Proteomic changes in schizophrenia & bipolar disorder

The first detailed research study of protein expression changes within the hippocampus in schizophrenia and bipolar disorder has not only shown striking overlap of changes between disorders but localised altered expression to specific subregions in this part of the brain.

The findings by a research collaboration involving the Royal College of Surgeons in Ireland (RCSI), Beaumont Hospital and UCD Conway Proteome Research Centre were published in the May issue of Archives in General Psychiatry, the highest ranking journal in the field.

Abnormalities in the hippocampus are among the most consistent findings in schizophrenia research and are also implicated in bipolar disorder. Using mass spectrometry, the research team identified 152 proteins, with 61 of these being differentially expressed in both disorders. These proteins are implicated in a range of different processes including cytoskeletal and metabolic functions.

Subsequent validation work carried out by the researchers confirmed changes in the cytoskeletal protein, septin11 and proteins involved in the membrane trafficking process of clathrin-mediated endocytosis in both disorders.

The hippocampus is subdivided into specific regions; cornu ammonis (CA) regions 1 through 4 and the dentate gyrus. These subregions differ anatomically, functionally and in their vulnerability to neurological disorders. The most prominent protein changes seen were in regions CA2 and CA3.

'These results give us greater insight into the nature and extent of region-specific protein changes in psychotic disorders and may provide valuable information about the underlying molecular mechanisms in these illnesses,' said Dr Melanie Föcking.

The proteomics research was conducted in collaboration with Conway Fellow, Professor Michael Dunn while Professor David Cotter led the research in RCSI and Beaumont Hospital. The work was funded by the Wellcome Trust, NARSAD and the Stanley Medical Research Institute.

Reference:

Common Proteomic Changes in the Hippocampus in Schizophrenia and Bipolar Disorder and Particular Evidence for Involvement of Cornu Ammonis Regions 2 and 3. Melanie Föcking, Patrick Dicker, Jane A. English, K. Oliver Schubert, Michael J. Dunn, David R. Cotter. Arch Gen Psychiatry. 2011;68(5):477-488

Pitching to 'Get Started'

Dr Patricia McGowan was awarded joint first prize from the TIDA / SFI 'Get Started' Technology Venture Programme organised by Science Foundation Ireland (SFI) and the Irish Technology Leadership Group (ITLG). She will participate in a week-long visit hosted by the ITLG to meet members of the venture community and leading technology companies in Silicon Valley, California.

A senior postdoctoral researcher, Dr McGowan works in the breast cancer research group, led by Conway Fellow, Professor Joe Duffy in the Education & Research Centre, St Vincent's University Hospital. Her winning elevator pitch focused on an innovative product targeted at the treatment of triple negative breast cancer that may have potential in the clinical setting.

SFI is working in partnership with Enterprise Ireland on the Technology Innovation Development Award (TIDA) to realise a greater economic impact from the state investment in oriented basic research by teaching business skills to university researchers and scientists.

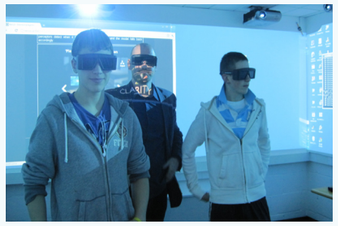
(L-R) Dr. Roisin Cheshire, Scientific Programme Manager, Science Foundation Ireland; Dr. Patricia McGowan (joint prize winner); Cian Hughes, Head of Operations, Irish Technology Leadership Group

Bright futures ahead for Team SAP Ireland

Conway Fellow, Dr Patricia Maguire recently hosted a visit by Team SAP Ireland, a group of six transition year secondary school students and their teacher, Mr Declan Askin from St Gerard's College, Castlebar.

This exceptional group of students are gaining national and international acclaim for their robotics and biomedical engineering applications. They received a British Science Association CREST award and represented Ireland in the First Lego League (FLL) World Finals in St Louis, Missouri, USA at the end of April 2011 where they won third place overall and the most inspirational team award.

