

CoRE of The Matter



NATIONAL RESEARCH CENTRE FOR
GROWTH AND DEVELOPMENT

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EDITION NO. 6

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1. From the Directorate

- Steve Hodgkinson

Welcome to the Autumn 2005 Edition of CoRE of the Matter. As I write this I am mindful of the enormous amount that has happened in the National Research Centre for Growth and Development since the last edition. If we can cover just some of our recent progress in this edition then it will be a success.

In my view since the last edition the NRCGD has come of age. 2004 saw considerable effort by Centre Members in translating the concept of a Centre of Research Excellence into a fully functional 'virtual' research organisation. By the end of 2004 I think the establishment phase was complete and as we advance through 2005 the NRCGD is moving into an operational phase.

The size of this establishment / implementation task cannot be underestimated. While the contribution of all Centre Members is gratefully acknowledged, a special vote of thanks must go to Professor Gluckman (Director) for his leadership, unwavering enthusiasm and commitment to the Centre concept and to Alison Paterson (Chair, Board of Governance) for her skilful steering through the numerous issues that needed to be resolved in the start up period.

Key matters that have been addressed include:- the development of a sense of shared identity, branding and profile for the Centre; development and operationalisation of a Science Plan; development of a unified science contracting, reporting and payment system that operates effectively across the Centre's 4 partners and (now) nine sites; development of a strategic view for our science through involvement of a pre-eminent Science Advisory Panel to advise on science direction, performance and progress; staff appointments; development of policy; effective communication systems with all stakeholders – both internal and external and, finally, our early successes and highlights as outlined in the 2004 Annual Report.

For me key milestones that underscore the transition of the Centre from an establishment to operational phase include submission of our 2005 Science Business Plan to TEC (December 2004), submission of the 2004 Annual Report (March 2005), the 'Mid Term' Review (April 2005) and planning for the Centre's first full review of science by SAP now scheduled for July 2005. The latter two are discussed further below.

As we move through 2005 though our thinking is not about mid term roll over of funding or about the 6 year funding term of the Centre – it is far more strategic than that. Our thinking is about how to capitalise on our

successes and profile in positioning for longer term sustainability.

2. High Profile Science

Theme 4 / Major Project 7 Scientists

Is bleach involved in causing Alzheimer's disease?

Alzheimer's disease (AD) is a chronic and progressive neurodegenerative disorder that is caused by atrophy and death of nerve cells in the brain. It is the most common cause of dementia in the elderly and affects over 30,000 New Zealanders. Tragically there are currently no effective treatments for ameliorating nerve cell death in AD and only partial symptomatic relief is possible. An understanding of the mechanisms of nerve cell death would aid the development of neuroprotective agents for this condition. AD is characterised pathologically by two key lesions: amyloid-positive neuritic plaques and tau-positive neurofibrillary tangles. Additionally, inflammation occurs in AD brain and this might involve the generation of oxidants that are also thought to play an important role in AD pathogenesis. In our Theme 4 / Major Project 7 NRCGD-funded work we are particularly interested in how oxidants and inflammatory processes might contribute to neurodegeneration in neurological disorders such as AD.

We (Tony Kettle, Ursula Byrne, Richard Faull, Henry Waldvogel, Christine Winterbourn, Hannah Gibbons, Wendy Brooks, Mike Dragnow) initiated a pilot project to investigate potential generators of oxidants in AD using post-mortem human brain material (from the New Zealand Neurological Foundation Human Brain Bank in the Dept. of Anatomy) and cell culture models. We have discovered a massive accumulation of myeloperoxidase (MPO) in AD brain (see figure) but not in normal human brain. MPO accumulated in structures resembling tangles and plaques. We also showed that human neuroblastoma cells could be induced to express MPO under pathological conditions. MPO generates hypochlorous acid (HOCl, bleach) from H₂O₂ and Cl⁻. HOCl is a highly reactive oxidant that cross links proteins, inactivates enzymes, and reacts with amino acids to produce reactive aldehydes. MPO also oxidizes numerous endogenous substrates such as serotonin, dopamine and tyrosine to reactive free radicals. Thus, MPO accumulation in AD brain might generate a number of highly toxic reactive oxidants that could participate in neurodegeneration.

