The Guide to 'Pain-free Biochemistry'

Based on a lifetime's experience of helping students with the concepts of biochemistry, Prof. Paul Engel's new book, Pain-free Biochemistry will be published this Autumn. Departing from the usual textbook pattern of lengthy chapters, Engel covers short topics in bite-size chunks written in an informal style. There is an extensive glossary offering simple explanations and a long section of appendices for those who want a little more depth to the topic. The book avoids unnecessary complexity, introducing long names and complicated structures only where they are essential to understanding. Although the 'pain' the book was designed to alleviate was that of student nurses, physiotherapists and radiographers, the book might well prove helpful for a wider audience and perhaps even the odd committed biochemist!

Guest Editors on 'Proteomics'

Dr Rosemary Clyne and postdoctoral fellow Dr Julia Grassl have been invited to edit of a special issue of the journal Proteomics (www.proteomics-journal.com) that will be published in October. The issue is a compilation of 22 original peer-reviewed research and review articles in the area of yeast proteomics. Included in the special issue are review articles from UCD Conway Fellows, Drs Gerard Cagney and Matthias Wilm. Julia's work on optimising sample preparation methods, which was done in collaboration with Conway Fellow, Prof. Mike Dunn's group and Denator AB (Sweden), was accepted for publication in the special issue. This work has also been presented as a poster at the 8th HUPO World Congress 2009 in Toronto. Rosemary presented this and other work at the 2nd Irish Proteomics Workshop held during September in UCD Conway Institute. Other presentations from the group include a talk by PhD student, Catherine Daly and best poster prize for PhD student Maria Iacovella at the Irish Fungal Meeting 2009 (UCD Conway Institute).

Ireland's First Protein Expression Factory Installed in UCD Conway

Conway Fellow, Professor Dolores Cahill and Professor Kenneth Dawson, UCD have been awarded funding from Science Foundation Ireland to secure the purchase of a protein expression factory for use in their research and in collaboration with other research groups locally, nationally and internationally.

The equipment facilities a high throughput process starting with PCR amplification of genetic source material, construction of expression vectors, transformation and expression of purified proteins or vectors. In addition to the four 96-well plates that allow processing of large quantities of genetic material, the protein expression factory provides faster and more accurate processing as well as software and technical support.

A virtual experiment planning process is facilitated using web based software. A researcher who wishes to proceed to executing this experiment can then use JobManager software to instruct the robotics and calculate the consumable requirements.

One of the initial planned projects in collaboration with Conway Fellow, Professor Pauline Rudd of the National Institute for Bioprocessing Research & Training (NIBRT) will look at the importance of glycosylation in the process of cell recognition within the immune system. The expression factory will assist in changing about 90 glycosylation sites on a T-cell receptor and put these mutants in vector constructs for further investigation within human cells.

Supplied by NextGenSciences and supported by eXeTech, this protein expression factory is the only instrument of its kind in Ireland. Currently in testing phase, it is hoped that the machine will be fully operational in November 2009. Researchers interested in using the instrument should contact Dr Alejandro Merino (alejandro.merino@ucd.ie) or visit www.cbni.eu/Technology.

NextGenSciences expression factory

Funded through the Programme for Research in Third Level Institutions, administered by the HEA.

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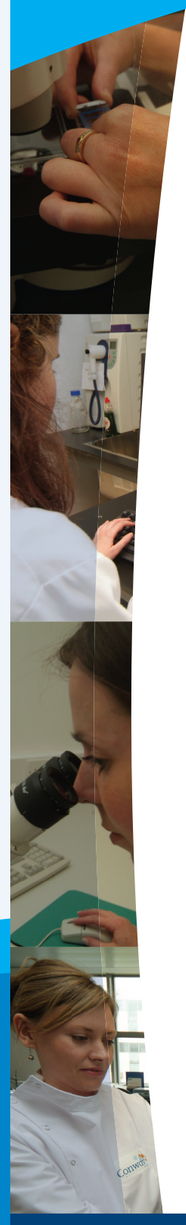
October 2009 Issue 8

