

CONNECTIONS

Bioplatforms Australia Quarterly Newsletter | Q3-2010

PROTEOMICS RESEARCH REVEALS IMPACTS OF RESPIRATORY SYNCYTIAL VIRUS AT THE CELLULAR LEVEL

Infectious disease research is of vital importance to Australia's biosecurity as illustrated by the world-wide swine flu epidemic.

To ensure our biosecurity we need to be alert to a variety of infectious disease agents so as to develop both adequate surveillance (diagnostics) and control measures (vaccines and therapeutics). For some infectious agents this means improving existing measures, however, there are many infectious diseases for which no vaccine and/or therapeutics exist. This is especially relevant in the context of climate change as tropical diseases such as Dengue virus are driven into more temperate regions. An important component of our defence strategy requires highly competent and experienced biosecurity researchers and relevant scientific infrastructure. One of the tasks of the Queensland Institute of Medical Research (QIMR) Protein Discovery Centre (PDC) is to fulfill a specialised role in the Proteomics Australia network by providing expertise in proteomic analysis of infectious diseases.

One virus for which there is no licensed vaccine or suitable therapeutic agents (e.g. antivirals like Relenza or Tamiflu used for influenza) is respiratory syncytial virus (RSV). RSV poses specialised challenges to individuals with underdeveloped or compromised immune systems. Consequently, infants and young children, adults on immunosuppressive therapy for other diseases and the elderly are all highly susceptible.

RSV is very infectious with most children experiencing infection by two years of age. Symptoms can vary from mild through to death. Furthermore, multiple infections occur throughout life due to the ability of the virus to evade our immune responses. Although vaccines were developed for mumps and measles many decades ago, the same approaches have not been rewarding for RSV. This lack of success is believed to reflect the ability of RSV to thwart antiviral systems used by our cells (e.g. the interferon response) to combat infection.



Prof Jeff Gorman (Director, QIMR-PDC and Convenor of Proteomics Australia) explains the operations of a Bruker MALDI-TOF/TOF mass spectrometer to the Hon. Nicola Roxon MP, Commonwealth Minister for Health & Ageing.

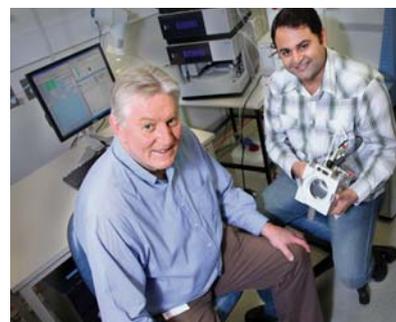
RSV uses a small protein (no-structural protein 1 or NS1) encoded by its own genome to block our interferon system, however, the mechanism by which NS1 achieves this is not understood properly. Unlocking this mechanism of action should provide new leads for developing much needed drug treatments for RSV infections and represents a current research goal.

The QIMR-PDC is collaborating with leading national and international experts (Dr Kirsten Spann, Sir Albert Sakzewski Virus Research Centre, University of Queensland and Dr Peter Collins, National Institute of Allergic and Infectious Diseases, US National Institutes of Health) to gain insights into the mechanism of action of RSV NS1 at the proteomic level. This research requires specialised proteomic infrastructure such as advanced mass spectrometers to determine changes in the cellular proteomes (including interferon induction of protein profiles) in response to RSV. The involvement of Dr Collins is a particular strength of the collaboration given he originally determined the complete gene structure of RSV and identified the existence and role of NS1. He was also the first to accomplish the enormous achievement of producing recombinant clones of RSV so that NS1 can now be mutated in the context of a replicating infectious virus. Dr Spann has worked closely with Dr Collins and also offers valuable expertise in this area.

Collaborative efforts involve the use of infectious RSV clones with iteratively mutated forms of NS1 in which each iteration of mutation is dependent on dynamic feedback between virological and proteomic experiments. Resulting

proteomic data should reveal the specific structural features of NS1 used to dampen our cellular antiviral responses and provide a basis for downstream drug design to combat RSV. Recently, results from this collaboration were presented to the Human Proteome Organisation Congress in Sydney (HUPO2010) and have been submitted to the leading proteomics journal, *Molecular and Cellular Proteomics*. These reports describe previously unknown impacts of NS1 on the ability of lung epithelial cells to mount antiviral responses.

The QIMR-PDC is also involved in similar projects on malaria with other QIMR scientists and Australian Army researchers as well as providing substantial proteomic expertise to a variety of significant disease targets including arthritis and cancer.



Prof Jeff Gorman and Dr Keyur Dave discuss the configuration of a high performance Orbitrap mass spectrometer used for high throughput, high precision proteome profiling of RSV infected cells.