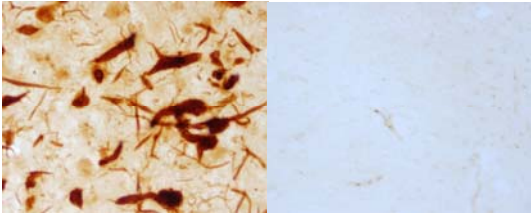


Figure - MPO expression in AD (left) and normal (right) human brain.

We are now engaged in a series of collaborative studies to determine whether MPO is active in AD brain and whether it plays a role in the pathogenesis of AD using a range of biochemical, histochemical, molecular and cell culture methods in our labs in Christchurch and Auckland. This project will provide important insights into the role of MPO and reactive oxidant species in AD and may identify novel targets and drugs for the treatment of AD.

3. Science Initiatives Fund

To create flexibility in resource allocation decisions for research areas of high strategic merit and priority a new contestable research fund has been established for 2005 with a provisional budget allocation of \$280Kpa. The Special Initiatives Fund is intended to respond to the challenge of the 2005 Science Business Plan which in turn has been informed by the Science Advisory Panel. A contestable funding round open to Centre Members was held in January / February 2005. The round attracted a great deal of interest from researchers and five applications totalling \$650K. These have now been fully assessed and recommendations will shortly be forwarded by a SAP sub committee to the Board for approval of funding decisions.

4. New Pilot Projects

Dr Geoff Asher

Gestational length in Red Deer and postnatal growth

Red Deer are unusual in that they vary the length of pregnancy in response to changes in maternal nutrition and this has a marked effect on the growth rate of resulting progeny. For this reason the Red Deer model may provide novel opportunities to understand hormonal mechanisms by which fetal nutrition influences postnatal growth and development. These observations are of great interest to our biomedical research. In a new collaboration, Liggins Institute Professor Jane Harding is teaming up with AgResearch's Dr Geoff Asher and other researchers to leverage off Dr Geoff Asher's existing trial and capability in corvine research. The team is measuring endocrine and metabolic parameters using methods available at the Liggins Institute to try to explain biochemical mechanisms of the phenomena.

Dr Mhoyra Fraser – Bettina Ikenasio-Thorpe

Central Mechanisms of Body Weight and Appetite Dysregulation in Obese Offspring – Prenatal and Postnatal Influences

Our Pilot Project aims to resolve major issues concerning our understanding of the mechanisms behind the association between nutritionally restricted intrauterine environments and the development of obesity in postnatal life. We will seek to identify the central mechanisms underlying the pathogenesis of body weight and appetite dysregulation, by investigating

steady state mRNA and protein expression of key energy regulating neuropeptides (pro-opiomelanocortin (POMC), agouti-related protein (AgRP), neuropeptide Y (NPY), and the leptin receptor-isoform B (ObRb) within the hypothalamus of obese offspring, which were prenatally exposed to undernourishment, and/or postnatally exposed to hypercaloric nutrition.

Results from these experiments will prove invaluable, since elucidation of the central mechanisms involved will markedly advance our understanding and may challenge current thinking regarding the etiologies of adult diseases.

5. Mid Term Review

The Mid Term (3 year) Review of the NRCGD was held at the Liggins Institute on April 20th. Acting Director Murray Mitchell, Chair Alison Paterson and Third Party Relations Manager – Steve Hodgkinson met with a joint Tertiary Education Commission and Ministry of Education based Committee led by Consultant Jordan Alexander. Professor Gluckman conferenced in from the UK. The NRCGD provided a written submission to the Committee in advance leaving the Meeting itself for more in depth discussion. The purpose of the review was to assess the Centre's performance against contracted objectives as part of the contract renewal process for its second 3 year funding period (July '06-June '09). However, even more importantly, the review was seen as an opportunity to profile the strategic nature of the NRCGD for NZ, our progress to date and direction. Overall the CoREs are achieving their potential and the investment to date (of all types) can be considered just too great for them to be considered purely in terms of their original 6 year life expectancy. Increasingly, therefore, the Centre's Board and management see a key role for themselves in profiling our contribution to NZ and positioning for a sustainable future. The review was very positive and constructive - we can expect a Report in June.