conway focus



Launch of Systems Biology Ireland Announced

Systems Biology Ireland, the new Science Foundation Ireland-funded Centre for Science, Engineering and Technology (CSET) was launched by the Minister for Science, Technology and Innovation, Conor Lenihan T.D. on September 15th 2009.
Systems Biology Ireland is led by UCD and supported by researchers in NUI, Galway. The new centre will receive €14.8 million from SFI and a further combined contribution of almost €4.7 million by the various industry partners - Ark Therapeutics, Hewlett Packard, Servier, Agilent Technologies, Siemens Ireland and Protagen AG.
Commenting on the announcement, Minister Lenihan said "(This) investment establishing Systems Biology Ireland is clear evidence of the Government's ongoing commitment to further enhancing Ireland's scientific base to aid our economic recovery."
Systems biology is a powerful new way to use the strength of computers and mathematics to understand biology. This research centre will try to unravel the complexities of cells through the use of models that predict biological behaviours. The research being undertaken will enable quicker and better treatments of a range of medical conditions, including various cancers and should allow for better therapies to be delivered more effectively to patients.
Professor Walter Kolch has relocated to Ireland from the Beatson Institute, Scotland to lead the SBI programme. He is joined by Conway Fellows, Professors Boris Kholodenko (deputy director),Des Higgins and Cormac Taylor. They will work with co-principal investigators, Professors Tim O'Brien and Frank Barry, the respective director and scientific director of the Regenerative Medicine Institute (REMEDI) based in NUI, Galway.
Outlining the potential of systems biology to speed up research and help target therapies to particular patient types, Professor Kolch said: "We will use systems biology to improve our understanding of cell mechanisms, cell communication networks with the ultimate aim of regulating cell activity. Our work will help speed up the experimentation process, thereby reducing by years the time it takes to develop a new drug therapy. We will also work on pin-pointing the efficacy of drug therapies on different patient types so that doctors can better identify those who will respond best to particular treatments."
Welcoming the announcement, Professor Des Fitzgerald, UCD Conway Director said: "SBI is a major development within the UCD Conway Institute, which has always had a strong focus on biomedical research, supported by proteomics and bioinformatics. SBI will train a new type of scientist with deep knowledge across the disciplines of biology, medical sciences, mathematics and computation."
Commenting on the investment by industry, Dr Laurent Perret, Président du Comité Scientifique du Groupe de Recherches Servier said: "SBI provides a further opportunity for Servier to engage in leading-edge research in Ireland and for us to work together to address unmet medical needs using an extraordinarily powerful technology".

Minister for Science, Technology and Innovation, Mr Conor Lenihan TD pictured with Professor Frank Gannon, Director General of Science Foundation Ireland (left), and Professor Walter Kolch, Director, Systems Biology Ireland (right) at the announcement of Systems Biology Ireland

Director's Message

Welcome! As we enter the last quarter of 2009, UCD Conway's involvement in the overall university PRTLI5 submission process continues with site visits into mid-November. Enabling works are now complete for the proposed Charles Institute and the newly launched Systems Biology Ireland (SBI), which form part of the capital programme. We are involved in several national access facilities including high-throughput screening and transgenics and are proposing a radiopharmaceutical research & services programme. Several Conway Fellows are involved in the various stands including PhD programmes involving MMI and SBI (strand 2) and emerging areas such as nanoremedies (strand 3).

Over the coming months, as part of the TCD-UCD Innovation Alliance, we will establish Conway Innovations to provide local support to facilitate the innovation process, develop strong links to our industry partners and assist graduate training through the innovation academy.

Regards

Professor Des Fitzgerald
Director

conway focus

Honouring a Research Career Dedicated to Memory Storage Mechanisms

Joint winner of the Nobel Prize in Physiology or Medicine in 2000, Professor Eric Kandel delivered the plenary lecture of the 9th annual UCD Conway Festival of Research & Innovation after receiving a Ulysses medal in recognition of his research on the mechanism of memory formation from Dr Hugh Brady, the President of UCD.

"Professor Kandel's story is one of a lifetime dedicated to investigating the mechanism of memory formation; a lifetime of research achievements in his quest, as he once said himself, to understand the brain - one cell at a time," said Dr Hugh Brady who presented the award in front of a capacity crowd. "This award is in recognition of his outstanding contribution to neurobiology, an inspirational story to set our resolve as scientists and researchers."

Born in Vienna on November 7, 1929, Kandel immigrated to America before the start of World War II. He believes that it was the traumatic events of his last year in Vienna living under Nazi rule that triggered his specific later interest in the mechanisms of memory.

His lecture entitled: The long and short of long-term memory, outlined his scientific work and discoveries, which culminated in the 2000 Nobel Prize in Physiology or Medicine (jointly awarded to Arvid Carlsson and Paul Greengard).

The three Nobel Laureates made pioneering discoveries concerning one type of signal transduction between nerve cells in the brain, known as slow synaptic transmission. The discoveries have been crucial to the understanding of the normal function of the brain and how disturbances in this signal transduction can give rise to neurological and psychiatric diseases.

Kandel found that the brain must chemically alter proteins to generate short-term memories and must additionally make particular kinds of proteins in order to transform short-term memories into long-term memories - the brain's way of filing important documents away, for potential future use. He was also among the first to detail the critical role played by serotonin in transmitting electrical messages between nerve cells. When serotonin is lacking, it can lead to depression, bipolar disorder and schizophrenia.

