

# CoRE Of The Matter



NATIONAL RESEARCH CENTRE FOR  
GROWTH AND DEVELOPMENT

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## From the Directorate

It's been a busy month. The Centre's first Annual Report has been completed bar finalisation of the accounts and Board signoff and will soon be available for distribution.

Murray, Trisha (Accounts), and I have moved into a suite of offices on the second floor of the Liggins Institute which gives us a physical presence there.

Much hard work has gone into advancing contracts. At a recent meeting on 14 May between CoRE representatives and representatives of the Research Offices of the Host and partner Institutes a key decision was taken to consolidate the ~85 or so Centre contracts currently under management around Major Projects. This will enable simplification of the contracts and a reduction in numbers of 85 to approximately 20 and allow us to get back to our key focus – science.

Finally Peter and I attended a meeting of CoRE Directors and Managers at Massey. All the CoREs especially the multi-partner ones have experienced delays in their start up years and face common issues. The Ministry of Education is currently producing a discussion document on the CoREs.

Best wishes, Steve Hodgkinson

## Genomics Facility

The Otago Genomics Facility (OGF) (<http://genomics.otago.ac.nz/>) was the first high throughput gene expression microarray facility to be established in New Zealand. To establish the facility a grant of \$1.5M was provided to Tony Reeve in 1999 from the University of Otago. Now with funding provided from the NCRGD this will allow the printing of MWG oligo arrays (20K human and 10K rat) for CoRE members, the wider academic community and commercial customers. The OGF has considerable experience using this technology and the data analysis tools (usually learning the hard way!) so please contact us through the web site if you have any questions.

## Comings and Goings

- Peter Gluckman and Alistair Gunn travelled to San Francisco for the Annual Meeting of the Pediatric Academic Society in San Francisco.

- Peter Gluckman, Peter Lobie, Mark Vickers, and Wayne Cutfield attended the Pfizer's Satellite Workshop: GH and IGF factors and presented papers in Geneva, Switzerland.

## Appointments

Last month the Centre formally welcomed recent Post Doctoral Research Fellow appointments and students who have started PhD programmes. This month we introduce some of them to you.

- Harriet Miles (Clinical Research Fellow, Major Project 3)

Harriet is a British paediatrician working as an Endocrine Research Fellow. She trained at Nottingham University Medical School receiving a B.Med Sci (Hons)2:1 in 1992 and graduating as Doctor of Medicine and Bachelor of Surgery in 1994. Harriet's post graduate medical training has been in Paediatrics, Obstetrics and Gynaecology in New Zealand and the UK. Harriet holds a Paediatric National Training Number at Addenbrookes Hospital, Cambridge and has arranged to have a three year research period in New Zealand.

Harriet arrived at the Liggins Institute in March 2003 to work with Wayne Cutfield, Paul Hofman, and Mark Harris as an Endocrine Fellow. Her job involves alternating months working on research projects and clinical work at Starship Hospital. She is involved in the planning and running of a collaborative research project with Family Associates as part of the CoRE to look at the effects of In vitro fertilisation on anthropometric characteristics, endocrine parameters and DNA methylation in children between the ages of 4 and 10 years.

- Farhad Shafiei (Major Project 5)

Farhad completed his undergraduate and Masters studies in the department of Biochemistry at Otago University and did his PhD in the department of Molecular Medicine at the University of Auckland.

Farhad's PhD project was to identify the signal transduction pathways and the transcription factors involved in regulating a particular group of cell-surface adhesion molecules called the  $\beta 7$  integrins, which mediate the homing and retention of lymphocytes to mucosal sites and chronically inflamed tissues. They showed that the pro-inflammatory cytokine TGF- $\beta$

induces  $\beta 7$  gene expression by activating the JNK and p38 MAPK signalling pathways. Farhad has recently joined the National Research Centre for Growth and Development as a postdoctoral fellow and is interested in looking at the epigenetic regulation of gene expression in a human breast cancer model.