Team SAP Ireland is currently working with SAP to develop a smart phone application, iCollapse. Using the accelerometer in the mobile phone, the application tracks the user's movements and detects a collapse. This sets off an alarm encouraging a passer-by to remove the user's phone and call the listed help contact(s). It also instructs the passer-by on how best to help the individual recover.



(L-R) Team SAP Ireland members Oisin Kyne, Mr Declan Askin (teacher) & Adrian Murphy pictured in Clarity during a visit to UCD.

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Summer 2011 Issue 14

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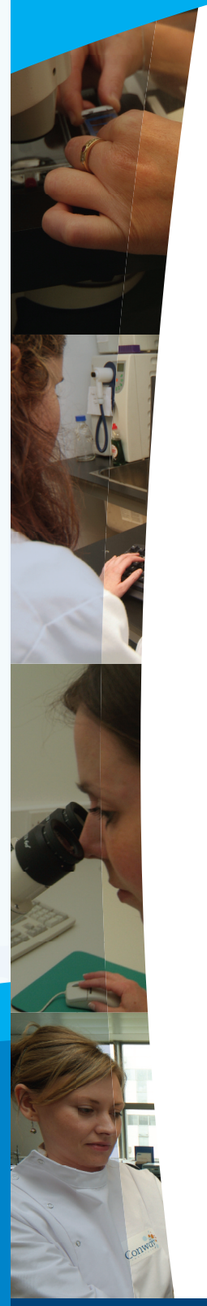


New avenue to tackle CJD and Alzheimer's disease

Two antibodies that could help block the onset of Alzheimer's disease in the brain have been identified in a collaborative research project involving scientists at the Medical Research Council Prion Unit at University College London, UCD Conway Institute and Trinity College Dublin.

The antibodies, ICSM-18 and ICSM-35, were already known to play a crucial role in preventing protein misfolding; the main cause of Creutzfeldt–Jakob disease (CJD), the human form of mad cow disease.

The study findings published in Nature Communications has shown in mice that these antibodies can block damaging effects on brain tissue caused by a toxic substance called amyloid beta. Cumulatively, amyloid beta becomes attached to the surface of nerve cells in the brain, stopping them from communicating effectively and causing memory loss. The results showed that the antibodies stopped the amyloid beta proteins from taking hold and damaging the brain.

The study also confirms findings from a 2009 paper by Yale researchers, which first indicated that prion proteins, which can change their shape and cause CJD, may be involved in Alzheimer's.

"With an ageing population and increasing numbers of families affected by Alzheimer's disease, there is an urgent need for new drugs that can help to preserve brain function and prevent memory loss, the symptom which most characterises the devastating impact of Alzheimer's," said Professor John Collinge, Director of the MRC Prion Unit at University College London, who led the study.

"We're thrilled that this discovery shows in mice that these two antibodies which we are developing to treat CJD may also have a role in treating more common forms of dementia like Alzheimer's disease. If these antibody drugs prove to be safe in use to treat CJD, we will consider whether studies in Alzheimer's disease should be carried out."

"A unique aspect of this study is that we used amyloid beta extracted from human brain, the same material we believe is causing memory loss in patients with this devastating disease, and we identified two antibodies that could block this effect," said Professor Dominic Walsh, Professor of Neurodegeneration at the UCD School of Biomolecular and Biomedical Science, and the UCD Conway Institute who was co-corresponding author on the research.

"The use of these specific antibodies is particularly exciting since they have already undergone extensive pre-clinical testing for use in treating CJD. So, a lot of basic work has already been done and could fast-track these antibodies for use in humans. The next step is further validation in other disease models of Alzheimer's and then safety trials in humans," he added.

Clinical trials to see whether drugs based on these antibodies can mitigate the damage caused to the human brain as a treatment for patients with CJD are due to begin in 2012.

Reference:

Interaction between prion protein and toxic amyloid β assemblies can be therapeutically targeted at multiple sites. Darragh B. Freir, Andrew J. Nicoll, Igor Klyubin, Silvia Panico, Jessica M. Mc Donald, Emmanuel Risse, Emmanuel A. Asante, Mark A. Farrow, Richard B. Sessions, Helen R. Saibil, Anthony R. Clarke, Michael J. Rowan, Dominic M. Walsh & John Collinge. Nature Communications Jun 7 2011 doi:10.1038/ncomms1341

Director's Message

Welcome!

