Is Eolai Mise

Rinneadh agallamh ar ceathrar againn ó Institúid Mhic Con Mhí do chlár nua ar RTE Raidio na Gaeltachta le deanaí. Rachaidh an chlár nua seo darbh ainm 'Ar Strae sa tSaotharlann' i ngleic leis an eolaíocht agus an timpeallacht. Labhair Sean MacFhearraigh, Sinead Nic An Ultaigh, Tiarnán Ó Máille agus mé féin faoin taighde éagsúil atá ar bun againn. Labhraíomar faoi neart réimsí taighde ó fiobrois scámhoige go galar Alzheimer. Rinneamar cur sios agus plé ar gnáth lá agus na rudaí a bhíonn ar siúl sa tsaotharlann anseo san institúid don lucht éisteachta. Mhiníomar dóibh go ndéanamar taighde áirithe chun eolas a fháil ar na galair éagsúla chun coir leighis a bhaint amach do na daoine a bhíonn ag fulaingt de bharr na galair seo. Tá an-chuid taighde tabhachtach ar siúl anseo san institiúd a d'fhéadfadh tionchar mhor a bheith aige ar shaol daoine inár dtimpeall. Is maith an rud e gur féidir plé a dhéanamh ar an taighde seo tri mhean na Gaeilge le mhuintir na Gaeilge. Bígí ag faire amach don chlár nua 'Is eolaí mise' ar Radio na Gaeltachta, ina dteannta is féidir é a fháil ar podcast ar http://www.rte.ie/rnag/arstraesatsaotharlann.html

Robert Lumsden

Guiding scientists through the glycan analysis maze

Postdoctoral researchers from the National Institute for Bioprocessing Research & Training, under the supervision of Conway Fellow, Professor Pauline Rudd, published a review of available technologies for protein glycosylation analysis in the October issue of Nature Chemical Biology.

Glycosylation, the most common post-translational modification conferred on proteins, is the feature that most influences the function of proteins and their biological activity. Due to their diversity, glycans are finely-tuned information carriers and there is now a renewed emphasis on their analysis.

With specific changes in the glycosylation process occurring in health & disease, glycan analysis can provide both diagnostic and prognostic information. It is also useful in drug discovery and production to comply with regulatory requirements for monitoring critical features of therapeutic glycoproteins and to establish connections between glycan structure and their functions.

However, researchers face a number of challenges in relation to glycan analysis primarily due to the diversity of molecular structure, construction sequence and the extent of possible linkages with lipids or peptides. Additionally, naturally occurring glycoproteins are typically only present at low levels and, currently, there is no universal method for rapid and reliable identification of glycan structure.

In reality, it is the research goals of the particular project that dictate the most appropriate method of analysis. Researchers must not only be aware of the techniques available but what information these techniques or combination of techniques will provide. The authors succinctly stratify the major technologies routinely used for structural N- and O-glycan analysis and describe the type of data each provides.

They classify the approaches according to whether glycans are in intact glycoproteins, are chemically, enzymatically released glycans or are glycoproteins themselves. Each approach can give complementary information so it is important at the outset to decide the level of data required, whether quantitative or qualitative data is needed and how much biological material is available for analysis.

This work was made possible through funding from Science Foundation Ireland, the EU FP6 Glyfdis and Eurospan programmes, the Royal Society and Chief Scientific Office of the Scottish Government.

Reference
A systematic approach to protein glycosylation analysis: a path through the maze. Karina Mariño, Jonathan Bones, Jayesh J Kattla, & Pauline M Rudd. Nature Chemical Biology (October 2010) doi:10.1038/nchembio.437

Investigating effects of vitamin–D_2 enriched mushrooms in the diet

Conway Fellow, Dr Lorraine Brennan and UCD colleagues, Dr Anne Nugent and Professor Mike Gibney from the Institute of Food and Health have been awarded funding from Monaghan Mushrooms to perform research on their vitamin D enhanced mushrooms.