■ Arjan Scheepens (Major Project 6)

Arjan has been working on perinatal hypoxic/ischemic brain injury and specifically on neuroprotection since 1995. He graduated with a PhD from the Department of Pediatrics where he remained working as a post-doc for a year. Following this Arjan was employed as a post-doc by Prof. Carlos Blanco at the University of Maastricht in The Netherlands for 2.5 years. While there, Arjan set up and led a research team looking into the effects of various injuries and treatments (perinatal asphyxia, adult chronic mild stress, adult learning and memory and prenatal betamethasone) on developmental and adult neurogenesis. This in combination with studying the possible underlying mechanisms of action, namely the spatio-temporal changes in neural neurotrophin and growth factor levels.

Arjan's current interest lies in the interplay between perinatal brain injury, neurotrophic growth factors, stress and learning and memory and their effects on developmental and postnatal neurogenesis. This, with the primary aim of designing neuroprotective/neural rescue strategies for use in infants and preterm babies.

■ Hannah Gibbons BSc (Hons) (Major Project 7)

Hannah arrived from England in 1997 and worked as a Research Technician in the Molecular Neurophysiology Laboratory headed by Professor Janusz Lipski. In December 1998, she moved to the Molecular Neuropharmacology Laboratory where she worked with Professor Mike Dragunow as a Research Technician. In July 2000, Hannah started her PhD in the area of neuroinflammation whilst continuing to work in the laboratory, assuming the position of an Assistant Research Fellow. The CoRE postdoctoral position (Major Project 7, Neuroinflammation) follows on from research undertaken in Hannah's PhD and has allowed her to stay in an expanding field that is known to play a crucial role in the pathogenesis of several neurodegenerative diseases.

■ Christopher Rumball (Major Project 1)

Christopher has recently arrived in Auckland from Invercargill having worked at Christchurch and Southland Hospitals over the past year, in both general medicine and emergency medicine. 2002 was spent studying at Liverpool in tropical medicine, followed by six months working for Medecins sans Frontieres, something he hopes to do again in the not-so-distant future. At the Liggins Christopher is beginning a PhD in foetal physiology supervised by Jane Harding.

■ Ayla Graf (Major Project 2)

Ayla trained as a technical biological assistant in Germany. In 1989 she immigrated to NZ and made use of the many opportunities NZ offered and explored various employments. As a tour guide, bushcraft instructor, and volunteer for DOC, Ayla was able to develop her passion for the great NZ outdoors. Her later work with people with physical and intellectual disabilities sparked Ayla's interest in studying psychology and education.

Thanks to the encouragement from her partner and family, Ayla began her tertiary education four years ago.

During her undergrad and Honours years, Ayla became particularly interested in applied and experimental behaviour psychology, as well as neuropsychology and neuroscience.

Now, Ayla is planning to explore these areas further by making use of the multidisciplinary approach at Liggins. Within her research group (CoRE Major Project 2), she will study the effects of early life nutrition on self-control behaviour and on changes in brain morphology in rats. Dams and offspring will be exposed to various nutritional environments, e.g. undernutrition during pregnancy or overnutrition during lactation. Differences in self-control behaviour between the experimental groups will be assessed in operant chambers by measuring several response dimensions, such as response latencies and frequencies. Self-control is defined as the choice of a large, delayed reinforcer over a small, immediate reinforcer. Therefore, to quantify this behaviour, rats will receive repeated simultaneous choices between a small reinforcer that is delivered shortly after a response to one alternative and a larger reinforcer that is delivered after a certain delay to another response alternative. The shorter delay will vary within a session, according to the rat's previous response. By changing the delay, the value of the larger reinforcer will increase, decrease, or equal the smaller reinforcer. The indifference point, the value at which the rat chooses either reinforcer with equal frequency, will be used to quantify self-control. Once the behavioural component of the experiment has been completed, I will assess the effect of the diets on differences in the morphology of brain structures. Measurements will include cortical, ventricular, hippocampal, hypothalamic, and arcuate nuclei volumes and neuron/glia ratio.

