Centre of Excellence hosts international workshop

As a European Centre of Excellence, the Department of Rheumatology in St Vincent's University Hospital was chosen to host an international two-day workshop on March 26th & 27th 2010. Sponsored by Roche Pharma, the Participate workshop gave twenty rheumatologists from centres in Europe and Australia the opportunity to witness the care of patients with rheumatoid arthritis (RA) at St Vincent's.

The Participate programme focused on advanced treatment regimens for RA in the clinic, including practical aspects of biologic therapy carried out in the accredited infusion suite that provides optimal care for RA patients. In addition to lectures from Conway Fellows, Professors Oliver FitzGerald and Douglas Veale, delegates heard from clinical nurse specialists about patient education, screening and monitoring of biological therapies.

Addressing the international guests, Ms Mary Duff, Director of Nursing and Ms. Kay Connolly, Assistant Director of Nursing for the Bone & Joint Unit expressed their hope that the experience of the multidisciplinary team from St Vincent's would provide a template for delegates to reproduce similar care and facilities for the management of RA patients in their respective countries.

Frog peptide structure selected for journal cover

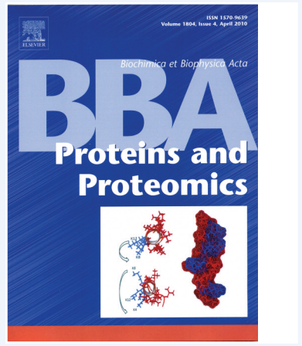
An image of the frog peptide structure central to the work of a UCD Conway research team was selected as the front cover image for the April 2010 edition of the scientific journal, Biochimica et Biophysica Acta (BBA); Proteins & Proteomics.

Peptides in the skin of many species of frog have anti-bacterial and anti-fungal properties as well as the ability to lyse or rupture mammalian cells. This innate immunity protects it from attack. These properties of frog skin peptides are exciting from the prospect of being developed into therapeutically valuable anti-infective and anti-cancer agents.

Conway Fellow, Dr Chandralal Hewage and his team carried out molecular modelling of the XT-7 peptide and its analogue [G4K]XT-7 in a variety of solutions in order to understand the structural basis for the difference in biological activity.

This particular XT-7 peptide, isolated from the skin of Silurana tropicalis, shows potential for drug development as it has impressive activity against the growth of bacteria and Candida albicans. However, this potential as an anti-infective agent is restricted by its haemolytic activity.

A change to the amino acid structure of the XT-7 peptide can create an analogue that retains anti-infective properties but without the complicating haemolytic activity. The single amino acid substitution (glycine replaced by lysine) improves the therapeutic potential of this naturally occurring peptide.



Cover of April 2010 edition of Biochimica et Biophysica Acta (BBA); Proteins & Proteomics.

Launch of Conway postdoctoral & graduate forum

A new fortnightly forum for Conway graduate and postdoctoral researchers will be launched in May 2010. This initiative will give early-stage researchers the opportunity to talk about science and issues that concern them in an informal environment with refreshments provided! Content for the forum will be decided by the members but it is envisaged that it will include a mix of technology overviews, informal and formal research seminars, PhD viva rehearsals and career development talks from within and beyond academia. Forum committee members, PhD student Mr Thomas Schwarzl (thomas.scharzl@ucd.ie) and postdoctoral researchers, Dr David Gomez (david.gomez@ucd.ie) and Dr Craig Slattery (craig.slattery@ucd.ie) invite suggestions for the forum schedule.

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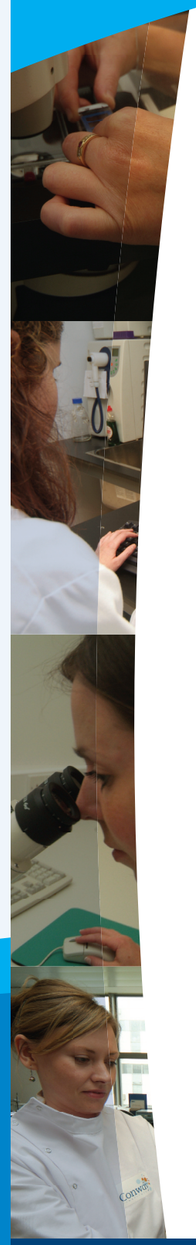


Worm research reveals cilia disease gene function

Research by Conway Fellow, Dr Oliver Blacque has revealed new information about a gene implicated in Joubert syndrome and related cerebellar disorders (JSRDs), characterised by blindness, bone abnormalities, cystic kidneys, developmental delay and loss of muscle tone and control. The findings of this research, funded through a Science Foundation Ireland President of Ireland Young Researcher Award (PIYRA) to Oliver Blacque, were recently published in the Journal of Cell Biology.