The major source of vitamin D is sunlight with diet providing a limited source. Vitamin D deficiency, reflected by circulating 25-hydroxyvitamin D [25(OH)D] concentrations less than 50 nmol/l is prevalent in as much as half of European and US populations. There is accumulating evidence to suggest that vitamin D status may play a role in the development of diseases beyond those related to bone metabolism.

There is a real need for enhancing dietary intake and vitamin D_2 enhanced mushrooms represent a novel vehicle for increasing vitamin D intakes. However, to date, their efficacy has not been demonstrated. This study will examine whether vitamin D_2 enhanced mushrooms can actually increase circulating levels of vitamin D (25(OH)D) and provide a novel vehicle for dietary delivery of vitamin D.

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Investing in Your Future

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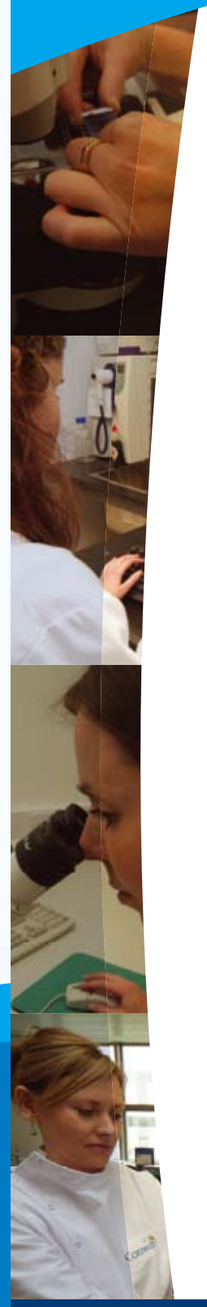

Role for cellular CO_2 sensor identified

UCD Conway researchers have found that carbon dioxide (CO_2) is not only involved in climate change and a waste product of respiration in cells but also plays an active role in regulating the genes involved in inflammation and innate immunity. Their research findings were highlighted in the October 1st issue of the *Journal of Immunology*.

The levels of oxygen (O_2) and carbon dioxide (CO_2) in cells can vary dramatically in health and in diseases such as chronic inflammation, ischemia and cancer where metabolism rates are significantly altered. Elevated CO_2 levels that occur during hypoventilation of intubated patients have been found to decrease mortality associated with acute respiratory distress syndrome or endotoxin-induced acute lung injury.

Acute CO_2 sensing is a feature of specialised cells in lower animal species such as flies and rodents but little is known about the effect of altered CO_2 on gene expression. This research group, led by Conway fellow, Professor Cormac Taylor examined the effect of altered CO_2 levels on gene expression in mammalian cells against a background of inflammation.

"Our results suggest that a molecular CO_2 sensor associated with anti-inflammatory and immunosuppressive signalling may exist. We found that elevated levels of CO_2 had a profound effect on a master signalling pathway called NF-κB", said Dr Eoin Cummins, postdoctoral researcher and lead author on this publication.

In previous work, the Taylor group demonstrated that the NF-κB master signalling pathway is induced by hypoxic (low O_2) conditions. In this study, the researchers now show that a central protein regulator within this pathway, IKKα reacts to CO_2 levels in a rapid, reversible and dose dependent manner.

Commenting on the significance of the research, Dr Cummins said, "The molecular mechanism of this CO_2 sensor may provide an alternative therapeutic route in those instances when suppressing the body's innate immune system or inflammatory response is clinically desirable. We now need to decipher the exact mechanisms of this CO_2-dependent intracellular signalling pathway".

The work, which was funded by Science Foundation Ireland and the Health Research Board of Ireland, is highlighted among the top ten percent of articles published in the issue of the *Journal of Immunology*; a further endorsement of the research.

As part of their wider programme of research, Professor Cormac Taylor and Dr. Eoin Cummins hosted a 2-day conference that focused on therapeutic aspects of hypoxia-inducible pathways. Sponsored by the HypoxiaNET EU COST action, the meeting attracted more than 100 scientists from Europe, the USA and Korea to UCD Conway Institute on October 7th & 8th 2010. The delegates heard and discussed the latest basic science, technology, pharmacology and translational medicine aspects of this hot topic in hypoxia research.

