Predicting patient responses to ovarian cancer chemotherapy

Late diagnosis, recurrence and chemoresistance all contribute to the high morbidity and mortality in ovarian cancer patients. Currently, there is no way to identify those women who will benefit most from the first line therapy of choice, a paclitaxel-based chemotherapy.

Research led by Conway Fellow, Dr. Amanda McCann PhD and collaborators in St. James', Holles Street and Beaumont Hospitals in Dublin has focused on the mitotic arrest deficiency protein 2 (MAD2). Their recent findings published in Cell Cycle gives further insight into how this protein is regulated and brings scientists closer to identifying its potential role in a cell's response to paclitaxel.

The team have previously shown that lowered levels of MAD2 induce cellular senescence, where cells are viable but not actively dividing. Importantly, these cells also display a compromised response to paclitaxel treatment. This study investigated how MAD2 is regulated in ovarian cancer focusing on the methylation status of the MAD2 promoter and the effect on MAD2 levels of tumour hypoxia; a common tumour microenvironment reflecting deprived oxygen levels that is integral to chemoresistance.

Commenting on the work, postdoctoral researcher Dr Maria Prencipe PhD said, "We found that aberrant methylation of the promoter region was not involved in regulating MAD2 expression. Using CAIX, a marker of hypoxia, we found less MAD2 protein expressed under hypoxic conditions. We also demonstrated that down-regulation of MAD2 is associated with up-regulation of p21 in hypoxia, suggesting a role for p21 in regulating MAD2 expression".

Regarding the future direction of this work, Dr McCann said "Up to 30% of patients may not respond to the current standard chemotherapy (paclitaxel /platinum combination). In order to improve patient outcome, it is crucial that we establish what factors influence an individual's response to chemotherapy and which factors explain why some patients fail to benefit from standard first-line chemotherapy while others get long-term remission".

This work was supported by IRCSET, Irish Cancer Society and the Eccles Breast Health Research Fund as well as internal UCD funding.

Reference:
MAD2 down-regulation in hypoxia is independent of promoter hypermethylation. Maria Prencipe, Aloysius McGoldrick, Antoinette S Perry, Anthony O'Grady, Sine Phelan, Barbara McGrogan, Patricia Fitzpatrick, Jenny A Watson, Fiona Furlong, Donal J Brennan, Mark Lawler, Elaine Kay and Amanda McCann. Cell Cycle Volume 9, Issue 14 Pages 2928 - 2937 July 15, 2010

UCD clinician scientist wins prestigious award

Postdoctoral research fellow, Dr Donal Brennan became the first Irish recipient of the European Young Researcher Award at the 2010 Euroscience Open Forum in Turin, Italy. The award recognises outstanding scientists in the early stages of their career who have already demonstrated excellence at national and European levels.

Dr Brennan, a specialist registrar in obstetrics & gynaecology at the Coombe Womens and Infants University Hospital, works in the research group of Professor William Gallagher. He has been using the latest in high-throughput protein screening technology to identify and validate new biomarkers of breast and ovarian cancer as well as trying to improve how assay data is interpreted in clinical laboratories.

Dr Donal Brennan pictured at ESOF 2010 in Turin, Italy

6th annual Conway Postgraduate Symposium

Doctoral students Adriana Michielsen and Edwina Cahill were joint winners at the 6th annual UCD Conway Postgraduate Symposium held on June 18th 2010. Adriana works in the colorectal research group under the supervision of Dr. Jacintha O'Sullivan in the Education & Research Centre, St Vincent's University Hospital. Her presentation was entitled "The effect of tumour microenvironment components on dendritic cell function in colorectal cancer". Edwina presented her research on the "Novel Autocrine Function of the BMP Antagonist Gremlin: a Key Role in Hypoxic Pulmonary Hypertension". She works in the group of Professor Paul McLoughlin.

Adriana Michielsen (left) and Edwina Cahill pictured with Professor Walter Kolch, Director, UCD Conway Institute

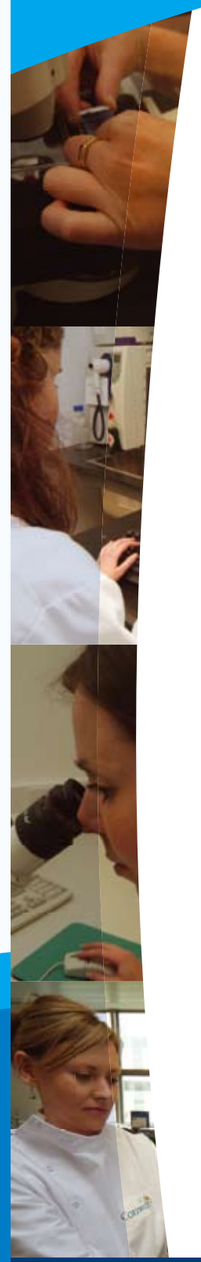
Elaine Quinn
Communications & Education Officer
UCD Conway Institute of Biomolecular & Biomedical Research
University College Dublin
Belfield, Dublin 4
Ireland

E: elaine.quinn@ucd.ie
T: (+353-1) 716 6706
F: (+353-1) 716 6701
W: www.ucd.ie/conway

Investing in Your Future

September 2010 Issue 11

conway focus



Systems model of signalling control

Fail-safe switches have been used in mechanics and electronics for years to control what devices do under different circumstances. They are based on the premise that two codes must be present for a signal to be turned 'on'. If only one or neither code is present, the signal is 'off'.

