Reporting in Nature; controlling good and bad bugs

New research in *Nature Immunology* shows Pellino3 protein acts like a braking system to prevent over-production of interferon in response to viral insult. This highlights both a new physiological role for Pellino3 and a new autoregulatory network for controlling type 1 interferon expression.

Conway Fellow, Professor Sean Callanan of UCD School of Veterinary Medicine collaborated on the project led by Professor Paul Moynagh, Institute of Immunology, NUI Maynooth.

"Pathology provided a valuable assessment of the effects of encephalomyocarditis virus in Pellino 3-deficient mice, enhancing the important translational aspects of this work that has implications in the development of therapies to tackle debilitating immune-mediated diseases", said Professor Callanan.

Gut microbiota composition correlates with diet and health in the elderly according to research published in *Nature* involving Conway Fellow, Dr Lorraine Brennan of UCD School of Agriculture & Food Science.

The study, led by Dr Paul O'Toole, University College Cork measured the faecal microbiota composition of 178 elderly people with an average age of 78 years and resident either in the community, day-hospital, rehabilitation or in long-term residential care.

The UCD team performed metabolomic analysis of faecal water and showed that the faecal metabolome differed based on the community setting of the subject and co-varied with measures of frailty.

"Collectively, the data support a relationship between diet, microbiota and health status, and indicate a role for diet-driven microbiota alterations in varying rates of health decline on ageing. It also highlights the potential role of metabolomics in identifying biomarkers of health and healthy aging", said Dr Brennan.

References

Claesson MJ et al. Gut microbiota composition correlates with diet and health in the elderly. Nature 2012 doi:10.1038/nature11319

Siednienko J et al. Pellino3 targets the IRF7 pathway and facilitates autoregulation of TLR3- and viral-induced expression of type I interferons. Nature Immunology 2012 13 (11); doi:10.1038/ni.2429

Conference Success

Conway Fellows, Dr Chandralal Hewage, Dr Lorraine Brennan and Professor Paul Malthouse were part of the local organising committee for the EUROMAR 2012 conference held from 27 June – 5 July in UCD.

EUROMAR is an international scientific society dedicated to advancing magnetic resonance research. 850 delegates from 46 countries attended plenary lectures, session lectures, tutorial sessions, oral and poster presentations and scientific exhibitions. Two satellite meetings were held in conjunction with the conference; XeMat 2012 and COST Action 'European Network for Spin Hyperpolarisation Physics and Methodology in NMR and MRI'.

Systems Biology Ireland (SBI) led by Professor Walter Kolch organised SysMed 2012; an international conference on systems medicine that took place in Carton House from 10- 13 September 2012. Systems medicine has emerged as a new approach to personalised health care that uses biological/medical data integrated with mathematical and computational modelling to understand the underlying mechanisms of disease and develop new strategies for individualised diagnosis, treatment and prevention.

Additionally, a pre-conference workshop showcased the FP-7 Health funded ASSET project that uses systems biology approaches to improve therapies for childhood cancers.

SFI Director, Prof Mark Ferguson (left) with Dr Chandralal Hewage at EUROMAR 2012.

(L-R) Prof Boris Kholodenko, SBI Deputy Director; Christina Kyriakopoulou, EC Health Directorate; Prof Walter Kolch, SBI Director at SysMed 2012

Grant Thornton Corporate 5k Team Challenge

Two UCD Conway Institute teams competed very successfully in the inaugural Grant Thornton Corporate 5k Team Challenge around Dublin Docklands on Thursday, September 6th 2012. The joint venture between Athletics Ireland and Grant Thornton is designed to encourage social running among employees from Dublin business communities

Nearly 450 teams, comprising 1700 individuals competed in the event that saw the 'Conway Tigers' coming home in 5th place in the mixed category and two of Conway runners finishing in 7th place in the men's and women's races.

Event ambassador; Olympian and former London Marathon winner Catherina McKiernan said "The spirit of the event was fantastic. It was a welcoming sight to see so many runners complete the course, while also managing to enjoy themselves at the same time".