With the recent launch of the National Institute for Bioprocessing Research and Training (NIBRT), we bid farewell to Professor Pauline Rudd and her team as they leave the Institute building for their new home across campus. Minister for Research & Innovation, Seán Sherlock TD officially opened the new 6,500sq metre facility that will support the biopharmaceutical industry in Ireland by educating and training highly skilled staff and conducting ground-breaking research in collaboration with industry. We look forward to maintaining close links with Pauline and rest of the NIBRT team through the many research collaborations established with other Conway Fellows.

The co-localisation of all imaging facilities to the lower ground floor of the Institute is now entering the final stage of completion. We anticipate that all electron microscopy equipment will be successfully transferred into the building over the summer months. I am confident that the consolidation of this core technology platform will have a positive impact on service delivery for our researchers.

Professor Walter Kolch
Director

conway focus

New prostate cancer biomarkers move closer to clinical use

Conway Fellow, Professor William Watson and Professor John Fitzpatrick, UCD School of Medicine and Medical Science and Mater Misericordiae University Hospital recently received a translational research award for the validation of a panel of serum biomarkers to inform surgical intervention for prostate cancer.

One of four research projects to be funded under the joint Health Research Board and Science Foundation Ireland initiative, this proposal ultimately aims to develop a clinically-applicable predictive tool to identify the grade and stage of prostate cancer and inform the clinician and patient of the most appropriate treatment strategy.

The proposal is based on recently published and preliminary data by the UCD prostate cancer group and will involve independent external validation of the panel of proteins by international collaborators in Austria and Australia prior to any commercial development taking place.

Dr Sheng-Fei Oon (MD research student) published reviews in Nature Reviews Urology and the BJU International that systematically identified, for the first time, all the areas of greatest unmet need for biomarkers in prostate cancer and has directed the focus of international biomarker research efforts to these areas maximising clinical utility.

Taking this as a guide, Mr Yue Fan (PhD student on the UCD Bioinformatics and Systems Biology PhD programme) used a proteomics approach and novel bioinformatics analysis to identify lists of potential candidate protein biomarkers. These findings, published in the Journal of Proteome Research, will help stratify prostate cancer patients into their appropriate treatment groups.

"There are many hundreds of biomarkers for prostate cancer but only one in clinical use because the others have either not succeeded in the validation phase or were not deemed useful at the bedside" stated Professor William Watson who leads the group and the Irish Prostate Cancer Research Consortium. "We have taken the approach of firstly identifying the relevant clinical questions and then designing appropriate discovery and validation efforts with a clearly defined comparison population using carefully calibrated and standardised collection, storage and processing protocols."

This multi-faceted, but unified approach is placing Irish-based prostate cancer research in the forefront of many international prostate cancer research interests.

Reference :
Fan Y, Murphy TB, Byrne JC, Brennan L, Fitzpatrick JM, Watson RW. Applying random forests to identify biomarker panels in serum 2D-DIGE data for the detection and staging of prostate cancer. J Proteome Res. 2011 Mar 4;10(3):1361-73.

Oon SF, Pennington SR, Fitzpatrick JM, Watson RW. Biomarker research in prostate cancer-towards utility, not futility. Nat Rev Urol. 2011 Mar;8(3):131-8.

Oon SF, Watson RW, O'Leary JJ, Fitzpatrick JM. Epstein Criteria for prostate cancer. BJU Int. 2011 Feb 14. doi: 10.1111/j.1464-410X.2011.09979.x. [Epub ahead of print]

Pictured at the HRB-SFI Translational Research Award announcement (L-R); Minister for Research and Innovation, Mr Sean Sherlock T.D; Professor William Watson; Minister for Health, Dr James Reilly T.D.

Protecting against adipose tissue inflammation in obesity

Obesity is a growing pandemic that imposes substantial health & economic burdens globally. Leading to metabolic complications such as insulin resistance and type II diabetes, obesity has significant ramifications for patients, families and communities.