Today, Eric Kandel's research group at the Centre for Neurobiology and Behaviour in Columbia University are studying selected examples of several major forms of memory storage.

Professor Eric Kandel, UCD Ulysses medal recipient and plenary speaker at the 9th annual UCD Conway Festival of Research & Innovation

Epigenetic Mechanisms in Schizophrenia wins Festival Medal

Dr Niamh O'Sullivan was awarded the UCD Conway Festival of Research & Innovation gold medal, sponsored by Roche, for her preliminary research to identify epigenetic mechanisms, which may contribute to disease characteristics seen in schizophrenia.

A postdoctoral researcher in the Applied Neurotherapeutics Research Group, Dr O'Sullivan was shortlisted from over 100 Conway scientists to present this original research at the 9th annual UCD Conway Festival of Research & Innovation on September 17th.

It is well established that multiple genetic and environmental factors contribute to schizophrenia. Dr O'Sullivan and her colleagues believe that these factors may interact at critical periods in early development to create a defective epigenetic state within certain brain structures. The knock-on effect of disrupting the functionality and connectivity of nerve cells within the brain may result in the onset of the symptoms associated with schizophrenia.

Niamh O'Sullivan outlined how she has begun to identify functional regulatory elements that control gene activation in different cell types, at different stages of development using a next-generation gene sequencing platform. Ultimately, she hopes that by revealing the sequence of molecular events responsible for the emergence of schizophrenia-like behaviour, scientists will then be able to identify new therapeutic targets for the disease.

Drs Sam Maher (PI: Prof. David Brayden) and Sara Hayden (PI: Dr Emma Teeling) were placed second and third in the competition for their respective preliminary research on improving drug permeability across the gastrointestinal tract and understanding the relationship between odours and the genes that govern our sense of smell.

The judging committees involved in the oral and moderated poster sessions were unanimous in their praise for the quality of research presented during the course of the 9th annual Festival. Kristina Gegenbauer, Sarah Kandil, David Magee and Brendan Dolan received prizes for delivering concise overviews of their work during the moderated themed poster sessions.

Delegates at the conference heard keynote lectures from Professor Kingston Mills, TCD and Conway Fellow, Professor Geraldine Butler. The event was sponsored by BioSciences, Servier Laboratories Ireland & Roche.

Pictured (L-R) Dr Niamh O'Sullivan, Dr Keith Murphy, Professor Des Fitzgerald, Ms Jenny Pearson, Roche representative.

Innovation Success for Kinsella Group

Researchers led by Conway Fellow, Prof. Therese Kinsella successfully filed a PCT patent in August 2009 covering a series of modified promoter sequences that are suitable for recombinant protein expression in wide range of cells of human origin, including stem cells. The research findings underpinning this invention centres on the human thromboxane A_2 receptor and have been recently published in the Journal of Lipid Research, Journal of Molecular & Cellular Medicine (in press) and the Journal of Molecular Biology (in press).

Thromboxane plays an important role in haemostasis and signals through the alpha and beta isoforms of the thromboxane A_2 receptor (TP) in humans. Both are encoded by a single gene but regulated by two distinct promoters, Prm1 and Prm3. Dr Anne-Marie Gannon carried out much of the group's recent work that centres on describing the factors regulating Prm1 and how this impacts on the expression of TPalpha.
The key transcription factors identified include the housekeeping Sp1 and inducible Egr1, a factor often seen to be up-regulated after an adverse cardiovascular event. Of particular note, and possibly reflecting the importance of the receptor within the vasculature, is the identification of NF-E2 as a key factor involved in its expression, and therefore the thromboxane receptor joins an elite group of genes, primarily associated with haematopoietic stem cells, established as being regulated by NF-E2. The data also establishes Wilms' tumour suppressor protein (WT1) as a critical repressor of the promoter. Given the importance of thromboxane receptor expression and function in both the vasculature and the kidney, this may explain, at least in-part, some of the renal dysfunction seen in the childhood cancer Wilms' tumour associated with genetic defects in WT1. Additionally, Prof. Kinsella has recently been awarded an Enterprise Ireland Technology Development Grant also based on her research on the human thromboxane A_2 receptor. In collaboration with Conway Fellow, Prof. Pat Guiry (CSCB) and Dr Helen Reid, the team hope to develop novel thromoboxane receptor antagonists geared to the anti-thrombotics area.

Ref: Regulation of the human thromboxane A2 receptor gene by Sp1, Egr1, NF-E2, GATA-1, and Ets-1 in megakaryocytes. Gannon AM, Kinsella BT.J. Lipid Res. 2008 Dec;49 (12):2590-604.