ARC funding of \$19.25 million has been awarded to the Centre of Excellence for Plant Cell Wall Biology

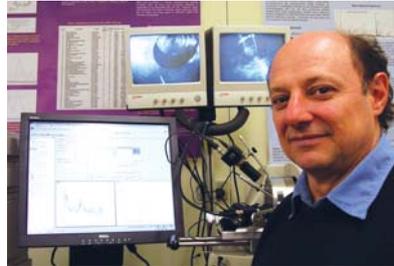
ARC CENTRE OF EXCELLENCE FOR PLANT CELL WALL BIOLOGY

Australian crop and food industries together with emerging industries related to renewable transport fuels and biomaterials will all gain from the new ARC Centre of Excellence for Plant Cell Wall Biology established at the University of Adelaide's Waite Campus.

ARC funding of \$19.25 million has been awarded to the Centre for the next seven years with an additional \$12 million of support from partner institutions and collaborators.

Plant cell walls represent the world's largest renewable carbon resource and have become major new drivers of international research in plant science due to their central roles as renewable sources of transport fuels, as functional foods to improve human health, and as a source of raw materials for industrial processes.

The Centre will define the regulatory mechanisms that control molecular, enzymic and cellular processes involved in the synthesis, deposition, re-modelling and depolymerisation of cell wall polysaccharides of cereals and grasses. Chief investigators include the Centre's director, Professor Geoff Fincher, who has many years agricultural and biotechnology research, and his University of Adelaide colleague, Dr Rachel Burton together with Professor Tony Bacic (University of Melbourne) and Professor Mike Gidley (University of Queensland). The Centre will build an international team with focus on scientific, technical and training aspects to generate outcomes that will significantly enhance biotechnologies that underpin Australian crop industries worth \$8 billion per annum, associated food industries valued at about \$40 billion per annum, and massive emerging industries related to renewable transport fuels and biomaterials.



Tony Bacic in front of the new ABI QSTAR Elite LC-QTOF-MS, University of Melbourne.

Bioplatforms Australia Ltd is a major sponsor of the Centre and will provide \$525,000 to promote access to its suite of functional genomics platform technologies and bioinformatics capabilities.

THE AUSTRALIAN PHENOMICS NETWORK: EVOLUTION OF ANOTHER 'OMIC'

Like Bioplatforms Australia, the Australian Phenomics Network (APN) was funded through the Commonwealth Government's NCRIS funding scheme in 2007. It was set up to develop the infrastructure to create, characterise and cryopreserve mouse models of human disease.

With further funding received from the recent Education Investment Fund (EIF) Super Science initiative as well as financial support from Bioplatforms Australia, APN is building a "pipeline" to validate and characterise mouse models resulting from infrastructure investments made to date.

This will be achieved with Next Generation Sequencing for the discovery of causative Single Nucleotide Polymorphisms (SNPs); dedicated bio-informatics; short hairpin (sh) and small interfering (si) RNA screens to discover genes of interest; and the production of inducible shRNA transgenic mice to validate researcher discoveries. This new level of investment provides an

accelerated and truly leading capability to make genetic associations with disease, and to fully describe resulting phenotype. Along with other infrastructure supported by Bioplatforms Australia, this will open up avenues for investigations into the mechanistic pathways and biological actions associated with disease.

Increasingly, the data that flows from these studies will need diligent curation and alignment with comparable data coming from human genome-wide association studies (GWAS). The new funding will boost the NCRIS funded

APN will continue at a revolutionary pace. Critical to this is the involvement of partners like Bioplatforms Australia

data management projects currently underway, including the Phenomics Ontology Drive Data management system (PODD), that will allow the capture, storage and discovery of raw phenomics data, and associated contextual data. Taking this and other data frameworks forward to the wider research community is an important area of two-way crossover between the Bioplatforms Australia and the APN, and the subject for discussions over the next few months.

The APN operates across twelve Australian institutions, and whilst mouse models remain at the core of its service offering, the pace of change in scientific research means the evolution of the



APN provides researchers with mouse models for the study of human and animal disease.

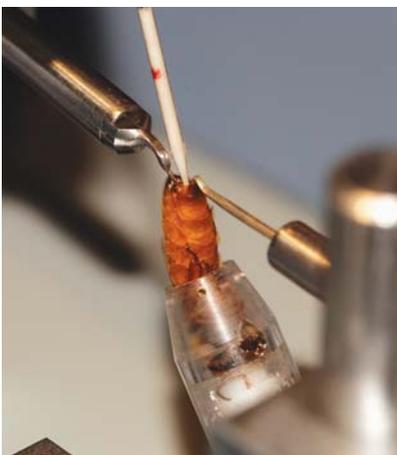
APN will continue at a revolutionary pace. Critical to this is the involvement of partners like Bioplatforms Australia in providing collaborating infrastructure for all researchers to use in a seamless way.

For further information about the APN services and details of the infrastructure development contact:

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CIBER BEE RESEARCH: WHAT MAKES MATED AND UNMATED FEMALE BEES SMELL DIFFERENT?