6. Science Review

The Centre is unusual in that it has involved its Science Advisory Panel at early stages of science programme development to ensure our research has every opportunity to meet the criteria of excellence, innovation, international competitiveness, knowledge transfer, training and network building. Now as the NRCGD enters its third year it is timely to assess the progress of our science towards the above goals. The Centre's first full review of science will be held July 12th – 15th and involve the following SAP members and many NRCGD researchers:

- Professor Bob Williamson, AO, FRS (Chair), University of Melbourne - molecular genetics
- Professor Sir Patrick Bateson, FRS, Cambridge University - population biology and genetics
- Professor David Edwards, Hammersmith Hospital - neonatology and neuroscience
- Professor Mark Hanson - University of Southampton - developmental biology
- Dr Ken McNatty AgResearch Ltd - reproductive endocrinology
- Professor Emma Whitelaw, University of Sydney - molecular genetics and imprinting
- Doug Wilson – pharmaceutical development - ex Boehringer Ingelheim

7. Comings and Goings

Professor **Bob Williamson** Chair of the Science Advisory Panel visited in early February for discussions. Bob spent a day and a half looking in some depth at the NRCGD's University of Auckland projects and collaborative projects with AgResearch. While here he also met with Directorate staff to map out Terms of Reference and Process for the SAP Review of science in July.

Late last year **Professor Peter Gluckman** was awarded the 2005 Inaugural Hood Fellowship. The Fellowships are provided by the Hood Fund, which was set up to mark Dr John Hood's contribution to The University of Auckland as Vice-Chancellor. It is an endowment fund which enables the University's top academics to travel to prestigious institutions abroad to further their research.

Peter is away for three months returning 7th July. He will be visiting Cambridge, Oxford, Glasgow, Edinburgh, Newcastle, Southampton and Tel Aviv to test new ideas he is developing as the basis for his ongoing writing and to support the design of empirical experiments. These visits will provide the opportunity for developing new insights into a number of theoretical challenges for testing with British collaborators, formalising new collaborations, and providing better awareness of the potential of some new epigenetic technologies.

Ayla Graf (Theme 1 - Major Project 2). Congratulations to Ayla and partner on the arrival of their son, Kaelin, born a few days ago. Ayla is on maternity leave and has suspended her PhD studies for one year. We would like to thank her for her commitment as student representative to the Executive Committee and wish her well in her new role as a mother.

Dr Jason Landon (Theme 1 - Major Project 2). Jason, who was one of the Centre's first post doctoral research fellows resigned at the end of April to take up a behavioural research position with the Ministry of Health. We would like to thank Jason for all his hard work and wish him every success in the future.

Mr Neil Prichard, Chief Operating Officer - We would like to say thank you and farewell to Neil who resigned recently. Unfortunately other commitments have made it impossible for Neil to continue to support the CoRE. We would like to acknowledge the enormous contribution he has made to the financial structure of the CoRE. We wish him and his family all the very best for the future.

A warm welcome to the following staff -

University of Auckland

Chris Krägeloh, Assistant Research Fellow, who is replacing Jason Landon working on Theme 1 - Major Project 2 with Bernhard Breier. His PhD research was about quantitative modelling of local preference changes in pigeons. Chris is excited about the opportunity of extending his behavioural research at the Liggins.

Fahimah Rahnema (Postdoctoral Research Fellow – Major Project 5). Fahimah started at the Liggins Institute at the beginning of February having completed her BSc (Hons) and PhD at Karolinska Institute, Stockholm. Fahimah's main project will be centered around epigenetic regulation of human implantation.

Her PhD project focussed on deciphering complexities that are associated with signal transduction in Basal Cell Carcinoma (BCC) of the lung which is the most common cancer in the Western world. Although BCCs hardly ever metastasize, invasive growth may cause

considerable local tissue destruction. BCCs mainly occur as sporadic tumors but can also be found in a hereditary form in the Nevoid Basal Cell Carcinoma Syndrome (NBCCS). The gene underlying the NBCCS is Patch 1 (PTCH1), a tumor suppressor gene that is mutated or deleted in these patients. Fahimah's thesis involved the cloning of a second receptor of the Hedgehog (HH) ligand (a key developmental gene), Patch 2 (PTCH2) and she continued her project to compare and investigate the role of these two homologues in the HH signalling pathway.

University of Otago - Christchurch

Karina Brown has recently joined the growing number of PhD students involved with CoRE research projects. She joined the Free Radical Research Group (Christchurch School of Medicine) last July after completing a MSc. (Biochemistry) at the University of Canterbury. Employed as an Assistant Research Fellow, Karina began working on a pilot project associated with Theme 5 looking at the effects of oxidative stress on global DNA methylation levels in a T-lymphocyte cell line. Our understanding is that after six months of employment Karina decided she was a student at heart and registered for a PhD.