New research by Conway Fellow, Professor Boris Kholodenko and collaborators in RIKEN, Japan has shown that evolution has provided a biological version of these switches with similar fail-safe mechanisms that control cellular reactions within our own cells. The findings of their research were published recently in Cell.

The cells in our bodies continually listen for signals in their local environment and then make appropriate decisions for proper body functionality. For instance, during pregnancy and after childbirth, a woman's body releases hormones that make certain breast cells develop the capability to produce milk; a process termed differentiation.

Such cellular listening processes are collectively called signal transduction, and 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.

Professor Kholodenko, deputy director of Systems Biology Ireland (SBI), is applying a systems biology approach to the task of understanding the mechanism cells use to turn on and off biological decisions.Dr Marc Birtwistle (SBI), one of the researchers involved in this study explains that "rather than taking a 'one piece at a time' approach to understanding how these complex signal transduction systems work together to create biological function, we consider the system as a whole. Central to the systems biology approach is casting our biological understanding into a mathematical formalism that allows us to use computers and maths to understand how the system works."

The focus in this publication is on understanding how breast cancer cells listen to two different signals using this systems biology approach. 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.

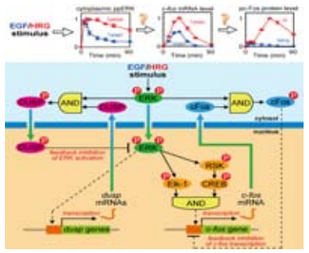
This work also solves the puzzle of how cells have unique responses to signals even when using the same chemical reactions to generate them. It reveals how cells rely on precise control of both the timing and location of these chemical reactions to create unique cellular responses out of seemingly identical chemical reaction networks.

The researchers also found that the listening system is incredibly robust to noisy signals, meaning it can still function properly despite major alterations to its components and inexact messages.

Commenting on the significance of the research, Professor Kholodenko said, "We now have a validated mathematical model that represents the behaviour of this cellular signalling system".

The research was funded through a Science Foundation Ireland Centre of Science and Engineering and Technology award and RIKEN.

Reference
Ligand-specific c-Fos expression emerges from the spatiotemporal control of ErbB network dynamics. Nakakuki T, Birtwistle MR, Saeki Y, Yumoto N, Ide K, Nagashima T, Brusch L, Ogunnaike BA, Okada-Hatakeyama M, Kholodenko BN. Cell, 2010 May 28;141(5):884-96



Graphical depiction of the complex cellular biochemical signalling network within human breast epithelial cells involving an intricately arranged cascade of "coherent feedforward loops" characterised by the pictured "AND gates", and negative feedback, characterised by lines ending with a "sideways T" rather than an arrow.

Director's Message

Welcome!

The publication of this issue coincides with preparations to celebrate the 10th anniversary of the UCD Conway Festival of Research & Innovation with a retrospective of outstanding research achievements and a showcase of current research projects. Even while pausing to reflect on the past decade, we are firmly focused on the future strategic direction of the Institute and securing the necessary funding to facilitate achieving the ambitions of our research projects.

We welcome the recent announcement of continued investment in Irish research by the Government, with the money channelled through the main funding bodies including Science Foundation Ireland (SFI), the Programme for Research in Third Level Institutions (PRTLI), Enterprise Ireland and IDA client companies. We also acknowledge the commitment of the European Commission to research and innovation through the 7th EU Framework Programme (FP7) and hope to secure the opportunities within this to work with research groups across Europe.

Professor Walter Kolch
Director

conway focus

SFI award for membrane trafficking research

Conway Fellow, Professor Jeremy Simpson has been awarded a Science Foundation Ireland Principal Investigator programme grant worth €1.58M to uncover the molecular machinery involved in transporting particles safely through the cell, and exploit this knowledge as a possible drug delivery pathway.

The area of membrane trafficking has intrigued Professor Simpson since doing his doctoral research on protein toxins and their passage through cells in the University of Warwick. He worked in the toxin research laboratory led by Professor Lynne Roberts where the gene for Ricin, the castor bean protein listed among the top 5 deadliest substances, was cloned.