(L-R) Representing UCD Conway Institute: Claire Robinson, Aidan Boland, Maike Jurgens, Dan Dowling, Roisin Neary, Dara Lundon, Paddy O'Leary, Leona Connolly

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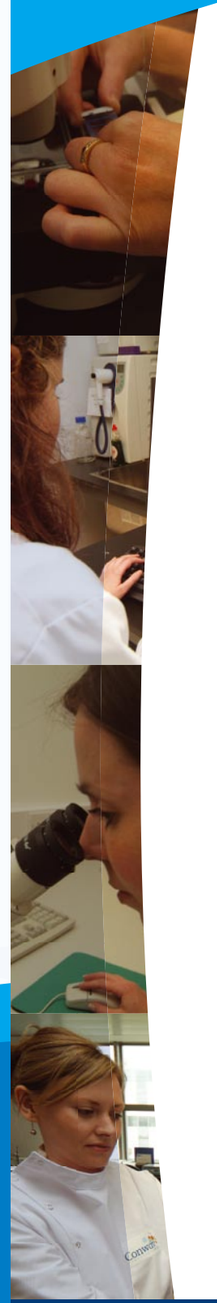
conway focus



Benefits of Low GI Diet in Pregnancy

Women who choose a low glycaemic index (GI) diet from early pregnancy will reduce the likelihood of excessive gestational weight gain and maternal glucose intolerance according to a research study involving 800 women attending the National Maternity Hospital, Dublin.

Conway Fellow, Professor Fionnuala McAuliffe led the randomised control trial of 800 women without diabetes on their second pregnancy who previously delivered an infant weighing more than 4kg.

400 women continued to follow their normal dietary pattern throughout the pregnancy without being given any specific advice on gestational weight gain.

400 women attended a dietary education session with the research dietician at 16 weeks to inform them of the healthy eating guidelines in pregnancy and encourage them to choose low glycaemic index foods such as high fibre cereal and brown rice without reducing their calorie intake. This group had two follow up sessions at 28 and 34 weeks gestation to reinforce this low GI diet regimen.

The findings of the research, published in the *British Medical Journal*, showed an average weight gain of 13.7kg among women who remained on their usual diet during their pregnancy, against an average weight gain of 12.2kg among women who changed to a low GI diet.

Commenting on the findings, Professor McAuliffe said, "Excessive weight gain during pregnancy is associated with an increased need for delivery by Caesarean section, a higher likelihood of post pregnancy weight retention, and a higher predisposition to obesity in later life.

This research has shown that switching to a low GI diet in pregnancy is a simple, safe & effective measure to improve maternal glucose homeostasis and reduce gestational weight gain."

Gestational weight gain is one of several factors influencing infant birth weight. Macrosomic or 'large for gestational age' infants are predisposed to a variety of adverse obstetric and neonatal outcomes, are more likely to be obese in childhood, adolescence and early adulthood and are at a greater risk of cardiovascular & metabolic complications later in life.

However, this study showed that a low glycaemic index diet in pregnancy did not reduce the incidence of 'large for gestational age' infants in a group of women at risk of foetal macrosomia.

This research by Professor McAuliffe and her team is part of a wider EU FP7 funded collaborative project entitled 'Early Nutrition' that aims to provide evidence-based recommendations for optimal early nutrition that incorporates long-term health outcomes. World Health Organisation statistics in 2010 highlighted 43 million children under five years were overweight. Childhood obesity predisposes individuals to other childhood diseases and premature death. Being overweight and obese is the 5th leading risk for deaths globally.

The 'Early Nutrition' project teams, including 30 academic partners, 3 industry partners and 4 small-medium enterprises, are exploring current key hypotheses on the likely cases and pathways of early programming of obesity risk.

Reference:

JM Walsh, C McGowan, R Mahony, ME Foley, FMcAuliffe. Low glycaemic index diet in pregnancy to prevent macrosomia (ROLO study): randomised control trial. BMJ 2012;345:e5605 doi:10.1136/bmj.e5605 (30 August 2012)

EARLYNUTRITION
Long-term effects of early nutrition on later health

Director's Message

Welcome!

The last quarter has been a busy time for the Institute. I congratulate all those who participated in the annual UCD Conway Festival of Research & Innovation on September 20th and especially the 2012 UCD Conway Festival medal winner, Kate Byrne. In addition to celebrating the achievements of Conway researchers in the previous year, the programme expanded to incorporate two dedicated open forum sessions focused on industry engagement and gender issues impacting early career researchers. More detail on the event can be read in this issue.

Members of the newly constituted scientific advisory board for the Institute met Conway Fellows and representatives of their research teams during the course of the first meeting on October 8th & 9th in the Institute. This group of leading international scientists from research areas aligned to that of the Institute will undoubtedly provide valuable critique of our research and innovation strategy as well as recommendations on future direction.

Professor Walter Kolch
Director

2012 UCD Conway Festival of Research & Innovation

Doctoral candidate, Kate Byrne was awarded the 2012 UCD Conway Festival of Research & Innovation gold medal, sponsored by Roche for her research to develop a mathematical model describing the signalling network activity controlling cancer cell migration.

