jans, in Melbourne; and George Mason University led by Assistant Professor Kylene Kehn-Hall, in Virginia, in the US, will collaborate on this project.

The research funding will allow Dr Kylie Wagstaff, from the Department of Biochemistry and Molecular Biology, and Professor Jonathan Baell, from the Monash Institute of Pharmaceutical Sciences, to identify, modify and assess suitable drugs, which will then be tested for efficacy on the live virus at George Mason University.

“I’m delighted that DTRA are supporting this international drug discovery program as there is an urgent need to develop new antivirals that tackle this significant disease threat to humans,” Dr Wagstaff said.

Professor Baell, who is a medicinal chemist, will be busy creating the best drug possible to treat VEEV.

“Often, the candidate compound that you obtain from a drug screen needs to be made more potent, selective and have better pharmacokinetics” he said.

“The medicinal chemistry required is expensive, but the DTRA funds should help us do this.”

Monash University will receive $803,000 USD in funding over three years from DTRA, and US scientists will receive $687,000.
Fellowships awarded to Department of Biochemistry Researchers

In the latest round of NHMRC and ARC fellowship announcements, three members of the Department of Biochemistry and Molecular Biology were successful. Professors Matt Wilce and Kate Loveland were awarded National Health and Medical Research Council (NHMRC) Senior Research Fellowships, whilst Dr Lee Wong was awarded a Future Fellowship by the Australian Research Council (ARC).

Professor Matt Wilce has received funding to investigate the molecular mechanisms underpinning protein-RNA interactions in innate immunity and the regulation of gene expression. RNAs and ribonucleoproteins underpin a vast array of critical cellular functions and offer a reservoir of therapeutic targets. Structural characterization of RNA and RNA-protein complexes is a challenging arena and is represented by a small percentage of all published structures. In the area of innate immunity Prof Wilce is studying the molecular basis of the signaling activation that occurs upon the detection of cytoplasmic RNA in viral invasion. In addition, his laboratory is also exploring the basis of recognition of RNA-binding proteins involved in gene regulation, including interactions that facilitate viral replication. An understanding of this will be important for the development of new antivirals. Thirdly his laboratory is investigating the way in which RNA-binding proteins affect gene regulation through direct interactions with miRNA and through the way they impact miRNA function. Ultimately such research will lead to new conceptual insights into disease processes and their prevention.

Professor Kate Loveland’s research program examines signalling events and molecules that control early steps in sperm development. Our understanding of the complex processes essential to healthy sperm formation is limited, and Prof Loveland’s research seeks the knowledge required for improved prevention, diagnosis and therapies for men with testicular pathologies. She has identified a key regulatory protein, activin, and will use the fellowship to determine when and how activin and other signalling proteins (e.g. Wnts, Hedgehog, Snail and importins) influence spermatogenesis. Prof Loveland’s laboratory uses an extensive range of mouse models, cell culture approaches and clinical samples and will also employ testis samples from testicular cancer patients to test potential interventions to reduce the growth of germine tumour cells. These findings are also relevant to other diseases affected by loss of genome integrity and those in which cellular differentiation outcomes are disturbed.

Dr Lee Wong studies how epigenetic factors control the activity of centromeres and telomeres. Epigenetics is a system that turns genes on and off without sequence alterations in the DNA. This process works by attaching chemical tags, known as epigenetic marks, to DNA. Centromeres and telomeres are chromosomal DNA domains essential for faithful chromosome segregation and genome stability. Their function and structural integrity are tightly regulated by specific epigenetic marks. Dr Wong’s project aims to assess the functions of key epigenetic factors including chromatin remodelers, histone variants and non-coding RNA in controlling centromere and telomere activity. The data should describe novel pathways that maintain the identity, transcription silencing, DNA replication fidelity and structural stability at these domains.

Viruses use ‘fake’ proteins to hide in our cells

Some viruses can hide in our bodies for decades and make ‘fake’ human proteins that trick our immune cells into believing nothing is wrong. Now researchers at the Imaging Centre of Excellence at Monash and Melbourne Universities have determined the basic structure of one of the two known families of these deceptive proteins.

Using synchrotron light on a common virus that lives in people happily and for the most part harmlessly, they have worked out the structure of the fake proteins. The research, published online by the *Journal of Biological Chemistry*, is an important first step towards producing better vaccines and drugs to fight viral disease.

The research team focused on the structure of m04 immunoevasin from mouse cytomegalovirus, a member of the m02 protein family. Cytomegaloviruses belong to the herpes virus family, which can cause glandular fever, chicken pox and cold sores. About half the population become infected with the virus, develop flu-like illness and then carry the virus for life. But the virus can be dangerous to pregnant women and people whose immune system becomes suppressed.