Cuticular hydrocarbons are chemical compounds found on the cuticle of most terrestrial arthropods. Originally thought to protect the animal against desiccation, it is now becoming increasingly clear that these chemical cues are also used during short range communication.



Seminal product substances influence important physiological and behavioural responses.



HONEYBEES

Honeybees are of central importance for human food production on a global level.

In many species of insects, mated and unmated females differ in their cuticular hydrocarbon profiles, and this variation provides males with information on a female's mating status. In social insects such as bees, differences in cuticular hydrocarbon profiles of mated and unmated queens may also provide workers with important information on queen fecundity.

CIBER, the Collaborative Initiative for Bee Research, located at the University of Western Australia facilitates interdisciplinary research on honeybees to better understand honeybees and counter the dramatic losses currently occurring. Honeybees represent significant agricultural importance as pollinators for major crops and are major sources of commercial honey, pollen, and wax production. Losses to bee populations through parasites and pathogens have been creating problems in pollination which impacts food prices. The aim of this CIBER research project, with help from Metabolomics Australia (Ricarda Fenske) and their GC-MS machine, is to determine if a difference in cuticular hydrocarbon profiles between mated and unmated queen honeybees is a result of substances transferred in a male's ejaculate during copulation.

In many species, substances other than sperm make up a substantial portion of the ejaculate transferred to females during copulation. The chemical content of the non-sperm portion of the ejaculate is typically complex, containing numerous substances with a wide variety of actions and are known as seminal products.

The actions of some of these substances are concerned directly with sperm, including effects on sperm survival, probability of fertilization and sperm transport. However, seminal product substances are also known to influence important physiological and behavioural responses in females, and there is some evidence to suggest that these substances may influence a female's chemical profile. To determine this, CIBER will artificially inseminate bees using different mixtures of ejaculates to determine if sperm, seminal fluids, or a mixture of these substances influences the chemical profiles of female bees.

Honeybees represent significant agricultural importance as pollinators for major crops and are major sources of commercial honey, pollen, and wax production.

This project is being run by Melissa Thomas (School of Animal Biology), Boris Baer (CIBER) and Maja Babis.



The Human Proteome Project will provide an essential benchmark to facilitate better understanding of human biology and disease

HUPO 2010 OFFERS AN INTERNATIONAL FORUM FOR BPA RESEARCHERS

With approximately 1,100 attendees from Australia and overseas the Human Proteome Organisation World Congress held in Sydney during September provided an international forum for a number of Bioplatforms Australia leaders to present their collaborative science.

Ian Smith (Monash University), Jeff Gorman (QIMR), Mark Molloy (APAF), Peter Hoffmann (University of Adelaide), Michael Crouch (TGR Biosciences) and Marc Wilkins (UNSW) presented a collection of scientific papers, ranging from proteomics investigations into cardiovascular disease, infectious disease and cancer through to technology developments in the area of pathway signaling.

Of particular interest was the launch of the Human Proteome Project, an ambitious program aimed at identifying and cataloguing all human proteins in a fashion analogous to the Human Genome Project. The Human Proteome Project will provide an essential benchmark to facilitate better understanding of human biology and disease.

BPA STRATEGY DISCUSSION WITH RALPH BRADSHAW

Bioplatforms Australia (BPA) sponsored the visit of Professor Ralph Bradshaw to attend HuPO 2010 as an invited speaker.

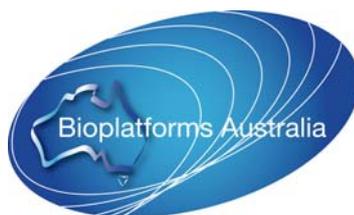
Professor Bradshaw currently holds chairs in the Departments of Physiology & Biophysics and Anatomy & Neurobiology at the University of California. Notably, Professor Bradshaw was the president of the Federation of American Societies for Experimental Biology from 1995-1996. During this time he was instrumental in lobbying efforts which secured the doubling in support for the NIH from the US Congress.

Professor Bradshaw is also well aware of funding issues affecting Australian health and medical research. His contribution as a member of the Australian Health and Medical Research Strategic Review Planning Committee in 1998 exposed him to the context of the Australian research sector and during his visit to Sydney, Bioplatforms Australia leveraged this knowledge to test our NCRIS and EIF Super Science investment strategies.

BPA's Director and Chair of the Scientific Advisory Committee, Professor John de Jersey met with Professor Bradshaw to describe the integrated vision BPA has for Australia's Systems Biology infrastructure, together with our intention to create and develop nationally strategic 'omic datasets. Professor Bradshaw concurred with our perspective on retaining relative balance in investments across Genomics, Proteomics and Metabolomics and acknowledged that our enhanced focus on bioinformatics was essential if these disciplines are to yield their research promise.



HUPO 2010



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