The big unanswered question in relation to Ricin, and a number of other toxins such as E. coli 0157 Shiga-like and Cholera toxin, is how they are so effective at entering and killing cells. According to Jeremy Simpson, if we understood how pathways between cellular compartments are controlled, this information could be used to help design drugs that can be better targeted to various sub-compartments of the cell.

As part of this research project, Simpson will initially add fluorescent labels to non-toxic subunits of Ricin, Shiga and Shiga-like toxins that are known to be involved in trafficking. On a genome-wide scale, he will then down-regulate each gene to see how this will impact on where a toxin travels to within the cell.

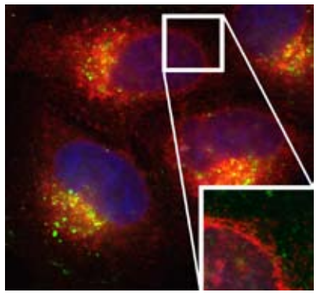
This systematic exercise should provide a list of candidate genes involved in getting toxins to the endoplasmic reticulum via the Golgi pathway rather than being destroyed in the lysosomal pathway. Using bioinformatic and proteomic tools, the team should be able to drill down and understand the molecules involved in more detail and potentially reveal the master regulators of the process.

In collaboration with Professor Kenneth Dawson, the team hope to be able to use this information to functionalise nanoparticles, move them into the Golgi pathway and provide a novel model for drug delivery.

Commenting on the award, Jeremy Simpson said, "While the technological challenges in this project are enormous, the potential benefits of improved drug design and delivery far outweigh them".

UCD College of Life Sciences have recognised the potential benefits of the high throughput imaging technology associated with this project by providing an additional €180K in supporting funding to meet infrastructural and resource requirements. This will allow Professor Simpson to establish a cell screening facility to meet not only the needs of this research but also those of UCD researchers campus-wide.

The UCD Cell Screening Centre will form part of the suite of Conway core technologies and will include liquid handling robotics, imaging equipment and analysis software as well as the expertise of a dedicated core facility manager.



Fluorescently-labelled Shiga-like toxin (red) is trafficked to the endoplasmic reticulum and nuclear envelope (inset), but avoids the degradative endosomal-lysosomal compartments (green)

EU FP7 funding success for Conway

Professor Walter Kolch, Director of Systems Biology Ireland and Conway Fellow, Professor William Gallagher will lead two cancer research projects worth €18 million under the latest round of the EU 7th Framework Programme for Research (FP7).

The first project led by Professor Kolch was awarded €12 million by the EU to explore genetic mutations that lead to the development of cancer cells. This project will use a systems biology approach to focus on understanding childhood cancers.

Professor Gallagher will lead the second project, awarded €6 million, to look at possible treatments for difficult-to-treat types of breast cancer. The research will explore the role of kinases, the key regulators of cell function, in these types of breast cancer in order to develop therapeutic targets that may inhibit the rate of activation of kinases in cancer sufferers.

Syscilia, a collaborative research project involving Conway Fellow, Dr Oliver Blacque, was awarded €11 million under this programme. Dr Blacque will receive €531K for his part of the project that will use a systems biology approach to dissect cilia function and its disruption in human genetic disease. Cilia are hair-like projections on the cell surface.

Potential key regulator identified in battle to target IBD

Research into inflammatory bowel disease (IBD) led by Conway Fellow, Professor Cormac Taylor with national and international collaborators has identified a key regulator involved in maintaining the functional integrity of the gut lining. The findings, published recently in Gastroenterology, provide information that may be important in developing a new therapeutic approach to the treatment of the disease.

The underlying genetic or environmental causes of inflammatory bowel disease remain largely unknown. However, the major problem associated with this chronic condition is that the lining of the gut becomes leaky, allowing material from the lumen of the intestine to pass through this barrier and trigger an inflammatory response.

The intestinal barrier works by maintaining a delicate balance between the proliferation and death of epithelial cells at the surface of the barrier. If the balances tips so that more cells die than grow, as is the case in IBD, the barrier is no longer intact and cannot function properly.

This latest research has shown that in the absence of an oxygen-sensing enzyme, prolyl hydroxylase 1 (PHD1), epithelial cell death is reduced and the intestinal barrier function is enhanced. Therefore, PHD1 may be a useful target for pharmacologic inhibition in IBD.

The team propose that by delaying or suppressing epithelial cell death, the gut lining would be given time to heal and the integrity of the intestinal barrier could be restored.

Commenting on the research, Professor Taylor said "Inflammatory bowel disease is a condition in need of new and improved therapeutic options. Our current results indicate that targeting the PHD1 enzyme may represent one such approach."