Monash Department of Biochemistry and Molecular Biology researcher, Dr Richard Berry, a senior author of the paper, said the discovery was important for understanding how this family of viruses can hide from our immune systems.

“Our work highlights how these viruses mimic the immune system in order to evade it,” said Dr Berry.

Immune T-cells patrol our bodies checking on the health of cells. One of the things they look for is a complex of proteins on the surface of cells. This major histocompatibility complex (MHC) presents a snapshot of what’s inside the cell. If bits of viral protein are detected by the T cells, they flag the infected cell for destruction.

Viruses fight back by disrupting the production of the MHC protein complex, thus reducing the numbers on the outer membrane.

But then, the next stage of what could be described as an evolutionary arms race kicks in. If there are too few MHC proteins on the outer membrane of a cell, then a different type of immune cell, termed the natural killer cell, will kill the cell just to be safe. Cytomegaloviruses have responded to this by making large families of fake cellular proteins that interfere with natural killer cell recognition. It is the basic structure of one of these families the researchers have revealed for the first time.

Professor Jamie Rossjohn, the other senior author and a Chief Investigator of the Imaging Centre, leads the research group.

“It’s been a race against our international competitors which we won with the help of the Australian Synchrotron. We were only able to produce very small protein crystals from which to solve the structures—too small to allow us to gain meaningful data with anything other than synchrotron X-rays,” Professor Rossjohn said.
Environmental Sustainability At Monash
Anyone concerned with any environmental issues should contact Shani Keleher (shani.keleher@monash.edu) or visit The Office of Environmental Sustainability (TOES) http://www.fsd.monash.edu.au/environmental-sustainability.
Schloss (castle). It was very picturesque, particularly during the warm seasons (see the picture below on a visit back there last year).

Working as a Postdoc in Heidelberg at the German Cancer Research Center was a very challenging but rewarding time. My group leader Prof. Gunter Schutz, directed a large research group and expected you to work hard (and get results!). I learnt a lot about research at Heidelberg – to work at the Baker IDI Institute in Prahran under the leadership of the then Director Prof. John Funder. I ran a small Molecular Genetics lab studying steroids, nuclear receptors and steroid modifying enzymes called the HSDs. This was a very productive and enjoyable period for my research and I made a number of strong collaborations with other research groups, particularly at Monash University. In 2001 the Baker underwent a big change in research direction and I decided it was time to move my lab and I was able to move to the University of Melbourne where I was offered a three year Fellowship back in my old Department (Biochemistry). It was great to be back where I had started my research career and on the back of two NHMRC project grants I was able to build a strong research lab under the Departmental leadership of the HOD at the time Prof. Mary-Jane Gething. It was about this time that I started to engage in more teaching aspects of University activities and began giving endocrinology lectures to Biomed Students and some molecular genetics lectures to Science undergraduates. In mid-2004 I made the leap to academia by accepting a T & R academic position at Monash University in our Department. This has turned out to have been a great move as my research has flourished with collaborative interactions and successful grant outcomes, significantly being part of back-to-back NHMRC Program Grants. My research continues to focus on the actions of steroids, primarily coordinating respiratory development and I have other projects investigating the actions of other steroid receptors and the biology of the HSD enzymes.

Link to Professor Tim Cole’s Lab: http://www.med.monash.edu.au/biochem/staff/tim-cole.html

PhD Top-Up Scholarships
Faculty of Biomedical and Psychological Sciences

The newly founded Faculty of Biomedical and Psychological Sciences comprising the School of Psychological Sciences, the School of Biomedical Sciences and the Australian Regenerative Medicine Institute (ARMI) is offering two top-up scholarships ($15,000 each) for new interdisciplinary collaborations between neuroscience researchers across our Faculty.

The top-up will be for PhD students that have been awarded a scholarship to commence their PhD in 2015.

Research proposals of no more than 200 words plus a short 100 word bio of each investigator with CV to be sent by Friday 26 September, 2014 to: directorresearchdegrees.psych@monash.edu

A minimum of two supervisors from at least two different schools within the Faculty is required.
Science in a nutshell

It’s the three-minute thesis season when PhD students across the nation explain their research to audiences with one PowerPoint slide to aid them.

At the Faculty of Medicine, Nursing and Health Sciences’ three minute thesis competition, Friday 22nd of August, Victor Suturin and Felix Deuss from the School of Biomedical Sciences competed with seven other PhD students for a place in the Monash University finals.