Kate is carrying out her studies under the supervision of Professor Boris Kholodenko in Systems Biology Ireland and UCD Conway Institute. She initially won the systems biology moderated poster category before joining five other category winners for a Dragons' Den style finale. Kate's concise overview of her project and its innovative potential most impressed the judging panel.

Cell migration is vital for cancer cells to invade and metastasise. The process is controlled by the dynamic interaction between two members of the same family of signalling proteins; Rac1 and RhoA, via an intermediary named PAK.Kate Byrne has developed a mathematical model that describes how these two signalling proteins interact and validated this model using experimental data from a breast cancer cell line.

"We were able to arrest cell migration completely by causing PAK inhibition and then maintain this using low inhibitor concentrations because of the bistable nature of the signalling network", she said.

This research shows early indications that PAK is a desirable drug target given that cell migration is completely dependent on PAK activity.

New additions to the 2012 festival programme were two open forum sessions. The early career researcher open forum, presented in conjunction with the UCD Research Staff Association, raised many of the issues facing young women in science today. The gender-science relationship is a particularly relevant topic in the context of the European Commission proposed framework for *Horizon 2020* that will highlight the need to use the potential and talent pool of women more extensively and effectively. The session on fostering industry-academia engagement was also timely given the increasing emphasis funding agencies are placing on industry collaboration in academic research. Dr Conor Hanly, ResMed Inc; Dr Ivan Coulter, Sigmoid Pharma and Dr Elaine Harris, Innovation21 had valuable insights into how scientists can work with industry successfully.

Professor Zena Werb, University of California San Francisco; Professor Finian Martin, UCD and Dr Eileen Furlong, European Molecular Biology Laboratory (EMBL), Heidelberg were the keynote presenters at the conference on September 20th in UCD Conway Institute.

Dr Hugh Brady, UCD President presents PhD student Kate Byrne with the 2012 UCD Conway Festival gold medal, sponsored by Roche.

Hierarchical Model for Evolution of Genetic Interactions

An unprecedented comparison of the genetic architecture of two organisms separated by an estimated 400 million years of evolution has revealed global trends that arguably exist in all eukaryotic species.

The findings of the international collaboration that included Conway Fellow, Dr Gerard Cagney; Professor Padraig Cunningham and Dr Derek Greene, UCD School of Computer Science & Informatics; and PhD student Colm J. Ryan were published in *Molecular Cell.* Genetic, or epistatic, interactions report on functional dependencies between genes. They can be used to describe the cross-talk between pathways and processes and to reveal how groups of proteins and complexes work together to perform higher level biological functions.

Until now, the only genome wide genetic interaction network available was for *Saccharomyces cerevisiae*, making it difficult for scientists to compare the evolution of genetic interactions across species.

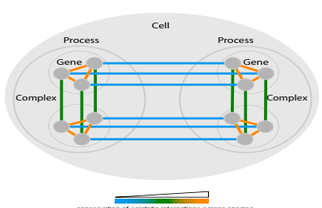
To address this, the research team constructed a genome scale, quantitative genetic interaction network for *Schizosaccharomyces pombe*; a fission yeast that in many ways (e.g. splicing, RNAi machinery) is more similar to metazoans than *S. cerevisae*.This provided phenotypic signatures for 60% of the nonessential *S. pombe* genes and assigned function to 144 previously uncharacterised genes including mRNA splicing & DNA damage checkpoint factors.

Comparison of the two networks provides evidence for a hierarchical model of the evolution of genetic interactions, with conservation highest within protein complexes, lower within biological processes, and lowest between distinct biological processes. Despite the large evolutionary distance and extensive rewiring of individual interactions, both networks retain conserved features and display similar levels of functional crosstalk between biological processes suggestive of general design principles of genetic interactions."

This analysis provides valuable insight into the evolution of biological systems and also has practical implications for the identification of epistasis in mammalian systems, a phenomenon believed to account for part of the missing heritability of complex human diseases." said author Colm J. Ryan.

"We hope that conserved trends identified in both species may be used as guidelines to improve the search for epistasis in genome wide association studies and also for the rational design of genetic interaction screens in metazoans."

Reference
Ryan et al. Hierarchical Modularity and the Evolution of Genetic Interactomes across Species. Molecular Cell 46, 691-704, June 8, 2012.



Depicting the conservation of epistatic interactions across species

EU Research Effort to Fight Diabetes using Oral Nanomedicines

The European Commission has awarded FP7 funding for a new research project as part of efforts to find more effective treatments for diseases such as diabetes.