Karina's PhD project is a continuation of the pilot project. She is currently evaluating the kinetics of enzymes involved directly with the methylation pathway. Methionine adenosyl transferase (MAT) synthesizes the principle methyl donor in the cell, S-adenosyl methionine (SAM), which is used by DNA methyltransferases (DNMT) to methylate specific cytosines within DNA. MAT and DNMT contain cysteine residues within their active sites, rendering these enzymes as potential targets for attack by reactive oxygen species (ROS). Under conditions of oxidative stress decreased DNA methylation levels could arise as a consequence of decreased activity of MAT (and/or DNMT), either through direct enzymatic attack or through inhibition of MAT by methionine sulfoxide (an oxidative product of methionine), resulting in reduced levels of SAM in the cell. Karina will investigate the impact of oxidative stress on DNA methylation levels in cells exposed to a variety of oxidative insults and determine how methionine oxidation specifically affects activity of enzymes influencing the methylation pathway.

Karina is a serious triathlete who fills most of her "spare" time training for events, racing or recovering! She also enjoys excursions away tramping, or mountain biking - crazy 12 hour events with mad work mates! Otherwise, you may find her attempting to be artsy-crafty or having fun times with friends and family.

University of Otago - Dunedin

Harriet Miles has temporarily relocated from the Liggins to Tony Reeve's Cancer Genetics Lab where she is validating real-time PCR methods for measuring DNA methylation in imprinted genes in IVF children. This project is part of Harriet's MD thesis which is in collaboration with Wayne Cutfield (Liggins) and Ian Morison (Dunedin).

Verity Oliver joined the lab one month ago with a freshly minted BSc Hons (1) in microbiology from Otago. Verity will be extending and refining Harriet's findings by applying the bisulfite sequencing method for measuring DNA methylation. This method has a much lower sample throughput than the real-time PCR method but

has the advantage that many CpG (DNA methylation sites) sites can be assessed simultaneously.

The Otago Genomics Facility had a significant boost at the beginning of February with the appointment of **Dongho Kim**. In two weeks Dongho will be submitting his PhD in biochemistry at Otago. Dongho is currently printing mouse 20K oligonucleotide arrays for CoRE members and other interested scientists. These arrays are of excellent quality and can be purchased by CoRE members at a discounted price.

Jun Watanabe joined the Cancer Genetics Lab one week ago as a postdoctoral research fellow. Following training as a urological surgeon Jun gained his PhD in cancer molecular genetics from Kyoto University Graduate School of Medicine. Jun is interested in cancer epigenetics as well as the modulation of the epigenetic programme by dietary and environmental factors.

8. Annual Report

I would like to take this opportunity to thank everyone involved in the compilation of the 2004 Annual Report which was submitted to TEC by the 31/3/05 deadline. The report has been very well received and without the cooperation and input of so many people would not have been produced to such a high standard. Special thanks also to the Graphics and Photography team of Val Grey and Warren Jones, University of Auckland for their excellent work in presentation of the report.

Many more photographs were taken than could be presented in the Report. The full set will shortly be available to members on CDs. Please e-mail

k.goldstone@auckland.ac.nz with requests. High resolution reprints are available from Warren Jones - e-mail w.jones@auckland.ac.nz with your order. We will shortly be distributing framed team photographs as a thank you.

Apologies to Tony Kettle for his inadvertent omission from the report on the MPO project and Alzheimer's disease (Annual Report, Page 15). As you can see from the 'High Science Profile' article above Tony is one of the main driving forces in this project.

9. Upcoming Events

1 June 2005

Board of Governance Meeting (Teleconference)

22 June 2005

Executive Committee Meeting (Teleconference)

11-15 July 2005

Scientific Advisory Panel – Review of Science

Date to be confirmed

NRCGD Epigenetics Workshop at the University of Otago. Contact Tony Reeve –

anthony.reeve@stonebow.otago.ac.nz

10. Contacts

Contributions to the next Newsletter are welcome and should be sent to Karen Goldstone (k.goldstone@auckland.ac.nz). If you would like to subscribe or unsubscribe to this newsletter or know of someone else who may want to receive a copy please contact k.goldstone@auckland.ac.nz