They performed exceptionally well. Victor (Department of Physiology) came second, scoring $500 for his presentation *The killer cure*; and Felix (Department of Biochemistry and Molecular Biology) won the People’s Choice Award for his presentation *To kill or not to kill*. He received a gift from the Monash Postgraduate Association.

On the day, the first prize was awarded to Kylie Dyson (School of Public Health and Preventive Medicine) for her presentation *Resuscitation: Does practice make perfect?* Ebonie Rio (School of Primary Health Care), who was third placed, received $300. The encouragement award went to Maria Nguyen from the School of Clinical Sciences and Monash Health.

Kylie Dyson will now compete with other Monash faculty winners in the Monash University final on Friday, 19 September at 1:00 pm at the Alexander Theatre.

### POSTGRADUATE MATTERS

**PhD Graduates**

**Ryan (Chaur Chia) Chai**

Thesis: “Investigation of the effect of HSP90 inhibitor treatment on tumour cell biology and the bone microenvironment”  
Supervisor: Dr John Price

**Tia Ditommaso**

Thesis: “Mouse models in cutaneous biology”  
Supervisor: Associate Professor Ian Smyth

**Ivan (Hong Wee) Ng**

Thesis: “Regulation and trafficking of the STAT3 transcription factor.”  
Supervisor: Professor David Jans

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

### Upcoming Seminars

1pm on Wednesdays in Lecture Theatre H1 (Building 11)

**September 24th**

Dr Traude Beilharz  
*What RNA-dynamics tell us about cellular transitions.*

**October 8th**

Prof. Merlin Crossley  
*Regulatory Single Nucleotide Polymorphisms (SNPs) in Human Gene Promoters and Genomic Editing.*

**October 15th**

Prof. Jenny Martin  
*The mystery of membrane fusion: structural biology of Munc18 proteins required for SNARE-mediated vesicle trafficking.*

**October 22nd**

Dr Marc Kvansakul  
*Structural insight into host-pathogen interactions*

### NOT DRS

**MBio Graduates**

making a world of difference

Link to MBio e-bulletin:  

For more Biochemistry news and events:  
please visit our website  
www.med.monash.edu.au/biochem
OHS MATTERS

HOW TO ACCESS CHEMWATCH
Go to Monash OHS web site at:

Click on the link listed under ‘MSDS Access’ Chemwatch MSDSs
Use this link to look up chemicals especially for storage & incompatibility purposes, First Aid info and how to handle spills.
If you use any chemicals no matter how safe you may think they are, you should know how to access Chemwatch to look up the Material Safety Data Sheets (MSDSs). Each lab group should also hold hard copies of all the MSDSs of chemicals they possess, in case there is no power to look up an MSDS electronically, if an Emergency situation arises.
All MSDSs should be kept up to date and <5 years old.

HOW TO STORE CHEMICALS IN YOUR LABORATORY
• Do you have an updated version of the MSDS of every chemical in a folder easily visible and accessible to all users?
• Do you have your chemicals segregated according to their classification & incompatibility sections in the MSDS?
• Do you have an updated list of chemicals visible at every location where you have chemicals stored? (Shelves, cupboards, cabinets, fridges, freezers, cool-rooms?)
• Do you have a standard operating procedure for ordering chemicals?
  • Do you really need it?
  • If high risk, is there an alternative of lower risk?
  • If high risk, to order the minimum amount?
  • Is it a Scheduled Poison? And how do you store it?
  • Do you have the appropriate storage location for it?
  • Do you have a Risk Management in place (Risk assessment) before using?

What do you do when.....

OXYGEN ALARM SOUNDING
• evacuate room immediately
• close door behind you
• notify first aider if feeling ill
• notify safety officer
• do not allow anyone to enter until room is deemed safe

SOLVENT ALARM SOUNDING
• do not ignore
• do not walk away
• check all floors
• do not enter
• follow instructions

CHEMICAL SPILL
• notify first aider if feeling ill
• Safety officer will instruct whether to isolate area and how to clean up spill
• 'orange' wheelie bin to be used

PAPER TRAIL
• hazard/incident report form to lodge ASAP
• First Aid Injury Report form to send to OHS Nurse ASAP

HEALTH ISSUE
• life threatening
• notify Safety Officer IMMEDIATELY

CALL 000
• call 333
• notify Safety Officer

CALL 333
• hazard/incident Report form to lodge ASAP
• First Aid Injury Report form send to OHS Nurse ASAP

IMMEDIATELY
• notify first aider
• visit doctor
• notify safety officer

PAPER TRAIL
• hazard/incident Report form to lodge ASAP
• First Aid Injury Report form send to OHS Nurse ASAP

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Newsletter: July/August 2014, Issue 44 Department of Biochemistry and Molecular Biology