The multi-disciplinary TRANSINT (oral nanomedicines) consortium combines expertise in pharmaceutical nanotechnology, biochemistry, immunology, toxicology, biology and physiology with the aim of developing novel nanocarriers to orally deliver a range of peptides for the treatment of diabetes, obesity and pain.

Diabetes is one of the most devastating diseases worldwide. In 2011, there were 366 million patients suffering from diabetes globally and at least 4.6 million people died from the disease.

TRANSINT researchers will use nanotechnology to explore new ways of successfully delivering insulin orally as an alternative to insulin injections currently used daily by diabetic patients to manage their disease. This convenient and safe way of taking the drug would significantly improve patient compliance with their medication and improve the quality of life of patients with diabetes. Two other unnamed peptides owned by large pharmaceutical companies are also being evaluated.

With a total budget of €11 million, the TRANSINT project brings together seventeen leading European research organisations and major pharmaceutical industrial partners, including Sanofi and Roche Pharma.

The TRANSINT project is led by Professor María José Alonso, University of Santiago (USC) and Conway Fellow, Professor David Brayden is the deputy coordinator.

Professor Brayden and his UCD research team will provide one type of nanocarrier, examine nanocarrier and peptide transport across intestinal tissue and use high content screening to look at particle uptake and cytotoxicity.

Professor Brayden commented: "This was a fantastic grant to secure as we were able to leverage the SFI Irish Drug Delivery Network in promoting three Irish partners, including UCC and Sigmoid Pharma as well as UCD. We will be working with some of the best oral delivery and 'nano' groups in Europe and, because 'big pharma' are involved, we have a real chance of translating positive preclinical data to patient care."

New Genes Associated with Diabetic Nephropathy Risk

An international consortium (GENIE) led by researchers at the UCD Diabetes Research Centre; Centre for Public Health, Queen's University Belfast; The Broad Institute of MIT/ Harvard and the University of Helsinki has discovered genes associated with risk of diabetic kidney disease.

Kidney disease is a common and serious complication of diabetes and it is associated with a greatly increased risk of heart attack and stroke. Globally, diabetic kidney disease is now the leading cause of end stage kidney failure requiring dialysis or kidney transplant.

Up to now scientists and clinicians were aware that only some patients with diabetes will develop kidney disease but the basis of this susceptibility was not known. The researchers carefully analysed over two million DNA markers in the genome of each person with diabetes who participated in the gene scan. In the largest study of its kind, the investigators recruited 4,750 patients with diabetic kidney disease and almost 7,000 patients with long-standing diabetes but with no evidence of kidney disease.

Their findings, published in the journal *PLoS Genetics*, demonstrate that changes associated with two genes; AFF3 and ERBB4, increase the risk of kidney disease. When the researchers experimentally altered the levels of these genes in kidney cells, they were able to mimic disease.

Conway Fellow and lead investigator of the UCD group, Professor Catherine Godson said, "These new research findings are very important as they define mechanisms that underpin the development of this devastating disease. This research helps accelerate development of new and effective therapies".

This work is supported by the US-Ireland research and development programme, a collaborative initiative funded by Science Foundation Ireland, the Northern Ireland R&D Office and the US National Institutes of Health.

Reference
Sandholm et al. New Susceptibility Loci Associated with Kidney Disease in Type 1 Diabetes. PLoS Genetics 8(9): e1002921 doi:10.1371/journal.pgen.1002921 September 2012

Regulating Protein Synthesis

New research by an international team of scientists including UCD Conway's Dr David O'Connell provides strong evidence that calmodulin interacts directly with functional ribosomes and plays an important role in the calcium dependent regulation of protein synthesis.

Calmodulin (CaM)is a calcium binding protein that is highly conserved within eukaryotic organisms. In response to intracellular calcium level changes, CaM regulates a large number of proteins in many signalling pathways.

Several studies have provided strong evidence that calcium plays a crucial role in regulating protein translation and indeed that CaM antagongists block the initiation of protein synthesis.

Protein translation takes place at the 80S ribosome, which consists of two smaller subunits: 40S and 60S. In this study, the team analysed the interaction of CaM with purified 80S ribosomes and polyribosomes using surface plasmon resonance technology.According to Dr O'Connell, "We identified putative CaM binding sites in two previously identified ribosomal CaM targets and synthesised these as linear peptides. Then, using a cell-free, in vitro translation system, we found these synthetic peptides to be potent inhibitors of protein synthesis".

Reference
Behnen et al. Calcium-Dependent Interaction of Calmodulin with Human 80S Ribosomes and Polyribosomes. Biochemistry 2012, 51, 6718-6727 doi:10.1021/bi3005939