One of seven genes associated with JSRDs, Arl13b codes for a protein already known to play roles in the formation and/or function of cilia, which are hair-like projections extending from the surface of the cell. However, the precise molecular details of what exactly Arl13b is doing in cilia have remained unclear.

Blacque's team studied the gene in the cilia of tiny worms (Caenorhabditis elegans) while collaborators in the University of Tokyo conducted parallel experiments in cultured human cells. Together, they confirmed that Arl13b proteins uses lipid anchors to associate with the ciliary membrane.

Much of the work on the project was carried out by UCD doctoral candidate, Sebiha Cevik. She and her colleagues went on to demonstrate in C. elegans how disrupting the function of worm Arl13b causes the ciliary membrane to bulge and become misshapen as well as affecting the ability of other proteins to properly distribute within the ciliary membrane.

They also found that a fully functional Arl13b protein is needed for the normal functioning of a protein transport system in cilia. This intraflagellar transport system (IFT) makes contact with the ciliary membrane. Based on these results, they proposed a new working model for Arl13b, where it functions at the ciliary membrane to regulate important ciliary membrane properties such as shape, transmembrane protein distributions and IFT.

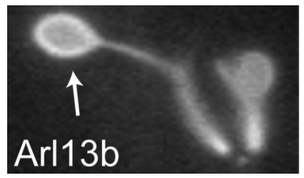
Up to only 20 years ago, many believed most cilia to be redundant cellular organelles that have fallen victim to mammalian evolution - a type of cellular appendix. We now know that these cellular antennae present on nearly all of our cells and serve fundamental roles in many motility and sensory functions, including signalling pathways critical to development.

It is now not surprising that defects in cilium structure and function are associated with an ever expanding range of human diseases and syndromes, collectively called ciliopathies, which have overlapping clinical features such as polycystic kidneys and livers, retinal degeneration, bone abnormalities, hydrocephalus, as well as complex traits including obesity, diabetes, mental retardation and even cancer.

Dr Oliver Blacque hopes that these findings will ultimately lead to a greater understanding not only of JSRDs, but also of closely related ciliopathies such as Meckel Gruber and Bardet-Biedl syndrome, as well as perhaps more common phenotypes associated with cilium dysfunction such as mental retardation and obesity.

He notes "That Arl13b associates with ciliary membranes and is required for cilium structure/function in both worms and mammals demonstrates the remarkable evolutionary conservation of how this small G-protein functions."

Reference
Joubert syndrome Arl13b functions at ciliary membranes and stabilizes protein transport in Caenorhabditis elegans. Cevik S, Hori Y, Kaplan OI, Kida K, Toivenon T, Foley-Fisher C, Cottell D, Katada T, Kontani K, Blacque OE. J Cell Biol. 2010 Mar 22; 188(6):953-69



Arl13b at ciliary membrane

Director's Message

I am delighted to welcome you to the Conway Focus and look forward to working with you in the coming months!

As an institute with an increasingly interdisciplinary research focus and expertise in specialist technology platforms, we are uniquely placed to participate in the education and training of the next generation of research scientists. The newly launched PhD programme in Bioinformatics and Systems Biology recently attracted 80 EU and 120 non-EU applicants for up to 15 studentships.

We introduced 4 new advanced core technology modules on a pilot basis this academic year; those covering principles and practical aspects of imaging and applied proteomics began in late March and will run until mid-June with a further two modules in genomics and flow cytometry taking place over week-long periods during the summer months.

We hope to determine from this pilot if demand for training from within UCD as well as from external academic centres and industry will dictate stand-alone delivery of these advanced modules or inclusion within larger programmes such as the new MSc in Imaging commencing in September 2010.

I hope that a number of new initiatives, including the early-stage researcher forum described in this issue, will not only strengthen the community of Conway researchers and forge new interdisciplinary links but will celebrate and heighten awareness of our research and innovation successes.

Professor Walter Kolch
Director, UCD Conway Institute

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Conway collaborator scoops Irish Times Innovation Award

Irish biopharmaceutical development company, Sigmoid Pharma recently scooped the overall Innovation of the Year award at the inaugural Irish Times All-Island Innovation Awards. The life-science SME, founded by UCD pharmacology graduate, Dr Ivan Coulter, has actively collaborated with Conway Fellow, Professor Cormac Taylor since being granted a Science Foundation Ireland industry research partnership award in 2004.

The Irish Times award recognises the stellar innovative performance of Sigmoid Pharma in their application of research and development. The company has developed two new drug technologies, LEDDS™ and SmPill™, which not only enhance the solubility and permeability of the drug but can deliver it to targeted locations in the gastrointestinal tract, including the colon.