Delegates at the HypoxiaNET EU COST action meeting in UCD Conway Institute in October 2010

Director's Message

Welcome!

This issue of Conway Focus comes as the TCD-UCD Innovation Academy opens its doors to the first cohort of PhD graduates to embrace a new culture of innovation within graduate education. This initiative and that of the Dublin Academic Medical Centre (DAMC) opens new possibilities for harnessing Conway's research for the innovation agenda and translation into clinical application.

As we define the research roadmap that will maximise the value of Conway research by tackling big questions in biology and biomedicine, fostering a dynamic innovative culture will be integral to our success. It will resonate throughout the scientific process; from discovery to translation in partnership with industry.

As 2010 draws to a close, I would like to take the opportunity to congratulate Conway researchers on their achievements in the past twelve months; a tiny fraction of which are highlighted here, and look forward to the challenges of the coming year.

Professor Walter Kolch
Director

conway focus

2010 Festival medal for signalling research

Dr Marc Birtwistle received the 2010 UCD Conway Festival of Research & Innovation gold medal, sponsored by Roche, for his research to decipher the mechanism cells use to turn on and off biological decisions. As part of this prize, Marc is selected as the UCD representative for the 2010 Roche Researcher of the Year competition.

A postdoctoral researcher in Systems Biology Ireland, Dr Birtwistle was initially shortlisted from over 85 Conway scientists to present his work at the moderated poster sessions held during the 10th annual UCD Conway Festival of Research & Innovation on Thursday, September 16th in the Institute.

He impressed the judging committee with the description of his work that uses a systems biology approach to understand how breast cancer cells listen to two different signals. One signal causes these cells to grow, whereas the other causes these cells to differentiate. These signals activate or inactive subsequent signalling potential, which when perturbed or faulty have been implicated in the progression of numerous types of cancer.

The cells in our bodies continually listen for signals in their local environment and then make appropriate decisions for proper body functionality. A major challenge in current biomedical research is to understand the language of this listening in terms of the chemical reactions occurring within the cell. Central to this systems biology approach is casting biological understanding into a mathematical formalism that allows the use of computers and maths to understand how the system works.

Dr Viviana Marzaioli, Dr Sandra Malynn, Melissa Morine, Karen Harford, Lisa Shine and Tauseef Ahmed received category prizes for delivering concise overviews of their work in the themed moderated poster sessions.

Conference delegates heard keynote lectures from Professor Rosemary O'Connor, University College Cork on the potential of signalling regulators as cancer therapeutics and Professor Michael White, University of Liverpool, spoke about systems biology approaches that are useful to study cell signalling.

Professor Ruedi Aebersold, ETH Zurich, delivered the plenary lecture of the Festival and described how proteomic experiments can generate complete, reproducible and quantitative data sets that are ideally suited to support the generation of mathematical models in systems biology research.

The 10th annual UCD Conway Festival of Research & Innovation was sponsored by BioSciences & Roche.

Prof. Walter Kolch, Director, UCD Conway; Simon Thorpe, Roche Diagnostics Ltd; Dr Marc Birtwistle, winner 2010 UCD Conway Festival gold medal; Dr Oliver Blacque, Chair, Conway Lecture & Seminar Series committee.

Science in the information age

The global scientific community In the information age is not only concerned with advancing scientific discovery but with improving the methodology of the scientific process. There are two recent examples of Conway researchers influencing this work.

Conway postdoctoral researcher, Dr Niall Haslam from the Complex & Adaptive Systems Laboratory (CASL) worked on the minimum information about protein affinity reagent (MIAPAR) proposal; an international effort to define a checklist of required information describing the properties of a protein binding reagent with every known binding partner.

Currently, there are multiple sources of information on affinity reagents in existence including commercial catalogues, experimental results published in scientific journals and web portals that centralise affinity reagent properties from many sources. However, the available information may be incomplete, inaccessible, unsubstantiated or may even appear contradictory due to lack of precision in target or sample descriptions.

