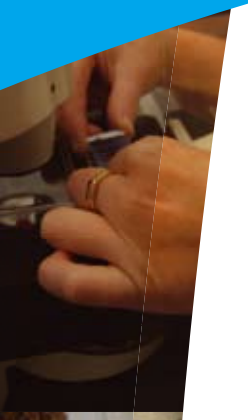
Issue 21, Spring 2014

conway focus



Prestigious awards to Conway Researchers

The Sir Henry Wellcome postdoctoral fellowship scheme aims to provide the most promising newly qualified postdoctoral researchers with a unique opportunity to develop independent research careers. For the first time, the Wellcome Trust has awarded this fellowship to an Irish early career researcher, Dr Colm Ryan.

Dr Ryan will work with Prof Walter Kolch, Systems Biology Ireland and Prof Alan Ashworth, Institute of Cancer Research, London to investigate how genetic changes impact on a targeted approach to cancer treatment.

A major challenge in cancer therapeutics is to kill tumour cells without harming other cells in the body. Cancer cells have genetic changes that distinguish them from healthy cells, and consequently may leave them vulnerable to targeted treatments.

A promising approach to developing such targeted treatments is to identify genes whose function is only essential for survival in the presence of a specific cancer-associated mutation. Such a phenomenon, where the function of gene A becomes essential only in the presence of a mutation in gene B, is called synthetic lethality. However, little is understood about how additional genetic differences between individuals might impact on their use.

Dr Ryan's fellowship will focus on understanding how such genetic changes impact on synthetic lethality treatments, and investigating whether certain treatments might be more robust to genetic differences than others.

The 11th St Luke's Young Investigator award was won by Irish Cancer Society research fellow, Dr Maria Prencipe at the Royal College of Physicians of Ireland on January 29th 2014.

This prestigious award supported by the Royal Academy of Medicine in Ireland and St Luke's Radiation Oncology Network, Dublin went to Dr Prencipe for her work to find a new molecular target for castration resistant prostate cancer (CRPC).

Dr Maria Prencipe and colleagues working with Conway Fellow, Prof William Watson recently identified the transcription factor named serum response factor (SRF) as an important target in CRPC using genetic and computational analyses.

When prostate cancer is detected early in patients, surgery and radiation treatments are effective therapies. Patients with locally advanced and metastatic prostate cancer are treated with androgen ablation (hormone depletion or chemical castration) therapy.

Despite an initial response, the majority of men progress to develop castration-resistant prostate cancer which, despite the emergence of new treatments, is challenging to treat. To meet this challenge head-on, clinicians and scientists need to understand the underlying mechanisms of resistance.

"Our study shows evidence of cross-talk between androgen receptor (AR) and SRF in advanced prostate cancer. At the core of this cross-talk is a negative feedback loop between SRF and AR that we were able to demonstrate in vitro, in clinical samples and is supported by a computational model", said Dr Prencipe. Prof Walter Kolch, Director said, "I congratulate both Colm and Maria on their achievements. It is fitting recognition for their dedication to fundamental cancer research and improving outcomes for patients with advanced disease".

Dr Maria Prencipe

Dr Colm Ryan

Director's Message

Welcome!

In the last quarter, the dedicated facilities for Systems Biology Ireland adjacent to UCD Conway Institute became operational; the new director of UCD Charles Institute of Dermatology, Prof Martin Steinhoff joined UCD from University of California San Francisco; and the Institute hosted the first UCD Ireland East cancer open house.

The UCD Ireland East cancer open house provided a unique opportunity for cancer survivors, patient advocacy groups and clinicians from across the Ireland East network to sit at the laboratory bench and talk with researchers about the projects they are working on in the battle against cancer. The dedication and passion of our early career researchers was clearly evident and, in turn, they were inspired by the individuals who might ultimately benefit from this research.

These developments create many integrative interfaces for collaboration and impact and will undoubtedly strengthen the Institute's strategic priority of building a strong translational medicine programme.

Professor Walter Kolch
Director

UCD DUBLIN
conway
focus

Institute hosts UCD Ireland East Cancer Open House

Cancer survivors and patient advocacy groups met academics, clinicians and scientists involved in cancer research in the first UCD Ireland East cancer open house.

The event provided a window to the myriad of stakeholders embroiled in the battle against cancer and the opportunity to personalise the contributions each are making. It emphasised the requirement for connectivity and engagement among all players in the battle against cancer in order to achieve improved outcomes for patients.

Participants in the cancer open house tours within the Conway Institute and Systems Biology Ireland on the evening of Thursday, 23rd January were given insights to the projects and technologies within the research pipeline by postdoctoral researchers and PhD graduates working at the coal-face of cancer research.

There were tours on topics such as *'How do cancer cells survive low oxygen?'*, *'How cancers change during treatment'* and *'Cancer cells cycling'*.

"We spoke to participants about how we use complex mathematical networks to model cancer systems with a view to developing new drugs and targeted therapies", said Philip Smyth, Education & Outreach Officer with Systems Biology Ireland.

Prof John Crown, UCD Newman Clinical Professor & consultant oncologist and St Vincent's University Hospital spoke to participants about the future of drug treatments as therapies become both personalised and targeted.