Even our bodies recognise the threat imposed by obesity as they mount a pathological immune response to the condition. Scientists believe that interrogating the biochemical pathways underlying this immune response may give insight into therapeutic options.

UCD researchers led by Conway Fellow, Professor Helen Roche are contributing to this effort and their recent findings have been published in the highest impact journal in this scientific field, Diabetes.

In obesity, cells of the immune system (macrophages & T-cells) respond to a high fat diet by entering adipose tissue and releasing proinflammatory cytokines (IL-1, IL-6, TNF-alpha). This creates a chronic state of inflammation that is further enhanced locally with secretion of pro-inflammatory cytokines from the expanding adipose tissue mass itself. This leads to both adipocyte specific and systemic insulin resistance.

The Science Foundation Ireland – funded Roche group have shown that inflammatory signals transmitted via the proinflammatory cytokine, interleukin-1 receptor (IL-1R1) play a key role in adipose tissue inflammation during obesity.

IL-1 must be converted to an active form by NLRP3-capase-1 inflammasome complex. The active form of IL-1 then binds downstream to its receptor IL-1R1 in order to control the inflammatory signals that mediate adipose inflammation in obesity.

The UCD team focused on downstream consequences of IL-1RI receptor signalling in this pathway using murine models. They evaluated macrophage recruitment, cytokine secretions and adipocyte insulin sensitivity. They found that a lack of IL-1RI protects against high fat diet induced insulin resistance and reduces local adipose tissue inflammation despite the equivalent immune cell recruitment.

'It would be an over-simplification of the process to say that IL-1 has a direct linear effect on the majority of adipose tissue inflammation,' said Professor Helen Roche. 'We surmise that crosstalk between adipose derived cytokines is the most likely scenario whereby adipose tissue inflammation is amplified.

However, the contribution of IL-1 is critical to the medley of pro-inflammatory, insulin-desensitising signals relevant to obesity-induced insulin resistance. As such, these findings expand our current understanding of the paracrine effect associated with the lack of IL-1R1 in adipose tissue'.

Reference :
Lack of Interleukin-1 Receptor I (IL-1RI) Protects Mice From High-Fat Diet–Induced Adipose Tissue Inflammation Coincident With Improved Glucose Homeostasis. Fiona C. McGillicuddy,Karen A. Harford, Clare M. Reynolds, Elizabeth Oliver, Mandy Claessens, Kingston H.G. Mills and Helen M. Roche. Diabetes doi:10.2337/db10-1278 June 2011.

c-Myc impacts alternate splicing of key signalling factors

New research shows that the proto-oncogenic factor, c-Myc directly affects the alternate splicing machinery of key signalling components in an effort to coordinate cell processes such as growth, proliferation, differentiation and apoptosis. The findings of the international collaboration led by Professor Walter Kolch, Director, Systems Biology Ireland & UCD Conway Institute were published recently in the journal, Cancer Research.

Occurring in more than ninety percent of genes, alternate splicing is a way of regulating protein expression and activity. It describes how a common strand of genetic information is cut or spliced to produce different mature RNA strands. These splice products or truncated proteins introduce diversity into cells even to the extent of producing antagonistic functions.

The research team report that protooncogenic factor, c-Myc directly controls the genetic expression of the splice factor, hnRNP H. Expression of hnRNP H is necessary to ensure that a-raf mRNA is spliced in such a way as to form a full length A-Raf protein. This protein can then inhibit apoptosis by binding to MST2 kinase, which is seen typically in human colon and head and neck cancers.

They also describe a novel splice product or truncated protein called A-Raf$_{SHORT}$ that occurs when low levels of c-Myc result in reduced expression of the hnRNPH splice factor in normal cells and tissues. It appears that A-Raf$_{SHORT}$ acts like a tumour suppressor protein by safeguarding against oncogenic transformation.

As A-Raf$_{SHORT}$ fails to bind MST2 kinase, it cannot regulate MST2 mediated apoptosis. However, it does bind and block activated Ras and consequently suppresses the Ras-ERK signalling pathway that is commonly activated in cancer.

'These results suggest that a concerted response of c-Myc, hnRNP H and A-Raf expression is part of a physiological programme defining how cells respond to different growth conditions. We were also able to demonstrate that c-Myc is coordinating this response,' said Professor Walter Kolch.