■ James Elworthy (Major Project 5)

James has recently commenced a PhD under Professor Tony Reeve. His project will form part of Project 5 of the CoRE and will investigate the relationship between DNA methylation patterns in response to heritable alterations in folate metabolism.

James completed his BSc (Hons) in Biochemistry at Otago University in 2001. For the next two years he continued to work in the Biochemistry department as an Assistant Research Fellow, investigating domain assembly of some quirky invertebrate haemoglobins. Most of his days were spent performing atomic force microscopy, LC/MS and computer-based protein modelling.

James' current project germinated from a paper describing how genomic DNA methylation levels are dramatically reduced in humans with a common polymorphism involved in folate metabolism, under low dietary folate conditions. DNA methylation is an important epigenetic trait, regulating DNA integrity and gene expression, and aberrant DNA methylation has been implicated in a number of pathologies, including heart disease and some cancers.

Firstly, he wants to see if by simply re-supplementing folate (a single-carbon source), he can restore normal genomic DNA methylation levels in these individuals. Additionally, James wants to see what specific elements of their DNA are being hypomethylated under low folate conditions, i.e. are any genes being preferentially hypomethylated and hence having their expression altered, that may be facilitating a propensity toward disease?

■ Larissa Christophidas (Major Project 6)

Larissa's interest in medical research led her to study a degree in science at the University of Melbourne, where she majored in Pharmacology. She particularly enjoyed her introduction to scientific research by way of a summer studentship and her Honours year research project, which focussed on the regulation of the hormone leptin by the sympathetic nervous system. Larissa has worked for two biotechnology companies. Her first position involved studying oxidative phosphorylation; the second involved screening natural product extracts for potential antibiotic compounds.

Based at the Liggins Institute Larissa's PhD project is part of Theme 3 Project 6: Saving the Immature Brain. Using the P3 rat brain injury model as a model for the brain injuries seen in extreme pre-term infants, her work will focus on endogenous repair factors induced in the brain after injury. Larissa has immensely enjoyed the beginning of her PhD studies and is looking forward to making more of a contribution to the CoRE over the next few years.

■ Sumudu Ranasinghe (Himani Sumudumalee; Major Project 6)

Sumudu arrived from Sri Lanka seven years ago. Her passion for science guided her to start her scientific career, at University of Auckland, as a Bachelor of Technology majoring in Biomedical Science in the year 2000. In 2002/2003 Sumudu had the opportunity to step into the practical aspect of science through the summer studentship programme, in which she investigated the changes in elastin content of small airways in chronic obstructive pulmonary disease.

In 2003, she did her honours project with Professor Richard Faull's research group, in which she demonstrated that cell proliferation occurs in the subependymal layer along the entire ventricular system of the normal adult human brain. Now, Sumudu is doing her PhD at the Liggins Institute with Professor Murray Mitchell and A/Professor Chris Williams, investigating the mechanisms of vulnerability in the immature brain injury.

■ Joanne Lim (Major Project 7)

Jo completed her Bachelor of Commerce (majoring in Marketing) and Bachelor of Science (majoring in Pharmacology) conjoint degree in 2001, at the University of Auckland. She continued her studies in science, and pursued a Masters degree in Pharmacology for the next two years. Jo's project was in the area of anti-cancer research, under the supervision of A/Prof James Paxton. During this time she also completed a summer project with A/Prof Nick Holford in pharmacometrics.

This year Jo is looking forward to her PhD in Prof Mike Dragunow's lab. She will be investigating mechanisms of neuroinflammation in the human brain. In addition, she is actively involved in postgraduate student affairs, and is Vice-President of the FMHS PGSA.

### NRCGD Science Day at Massey University

Contributed by Hugh Blair and Catriona Jenkinson

■ The effects of periconceptual feeding of lotus on ewe and lamb endocrinology and fetal and lamb survival - Tom Barry and Tim Parkinson

Experiments have been conducted on Massey's dryland farm in the Wairarapa, near Masterton. Control ewes were mated on perennial ryegrass-based pastures, the

normal feed on NZ farms. Treatment ewes were mated on the condensed tannin-containing legume *Lotus corniculatus* for 63 days, which increases the absorption of essential amino acids. Ewes mated on lotus consistently had higher lambing % and in one study lamb mortality between birth and weaning was reduced. Other experiments have been conducted with ewes grazing drought pasture during mating and therefore losing weight.