The MIAPAR proposal, which was outlined earlier this year in a communication to Nature Biotechnology, allows subsequent users to make a fully informed evaluation of the validity of conclusions drawn from use of a particular product.

Dr Niall Haslam explains that "by providing MIAPAR compliment documents for the affinity reagents used in experiments along with the scientific communication of the research, scientists can support the efficient use of the products for the benefit of the entire scientific community."

Conway Fellow, Dr Jens Erik Nielsen and his team have created a protein engineering analysis tool (PEAT) that facilitates the analysis of experimental data generated in the course of a research project as well as ensuring that this valuable data is available for future use. The team recently described the application in the journal, Nucleic Acids Research.

PEAT is not simply a laboratory information management system, but has been designed to address specific tasks encountered in a typical protein engineering project while integrating data deposition in the process.

Commenting on the benefits of PEAT, Dr Nielsen said, "PEAT incentivises data storage by integrating the process with the analysis tools in a single application. Through widespread use of PEAT, we can create and share high quality datasets on the connections between protein sequence, structure and function".

The work on MIAPAR was supported through funding received from European Union Framework Programmes (EU FP) 6 & 7. PEAT is being funded through awards from Science Foundation Ireland, the Health Research Board, Higher Education Authority and a UCD Ad Astra scholarship. PEAT is available at http://enzyme.ucd.ie/PEAT

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Bourbeillon J et al.Minimum information about a protein affinity reagent (MIAPAR). Nature Biotechnology 2010 Jul;28(7):650-3.

Farrell D et al. Capturing, sharing and analysing biophysical data from protein engineering and protein characterization studies Nucl. Acids Res. (2010) 38(20): e186 doi:10.1093/nar/gkq726

Mismanagement of cellular waste linked to Alzheimer's

UCD Conway researchers believe that a failure to maintain an efficient flux of cellular waste through lysosomes is a risk factor for developing Alzheimer's disease. The findings of their research were recently published in the Journal of Biological Chemistry.

The metabolic state of living cells strikes a fine balance between growth and degradation. Cells maintain this equilibrium by constantly making new, and removing old, parts of themselves. They package their own waste into vesicles that are degraded by acidic organelles known as lysosomes. This process of cellular rubbish disposal involves cells eating parts of themselves and is known as autophagy (self-eating). During autophagy, waste material is digested into basic building blocks (sugars, amino acids and lipids) that can then be reused to make new parts of the cell. Neurons survive for many decades in the human brain and have exceptionally efficient autophagy. However, in brains of people affected by Alzheimer's disease, the ability of neurons to clear out cellular waste is compromised. This leads to an accumulation of waste containing vesicles or autophagic vacuoles (AVs) that impair neuron function and may underlie the cognitive loss associated with Alzheimer's disease.

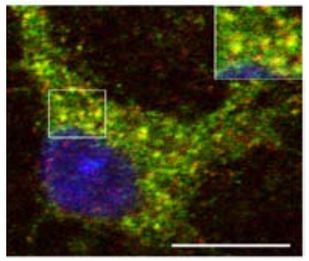
In a study led by Health Research Board-funded research fellow, Dr. Barry Boland, under the co-supervision of Conway Fellow, Prof. Dominic Walsh and Prof. Frances Platt (University of Oxford), AVs were shown to accumulate inside neurons when lysosomes cannot digest AVs and when AVs are not delivered to lysosomes.

The team used this model to investigate whether a protein associated with plaque formation in Alzheimer's disease, amyloid precursor protein (APP), is delivered to lysosomes by AVs. They found that fragments of APP are degraded by lysosomes but not delivered to lysosomes by AVs. Instead, their research indicated that amyloidogenic APP fragments are delivered to lysosomes from the plasma membrane via endocytosis.

Commenting on the study, Dr. Boland said, "This highlights the important role that lysosomes play in removing cellular waste from neurons, while clarifying the route APP fragments take on their delivery to lysosomes. We believe that therapies aimed at improving lysosomal waste disposal could prevent and alleviate the neuronal dysfunction associated with Alzheimer's disease."