The Sigmoid Pharma-Taylor collaboration is facilitating the development of a new therapeutic approach for the treatment of inflammatory bowel disease (IBD) by bringing together the research methodology of the Taylor group with the proprietary liquid/emulsion drug delivery system, LEDDS®, developed by Sigmoid Pharma.

Commenting on the award, Professor Taylor said, "We are delighted for Dr Coulter and his team and indeed it reflects well on our partnership. A key driver of successful scientific research in 2010 is meaningful interaction of academia with industry that results in both academic outputs and the application of research toward clinical product development with indigenous companies."

Commenting on the Taylor collaboration, Dr Coulter said, "The collaboration with the Taylor laboratory clearly demonstrates the potential that can be realised through focused application of basic research. The development of a smart economy will depend on like-minded collaborative partners identifying opportunities and realising basic and applied research synergies. This collaboration, initiated through a SFI research supplement, highlights the potential that innovative indigenous companies working with academia can realise."

Taylor's collaboration with Sigmoid Pharma has certainly been successful by these metrics with three co-authored publications to date in two of the highest ranking scientific journals in the field, Gastroenterology and Proceeding of the National Academy of Sciences, as well as the generation of proprietary innovative products and the creation of high-skilled jobs.

More than 15,000 people in Ireland and millions of people worldwide are living with the symptoms IBD today. Current therapeutic options for this chronic debilitating disease are very limited with surgery often being the only viable option. The Sigmoid product, currently in a phase II clinical study, uniquely enables oral delivery of a powerful drug without causing systemic side-effects.

Under normal conditions, the gastrointestinal tract is lined with cells that block the contents of the gut from leaking into the intestine. In an IBD patient, this barrier is broken and the contents of the gut leak out into surrounding areas. The research team in UCD Conway used a model of IBD and, by applying a new class of drugs known as hydroxylase inhibitors, were able to almost completely reverse the symptoms of the disease.

"When we applied these new drugs to our IBD model, the gut was tricked into thinking that it was being deprived of oxygen. This activated protective pathways, which in turn prevented the death of the cells that line the gastrointestinal tract," explained Professor Taylor. "Our pre-clinical trial data can now inform the next phase Sigmoid Pharma product development pipeline".

In addition to the product that is currently in phase II clinical studies, Sigmoid Pharma is developing a LEDDS™-enabled formulation of the hydroxylase inhibitor dimethyloxaloylglycine (DMOG) to bring about effective, safe and targeted delivery of this potential therapeutic agent.

Bioinformatic analysis of HIV progression studies

Meta-analysis by UCD researchers led by Conway Fellow, Professor Denis Shields has determined that there is no clear evidence that particular defective viral sequences in the HIV-1 nef gene or certain regions of the protein play a significant role in disease progression.

HIV-infected patients can be categorised on the basis of the number of years it takes for them to progress to AIDS. Some patients maintain stable CD4 lymphocyte counts and do not go on to develop AIDS even after more than 10 years of infection.

Scientists are curious as to why these long-term, non- progressor (LTNP) patients do not develop AIDS. This may reflect differences in the host, viral genetics or environmental factors that could potentially be exploited for the treatment of the disease.

Studies in model organisms have shown that infection with nef-deficient virus shows an attenuated course of infection and some studies in humans have shown that non progression was associated with gross deletions in the nef gene.

However, much of the research in the area to date has been based on observational or case studies rather than rigorous, systematic scientific evaluation. This work by doctoral candidate Ravindra Pushker set out to determine in a substantially larger sample set if any association exists between disease progression and particular amino acid differences or deletions within the nef gene.

On a per patient basis, there was no excess of LTNP patients with one or more defective nef sequences when compared to progressors. While the high frequency of amino acid replacement at particular residues is indicative of rapid evolvement, permutation testing showed that residues with more replacements than expected were not statistically significant.

The researchers conclude that current data provides no evidence that individual residues of HIV nef are critical in determining the rate of disease progression. Professor Denis Shields believes that searches for modifiers of progression rates should now focus on other host and viral factors. "Systematic evaluation of large quantities of data by bioinformatics can be just as important in refuting hypotheses that are current in the literature, as it is in discovering unknown patterns", he said.

This research was funded through Science Foundation Ireland and University College Dublin.

Reference:
Meta-analysis to test the association of HIV-1 nef amino acid differences and deletions with disease progression. Ravindra Pushker, Jean-Marc Jacquē, Denis C. Shields. Journal of Virology, Apr 2010 p3644-3653

Success in EU FP7 call

Conway researchers led by Dr. Tara McMorrow and Professor Michael Ryan have successfully secured €485,500 in funding as part of an overall award to the Systems Biology towards Novel Chronic Kidney Disease Diagnosis and Treatment (SysKid) consortium under the European Union FP7 programme.