Supplementing with willow cuttings for 70 days during mating increased lambing % and reduced lamb mortality in some but not all experiments. Willow contains condensed tannins and is higher in protein content than drought pasture; it can therefore be expected to also increase the absorption of essential amino acids.

These experiments suggest that increasing the absorption of essential amino acids in ewes during mating and early pregnancy definitely increases lambing % and may reduce lamb mortality between birth and weaning. Analysis of the data suggests that to measure effects on lamb mortality we need to increase ewe numbers per group from 100 to 300-500. We have increased ewe numbers to 300 in our 2004 expt. and have also fed lotus longer into pregnancy than in previous years. Mating has been more condensed this year, by running all ewes with vasectomised rams before intact rams were introduced. We have also taken blood samples from 100 ewes/group this year, at intervals throughout the study. Ultrasound pregnancy scanning will be done in early June.

The field studies are supported by a grant from Meat and Wool Innovations (i.e. sheep farmer levy money). We are applying to the CORE to investigate the mechanisms of how these nutritional treatments at mating/early pregnancy might increase lamb survival between birth and weaning.

■ The effects of dam's uterine environment on the development of her daughter's mammary gland and uterus - Catriona Jenkinson

A low plane of nutrition during pregnancy restricts the growth of the ovine fetal mammary gland. Discussion was centred round an experimental design to firstly, verify that these large effects on fetal mammary gland development are repeatable and, secondly, to determine if the inhibition of growth in the fetus restricts future lactational performance.

■ Preliminary results from the 2003 mid-pregnancy stress trial - Rene Corner

Lamb birthweight has important implications for survival particularly in multiple born lambs. Farmers can manipulate birthweights to a degree by either feeding pregnant ewes on a high level of nutrition or by mid-pregnancy shearing. The mechanism by which shearing increases birthweight and the post-natal effects on the progeny in terms of hypothalamic-pituitary-adrenal axis function, metabolism and behaviour are unclear. In addition the intergenerational effects of dam nutrition during pregnancy on twin and triplet born lambs has not been well characterised.

We conducted two studies in 2003. The first study explored the effects of mid-pregnancy shearing. The findings of that study were yarding plus the 24 hour fast commonly associated with shearing did not produce an increase in birthweight. However shearing produced an increase of 0.3kg in lamb birthweight compared with lambs born to control animals. Therefore indicating that the birthweight effects of shearing is not due to fasting

and yarding associated with shearing. Mid-pregnancy shearing had no significant effect on ewe and lamb behaviour in the 12 hrs after birth. The lamb's cortisol response to castration was significantly different between singleton and twin lambs born to mid-pregnancy shorn ewes with single lambs from shorn ewes having the greatest cortisol response. In 2004 we aim to repeat this study in order to determine the repeatability of this finding. The second study explored the effects of mid- to late-pregnancy nutritional stress in twin and triplet lambs. The behaviour of the year old twin and triplet ewe hogget progeny born to either adequately or inadequately fed ewes was assessed using an Arena test and the results showed no differences in behaviour. An insulin tolerance test was also conducted on the ewe hoggets and the results showed no difference in the cortisol and glucose response. In 2004 we aim to determine the reproductive success of these hoggets by recording mating success and lamb birthweights.

- The effects of dam's uterine environment on the development of her offspring's skeletal system - Elwyn Firth

Further discussion was requested on the use of singletons as opposed to twins in studying the effect of genetics (fat/lean) of the fetus on birth weight and size, as well as the relationship between lean and mineral masses in the new born and growing lamb.