Science Foundation Ireland and the German Research Foundation funded this research

Reference
Loss of prolyl hydroxylase-1 protects against colitis through reduced epithelial cell apoptosis and increased barrier function. Murtaza M. Tambuwala, Eoin P. Cummins, Colin R. Lenihan, Judith Kiss, Markus Stauch, Carsten C. Scholz, Peter Fraisl, Felix Lasitschka, Martin Mollenhauer, Sean P. Saunders, Patrick H. Maxwell, Peter Carmeliet, Padraic G. Fallon, Martin Schneider, Cormac T. Taylor. Gastroenterology - 02 July 2010 (10.1053/j.gastro.2010.06.068)

Soluble amyloid β-protein implicated in Alzheimer's disease

Alzheimer's disease (AD) is the most common human dementia and confers a huge burden on patients, caregivers and society. The molecular pathways leading to AD are not well understood, but substantial data indicate that the amyloid β-protein (Aβ) plays a central role.

It is proposed that a defect leading to over-production or decreased clearance causes Aβ to accumulate and ultimately lead to the cognitive deficits that characterise AD. The protein can form large insoluble aggregates called amyloid plaques. Since plaques are pathologic hallmarks of AD, it had been assumed that they also caused the disease.

However, the quantity and temporal progression of amyloid plaques do not correlate well with disease status, which raises the question: if Aβ causes AD, why does the amount of Aβ in the form of amyloid plaques not relate to the severity of dementia?

Studies recently published in Brain by the group of Conway Fellow, Professor Dominic Walsh, looked at the relationship between biochemically distinct forms of Aβ and the presence of AD-type dementia in 43 brains obtained from the MRC Cognitive Function and Ageing Study.

Analysis revealed that the level of SDS-stable Aβ dimers strongly correlates with the presence of AD-type dementia. These exciting findings build on earlier publications from the Walsh group that SDS-stable Aβ dimers can impair neuronal functions necessary for memory formation and suggest that targeting Aβ dimers may alleviate the memory loss typical of AD.

The MRC have awarded the Walsh group €550,000 for follow-up research on a larger scale that should allow for further validation of Aβ dimers as mediators of disease. Parallel studies (funded by NIH, EU, SFI and HRB) aimed at developing antibodies and small molecules, which bind to Aβ dimers and neutralise their activity, are ongoing.

Reference
The presence of sodium dodecyl sulphate-stable Ab dimers is strongly associated with Alzheimer-type dementia. Jessica M. Mc Donald, George M. Savva, Carol Brayne, Alfred T. Welzel, Gill Forster, Ganesh M. Shankar, Dennis J. Selkoe, Paul G. Ince and Dominic M. Walsh on behalf of the Medical Research Council Cognitive Function and Ageing Study. Brain 2010: 133; 1328–1341

New regulator of TGFβ signalling identified

The signalling pathway that originates from transforming growth factor-beta (TGFβ) controls important cellular processes such as growth, differentiation and apoptosis. A wide range of human disorders, including vascular disease and cancer, display dysfunctional TGFβ signalling.

Research led by Conway Fellow and SFI Stokes Professor, Dr Johan Ericsson has identified the tumour suppressor Fbxw7 as a novel regulator of TGFβ signalling. The findings, published in Oncogene, describe the mechanism by which Fbxw7 regulates this important signalling cascade.Fbxw7 acts by marking target proteins for destruction. In their manuscript, the authors identify transforming growth factor-beta induced factor 1 (TGIF1) as a new target for Fbxw7-dependent degradation.

TGIF1 is a negative regulator of TGFβ signalling and the Ericsson group now demonstrate that inactivation of Fbxw7 results in the accumulation of TGIF1 within cells and reduced TGFβ-dependant signalling. In addition, they demonstrate that TGFβ signalling is disturbed in cancer cells with mutations in the Fbxw7 gene.

Dr Maria Bengoechea-Alonso, a senior postdoctoral researcher in the group, explained, "When TGIF1 accumulates in cells, it recruits other proteins to shut down the transcription of TGFβ-dependent target genes".Recent work in the Ericsson laboratory has described a number of new Fbxw7 targets, including SREBP1 and C/EBPβ, both of which are involved in the production of fat cells. Interestingly, another group of scientists recently demonstrated that TGIF1 is also involved in adipogenesis. Taken together, these results may point to an important role for Fbxw7 in fat cell differentiation and opens the possibility of Fbxw7 being a novel target for obesity drugs. Professor Ericsson now proposes to use advanced transcriptomic techniques to identify all the genes regulated by TGIF1 during the differentiation of fat cells. "By identifying these genes, we hope to enhance our understanding of adipocyte differentiation and the roles of Fbxw7 and TGIF1 in this process".

Reference
Tumor suppressor Fbxw7 regulates TGFβ signaling by targeting TGIF1 for degradation. M T Bengoechea-Alonso, J Ericsson. Oncogene (12 July 2010) doi:10.1038/onc.2010.278