Syskid (www.SysKid.eu) was established to further our understanding of chronic kidney disease (CKD) and improve patient treatment, with particular focus on CKD arising from diabetes and hypertension. The multi-disciplinary research consortium has 25 partners (16 universities, 9 industry partners) from 15 countries and the project is due to run for five years.

The UCD Conway team, including postdoctoral researchers Dr. Craig Slattery and Dr. Natalia Martin, will utilise cell culture and animal models to identify processes involved in early CKD progression and investigate novel strategies for preventing and slowing the progression of the disease. These studies will be integrated with clinical and epidemiological studies across the consortium using systems biology methodologies in order to develop new diagnostic strategies and treatment options to prevent CKD development. Email tara.mcmorrow@ucd.ie for details of a PhD position currently available.

GlycoExtractor advances glycan data manipulation

Glycomics needs the supporting framework of extensive, well-curated databases and flexible analytical tools. Currently, this field of study lacks the established, comprehensive and centralised data collections, standards and information reporting protocols that exist within genomics and proteomics.

Researchers, Dr Natalia Artemenko and Dr Matthew Campbell from the National Institute of Bioprocessing Research & Training (NIBRT) led by Conway Fellow, Professor Pauline Rudd have developed an open access, web-based interface that facilitates extraction, querying and sharing of HPLC-glycan data generated in high throughput processes.

Glycosylation is the most common and structurally diverse post-translational modification of proteins. More than half of all gene products have been shown to be glycosylated. With many specific glycans or glycoforms showing potential as cancer biomarkers, there is an increasing need to develop high throughput, highly sensitive and robust strategies that detail the glycome of cells, tissues and fluids.

Commercial packages that support HPLC instruments cannot facilitate the extraction of large quantities of data. In an effort to alleviate this bottleneck within high-throughput glycomic projects, the NIBRT team have developed a web-based tool that interfaces with the Waters chromatography software package to improve and automate the export of data to various file formats for subsequent analysis. The modular architecture of the tool also facilitates the manipulation of data from other data management systems.

The NIBRT team are now working to integrate GlycoExtractor with the EUROCarbDB framework to provide a comprehensive high-throughput HPLC data analysis platform for the storage and annotation of experimental data. The integration of next generation bioinformatic tools will further the development of unified approaches for handling large scale glycomics data initiatives with applications in biomarker discovery

This research was partially supported by EUROCarbDB, a research infrastructure design study funded by the EU 6th Framework Programme. Prospective users can access the GlycoExtractor tool on http://glycobase.nibrt.ie:8080/DemoGlycoExtractor/mainPage.

Reference
GlycoExtractor: A web-based interface for high throughput processing of HPLC-Glycan data Natalia V. Artemenko, Matthew P. Campbell, and Pauline M. Rudd Journal of Proteome Research, 2010, 9 (4), pp 2037–2041

NIBRT researchers Dr Matthew Campbell and Dr Natalia Artemenko who developed GlycoExtractor

Zebrafish model gives insights into diabetic blindness

New research led by Conway Fellow Dr Breandán Kennedy indicates that treatment of diabetic blindness should look at protecting the neurons responsible for colour vision in the eye and not just targeting the blood vessels as is currently the practice.

Nearly 2.5 million people worldwide are blind due to diabetic retinopathy. This secondary complication of diabetes activates the growth of new leaky blood vessels in the eye and is responsible for the death of photoreceptors, the neurons that send visual messages to our brain.

Until now, it was unclear if the changes to vessels and neurons occurred independently of one other and which type of retinal neuron is most likely to die as a result of the raised glucose levels seen in diabetes.

Dr Kennedy and his team found that new blood vessels and the neuronal cell death in diabetic retinopathy can arise independently of each other. In addition, they identified that cone photoreceptor neurons, those involved in colour vision and used in daylight, are most affected by the high glucose levels.

The research team made their observations using a novel zebrafish model of diabetes, which resembles the early stages of diabetic retinopathy in humans. It is an exciting development for the group who now hope to further extend their research and establish a model of late stage diabetic disease.

Commenting on the research, Dr Kennedy said, "By establishing a robust model for early and late stage diabetic retinopathy, we would hope to better understand the progression of the disease and pave the way for identifying new drug targets for its successful treatment".

The research was funded through Science Foundation Ireland and the Health Research Board.

Reference:
Predominant cone photoreceptor dysfunction in a hyperglycaemic model of non-proliferative diabetic retinopathy. Yolanda Alvarez, Jenneth Chen, Alison Reynolds, Nore Waghorne, John J. O'Connor, Breandan Kennedy. Disease Models & Mechanisms (2010)