Cancer Research UK and Science Foundation Ireland supported this research that also involved researchers from the Beatson Institute for Cancer Research, Glasgow; University of Sheffield, UK; Garvan Institute of Medical Research, Australia; Ludwig-Maximilians University, Germany.

Reference
c-Myc regulates RNA splicing of the A-Raf kinase and its activation of the ERK pathway. Jens Rauch, Kim Moran-Jones, Valerie Albrecht, Thomas Schwarzl, Keith Hunter, Olivier Gires & Walter Kolch. Cancer Res(E-Pub) April 21, 2011. doi:10.1158/0008-5472

Lipoxins attenuate renal fibrosis

While inflammation is an integral part of the body's natural immune response, it can become part of a greater problem if it runs past its course. Unresolved inflammation can lead to the development of fibrosis and organ failure with limited therapeutic options available to patients.

UCD researchers led by Conway Fellow, Professor Catherine Godson believe tackling unresolved inflammation may be a viable therapeutic option in renal fibrosis and chronic renal disease including diabetic nephropathy.

In a recent edition of Faseb Journal, the team describe the impact on a model of early renal fibrosis of lipoxin (LXA4), and its synthetic counterpart benzo-lipoxin, developed by Professor Pat Guiry, Conway Fellow & Director of the Centre for Synthesis & Chemical Biology. While the anti-inflammatory effects of these lipid mediators have previously been described, the anti- fibrotic effects found by the researchers are novel.

Lipoxins stimulate the resolution of inflammation through a number of converging processes involving macrophage activation and the clearance of dead cells or efferocytosis.

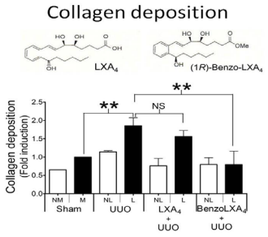
Explaining the novel anti-fibrotic effects seen, PhD student Emma Börgeson says, 'Fibrotic scar tissue forms when collagen is deposited at the site of inflammation. We found that benzo-lipoxin significantly reduced the amount of collagen laid down in our model and that collagen gene expression was reduced by both the natural and synthetic lipoxin.

Both LXA4 and benzo-LXA4 also caused a trend towards reducing renal cell death and we think this may reflect the fact that the inflammatory milieu is being pushed to resolution by lipoxin inhibiting the production of pro-inflammatory cytokines.'

Professor Catherine Godson believes that, 'Lipoxins may represent a potentially useful therapeutic strategy in renal fibrosis. We would hope to further investigate if lipoxin and its analogues, as well as other lipid mediators, can accelerate recovery in progressive forms of early renal fibrosis.'

This collaborative research project also involved Dr Neil Docherty, Trinity College and Dr Roel Goldschmeding, University Medical Centre, Utrecht. It was supported by Science Foundation Ireland, Health Research Board, Enterprise Ireland, the Irish Government's Programme for Research in Third Level Institutions as well as an IRCSET Embark postgraduate research scholarship to Emma Börgeson..

Reference
Lipoxin A4 and benzo-lipoxin A4 attenuate experimental renal fibrosis. E Börgeson, N.G Docherty, M Murphy, K Rodgers, A Ryan, T O'Sullivan,P Guiry, R Goldschmeding, D. F. Higgins, C Godson. Faseb J. (E-pub) May 31, 2011, doi: 10.1096/fj.11-185017



ISAC Scholar award

Dr Alfonso Blanco has received the 2011 ISAC Scholar award from the International Society for Advancement of Cytometry. The 5-year ISAC scholarship programme is designed to enhance the scientific and leadership potential of emerging leaders in this specialist field. It provides valuable training and mentoring opportunities for awardees.

Dr Blanco established the UCD Conway flow cytometry core facility in 2004. He is the founder member and president of the Irish Cytometry Society and a founder member of the European Cytometry Network. He designs and implements various cytometry education and training programmes and organises national and international cytometry meetings and conferences such as the 11th European Clinical Cytometry meeting, scheduled for the Convention Centre Dublin during September 2011.