- The long-term effects of being born to an overfed teenage mother - Paul Kenyon, Steve Morris and Dave West

Currently 30% (2.4 million in total) of hogget's (7 – 8 months old) in New Zealand are mated to lamb at 12 months of age, instead of the traditional 2 years of age system with the proportion increasing each year. Currently farmers are offering very high levels of herbage to their in-lamb hoggets to try to ensure that her mature weight and lifetime performance is not impaired. The effects of this are not well understood. Studies conducted at the Rowett lead by Jacqueline Wallace have examined the affects of pregnancy nutrition in adolescent ewes on lamb birth weight and survival with high level of nutrition being associated with small birth weights and low survival rates. However the hoggets in these studies are significantly younger (5 – 7 vs. 8 – 9 months) than hoggets traditionally mated in New Zealand, they tend to have higher mating weights (44 – 48 vs. 32 – 45 kg), they are fed concentrates rather than pasture, embryo transfer is used. Therefore extrapolation of these results into the New Zealand farming system is problematic.

In the 2003, Massey conducted study 206 singleton-bearing eight-month-old ewe hoggets were randomly split into 3 nutritional treatments 13 days after the mid-point of mating. The 'low', 'medium' and 'high' nutritional groups were managed in such a manner that they increased total live weight during pregnancy by 12, 20 and 28 kg respectively. 'High' group hoggets had a greater depth of body fat in late pregnancy (2.5, 3.8 and 5.4 mm respectively for 'low', 'medium' and 'high' hoggets). However, these treatments failed to affect lamb birth weight although by weaning 'low' group lambs were significantly lighter than all other groups (by 2 kg).

Potential future studies of the offspring were discussed. In addition a further study is being conducted at Massey University in 2004 to re-examine the effects of pregnancy nutrition, under pastoral conditions on lamb

birth weight and survival and therefore another co-hort of offspring will be available.

- 2003 results from the Suffolk x Cheviot maternal constraint model - Hugh Blair

A summary of the key outcomes to date, were presented. Data analyses showed that the Cheviot mothers suppressed the birth weights of crossbred lambs to about the same weight as cheviot lambs. Suffolk mothers elevated birth weights of crossbred lambs to about the same weight as Suffolk lambs. Experimental procedures for 2004 were discussed.

- Integrating the effects of individual loci with quantitative genetic and environmental variance into a model of fetal growth - Patrick Morel, Hugh Blair and Ryan Sherriff

Growth in animals is a complex process, which involves interaction between animal genotype and environment. A superior understanding of the growth process can be obtained when all the available information and concepts are synthesized, transformed into mathematical algorithms, and integrated into a growth simulation computer program. Recently, a theoretical simulation model linking individual gene actions, pig growth modelling and non-linear optimisation mathematics has been developed to investigate genome by diet nutrient interaction.

- Finding Quantitative Trait Loci (QTL) for muscle and fat traits in Texel sheep - Patricia Johnson

By mating Texel sires that are heterozygous at DNA markers around Myostatin to commercial dams, we produced two identifiable groups of progeny (those inheriting different copies of the marker from their sire). We were able to show that those progeny that inherited a particular copy of the marker had increased leg muscle weight and decreased leg fat weight but with no differences in leg bone weight or meat quality. Such QTL searches offer the opportunity to define regions of DNA where variations in the DNA account for variations seen in phenotypes, which can then lead on to the discovery of the underlying gene/s involved.

## Upcoming Dates

8 or 9 June (To be confirmed)

Science Planning Day, Dunedin. Focus on genomics projects.

28 June

New Zealand Society of Animal Production/NRCGD joint session on *Forming the partnership between animal production and medical science: Influence of early development on lifetime outcomes across agriculture and health including models for the study of metabolism and health*. For further details, contact Steve Hodgkinson.

Agenda items for Executive Committee Meeting to Barbara Sessions, (k.goldstone@auckland.ac.nz) 1 June.

Executive Committee and Board of Governance Meetings 9 June (by Teleconference).

## Summary

Contributions to the next Newsletter are most welcome and should be sent to k.goldstone@auckland.ac.nz by the second Friday of each month.