This work was supported by grants from the Health Research Board of Ireland, the Wellcome Trust, Science Foundation Ireland and UCD Seed Fund.

Reference
Boland B, Smith DA, Mooney D, Jung SS, Walsh DM, Platt FM (2010) Macroautophagy is not directly involved in the metabolism of amyloid precursor protein. Journal of Biological Chemistry 285:37415-37426.



Cortical neuron showing the co-localisation of autophagic vacuoles (LC3, green) with lysosomes (LAMP1, red)

Conway researcher recognised for biomarker validation research

Dr. Elton Rexhepaj received the European Society of Toxicologic Pathology (ESTP) thesis award in Budapest, Hungary on September 30th 2010. This prestigious prize, sponsored by Boehringer Ingelheim Pharma GmbH & Co. KG, is offered every second year for a thesis in toxicological pathology.

Rexhepaj's doctoral thesis describes an automated, image analysis approach for clinical pathologists and biomedical researchers in histopathology laboratories to automate immunohistochemistry (IHC) annotation and facilitate the translation of biomarker discovery to clinical implementation.

Dr. Elton Rexhepaj, together with Conway Fellow, Professor William Gallagher and clinician-scientist, Dr. Donal Brennan created IHC-MARK; a novel, proprietary image analysis toolkit for the assessment of IHC-based markers. This technology, termed IHC-MARK, is currently in beta-testing phase and provides a non-supervised approach to the discrimination of biomarker protein expression at the subcellular level. The applicability of IHC-MARK in oncology has been demonstrated across multiple marker and tumour types, including breast, colorectal, bladder and ovarian cancer.

Dr. Rexhepaj is now employed by UCD spin-out company OncoMark Limited where he hopes to further progress the commercialisation aspects of IHC-MARK and complementary image analysis approaches in histopathology.

New genetic insights to psoriasis and psoriatic arthritis

More than 500 DNA samples from well characterised patients with psoriasis and psoriatic arthritis in St Vincent's University Hospital (SVUH) were analysed as part of two separate genome-wide association studies (GWAS). The results of both studies were recently published in Nature Genetics.

The Irish contribution to these international collaborative projects was coordinated by clinician scientists in the SVUH Education & Research Centre; Dr. Brian Kirby (dermatology) and Conway Fellow, Professor Oliver FitzGerald (rheumatology). Both studies have confirmed known genetic associations but additional associations have also been identified.

Psoriatic arthritis (PsA) is an inflammatory joint disease that is distinct from other chronic arthritic conditions. It is frequently accompanied by psoriasis vulgaris (PsV), a common chronic inflammatory disease that affects the skin and is mediated by T cells.

A strong genetic component for PsA had previously been suggested by several studies but until now there was limited knowledge of the genetic components contributing to PsA. The findings outlined in this publication identified a new genetic variant on chromosome 6 that codes for a protein, known as Act-1, which is thought to play a key role in both humoral and cellular immunity.

The genetic variant identified may result in upregulation of the IL-17 pathway, a key pro-inflammatory cytokine, which may be critical in explaining why some people with psoriasis develop arthritis. This important observation opens up new avenues of research and potential for novel therapeutic strategies.

The second study investigated genetic variants that increase susceptibility to psoriasis and found associations at eight previously unreported genomic loci. Seven loci harboured genes with recognised immune functions (IL28RA, REL, IFIH1, ERAP1, TRAF3IP2, NFKBIA and TYK2). These findings implicate pathways that integrate epidermal barrier dysfunction with innate and adaptive immune dysregulation in the pathogenesis of this skin condition.

Reference
Common variants at TRAF3IP2 are associated with susceptibility to psoriatic arthritis and psoriasis. Hüffmeier U et al. Nat Genet. 2010 Nov;42(11):996-9. PMID: 20953186

A genome-wide association study identifies new psoriasis susceptibility loci and an interaction between HLA-C and ERAP1. Strange A et al Nat Genet. 2010 Oct 17. PMID: 20953190