The Wilms' Tumor Suppressor Protein WT1 acts as a key Transcriptional Repressor of the Human Thromboxane A Receptor Gene in Megakaryocytes. Gannon AM, Kinsella BT.J Cell Mol Med. 2008 Nov 22

Regulated Expression of the alpha Isoform of the Human Thromboxane A(2) Receptor during Megakaryocyte Differentiation: A Coordinated Role for WT1, Egr1, and Sp1.Gannon AM, Turner EC, Reid HM, Kinsella BT. J Mol Biol. 2009 Sep 8. [Epub ahead of print]

New Insights to the Metabolic Control of Insulin Secretion

The results of a recent study by Conway researchers and collaborators in the University of Geneva and University of Ulster have identified Aralal (aspartate-glutamate carrier 1 AGC1), a malate-aspartate NADH shuttle member, as a key metabolic control site in insulin secreting cells. The work was highlighted when published recently by the journal Clinical Science.

In pancreatic beta-cells, nutrient metabolism and insulin secretion are tightly coupled. The NADH shuttle system is primarily made up of the malate-aspartate and glycerol-3-phosphate shuttles. The former is thought to play an important role in the amplification of insulin secretion.
The research group led by Conway Fellow, Professor Philip Newsholme hypothesised that overexpression of Aralar 1, a calcium sensitive isoform of the aspartate-glutamate exchanger and integral component of this shuttle, would affect cellular nutrient metabolism and insulin secretion.
Dr Katrin Bender looked at the effects of amino acid and glucose metabolism in a clonal beta-cell line BRIN-BD11, derived from rat islet cells and RINm5F cells through electrofusion. She found Aralar1 overexpression increased glucose- and amino-acid stimulated insulin secretion, cellular glucose metabolism, L-alanine and L-glutamine consumption, cellular ATP and glutamate concentrations, and stimulated glutamate release. However, cellular triacylglycerol and glycogen contents were decreased as was lactate production.
Significantly, Dr Bender showed that the addition of glucose and alanine caused the greatest increase in insulin secretion in comparison with any other nutrient combination in Aralar-1 over expressing cells.
Dr Katrin Bender completed this research as part of her doctoral thesis supervised by Prof. Newsholme. It was funded through the Health Research Board.

Ref: Overexpression of the malate-aspartate NADH shuttle member Aralar1 in the clonal beta-cell line BRIN-BD11 enhances amino-acid-stimulated insulin secretion and cell metabolism. Katrin Bender, Pierre Maechler, Neville H. McClenaghan, Peter R. Flatt and Philip Newsholme. Clinical Science (2009) 117, 321–330 doi:10.1042/CS20090126

Controlling the Release of Platelet Granules

Conway Fellow, Dr Albert Smolenski and his group have identified new proteins involved in the secretion of platelet granules. The research outlining their discovery that synaptotagmin-like protein 1 (Slp1) and the GTPase-activating protein Rap1GAP2 control dense granule release was recently published in Blood, the leading journal in haematology research.

Platelets have an important role in the pathogenesis of atherosclerosis, myocardial infarction and stroke. They circulate in the blood stream and bind to injured vessel walls providing a seal that prevents bleeding. At sites of atherosclerotic damage, platelets can adhere and aggregate leading to occlusion of the vessel followed by irreversible damage to the tissue supplied by the artery.
Platelet activation involves the release of storage granules containing many bioactive molecules that reinforce platelet functions. Platelets contain three different granule types but the mechanisms controlling their secretion are not well understood. The Smolenski group were able to show that Slp1 strongly inhibits whereas Rap1GAP2 enhances dense granule release. The effect of Rap1GAP2 requires binding to Slp1 and the group identified a new protein motif that mediates the interaction between the two proteins.
The discovery of synaptotagmin-like protein 1 and Rap1GAP2 might pave the way for the development of more efficient and specific antiplatelet therapies. Currently, antiplatelet therapy using molecules like aspirin or the ADP receptor blocker, clopidogrel is limited by side-effects such as an increased risk of bleeding.
The work originated in earlier studies by the group that led to the identification of Rap1GAP2 as the only GTPase-activating protein of Rap1 in platelets. This protein regulates cell adhesion and platelet aggregation. The group characterised Rap1GAP2 as a phosphorylated substrate of cyclic nucleotide-dependent protein kinases. The cyclic nucleotide signalling network is a built-in inhibitory system in platelets that regulates most aspects of platelet function. The unexpected finding of Rap1GAP2's role in granule secretion suggests that both aggregation and granule release might be closely coordinated. A SFI principal investigator programme grant funded the work.

Ref: Synaptotagmin-like protein 1 interacts with the GTPase-activating protein Rap1GAP2 and regulates dense granule secretion in platelets (2009)Neumüller, O., Hoffmeister, M., Babica, J., Prelle, C., Gegenbauer, K. and Smolenski, A.P. Blood 114: 1396-1404.