Clinicians and academic partners met the following day to discuss the potential for advancing the scientific programme of cancer research within the Ireland East Hospital network; a catchment population of 1.7 million people.

This critical mass of clinicians and researchers within this network provides huge opportunities for enriched basic research collaboration and crucially will greatly enhance interactions with the pharmaceutical and medical device industries.

Prof Walter Kolch, Director said, "As a scientist, you often become engrossed in the complexities and painstaking detail of the experimental process, losing sight of the wider perspective. This cancer open house event provides a unique opportunity to connect with and be inspired by the people I hope will ultimately benefit from our fundamental research programmes."

UCD Ireland East cancer open house was organised by Conway Fellow, Dr Amanda McCann along with colleagues in the UCD Translational Oncology research group and UCD Medicine Research.

Conway Fellow, Dr Darran O'Connor speaking with participants touring laboratory facilities during the UCD Ireland East cancer open house.

Continued funding successes

During the economic crisis, Institute grant funding fell by more than 40% but Conway Fellows have managed to reverse this trend by increasingly securing non-exchequer and industry funding.

Prof Boris Kholodenko is a partner on the EU FP7-KBBE project entitled *Synthetic Cellular Signalling Circuits (SynSignal)* that aims to deliver a synthetic biology toolbox and finished products custom designed for major present and future industrial applications of cellular signalling.

Cellular signalling systems are crucially important for a broad range of critical health and disease areas and high value industrial applications.

SynSignal will dramatically impact on the accessibility of drug discovery technologies, particularly for cancer and diabetes, and for enabling technologies to create the next generation of flavours, fragrances, and nutritional ingredients.

Dr Chris Watson (UCD Conway), Dr Mark Ledwidge (SMMS), and Prof Ken McDonald (SVUH), have been awarded EU FP7 funding for the FIBRO-TARGETS research project.

With 11 European partners in 6 countries from public research organisations and industry, FIBRO-TARGETS aims to target cardiac fibrosis for heart failure treatment. More than 6.5 million people suffer from heart failure in Europe.

Specifically, the focus will be on clarifying the mechanisms involved in myocardial interstitial fibrosis that contribute to heart failure and are likely to become therapeutic targets for this disease.

Prof Walter Kolch is part of another recently funded EU FP7 collaborative research project focused on cardiovascular disease. *Systems Biology to Identify Molecular Targets for Vascular Disease Treatment (sysVASC)* aims to identify the causative events in cardiovascular diseases in order to predict novel therapeutic targets.

The sysVASC consortium includes 17 partners from 10 countries and, for the first time in a large research consortium, uses modern, systematic medical approaches that can contribute to early and individual diagnosis and treatment through the use of new biomarkers from blood and urine.

Conway Fellows continue to secure national funding under programmes such as the Food Institutional Research Measure (FIRM) by the Dept of Agriculture, Food & the Marine. Prof Helen Roche and Dr Fiona McGillicuddy and colleagues in Teagasc (Dr Aidan Moloney) and the UCD Institute of Food & Health (Dr Frank Monaghan, Dr Anne Nugent) received funding through this scheme to examine if a novel fatty acid (CLA) found in beef has beneficial effects with respect to diet-induced diabetes and cardiovascular health.

(l-r): Dr Aidan Moloney, Teagasc; Minister for Agriculture, Food & the Marine, Mr Simon Coveney TD; Professor Helen Roche, UCD Conway Institute and Minister of State at the Department of Agriculture, Food and the Marine, Mr Tom Hayes TD.

Imprinting hypoxic signature to help resolve inflammation

The Taylor group in collaboration with colleagues in the University of Colorado, Denver including lead author and Conway alumnus, Dr Eric Campbell have recently shown how immune cells can shape the microenvironment of an inflamed tissue to effect disease progression.

Neutrophils or polymorphonuclear leukocytes (PMNs) are a specific type of immune cell with a vital role to play in host defence. They move to regions of injury or infection to detect and kill invading microbes. These actions involve energy demanding processes that consume significant amounts of oxygen.

This study investigated how neutrophils contribute to inflammation in diseases such as Crohn's disease and ulcerative colitis. The research team were able to show that activated neutrophils are capable of depleting local oxygen to such an extent that epithelia in close proximity sense this and trigger genetic changes to promote tissue survival.

Conway Fellow, Prof Cormac Taylor said, "Initial studies carried out in UCD Conway Institute demonstrated that immune cells when stimulated, consume significant amounts of oxygen. Using microarray analysis, the team uncovered a set of hypoxia-responsive genes regulated by cross-talk between neutrophils and epithelial cells in the mucosal tissue.

This study, led by Prof Sean Colgan at the University of Colorado, Denver, suggests that neutrophils initiate a hypoxic microenvironment that prompts surrounding mucosal tissue to take corrective action to restore the balance of gas levels even after the neutrophils have been cleared away. These findings may provide insight into new therapeutic approaches to inflammatory disease.

Reference
Transmigrating Neutrophils Shape the Mucosal Microenvironment through Localized Oxygen Depletion to Influence Resolution of Inflammation. Campbell EL et al. Immunity 2014 Jan 16;40(1):66-77.

Personalising treatment in idiopathic pulmonary fibrosis

Researchers led by Conway Fellow, Prof Seamas Donnelly have identified a potential biomarker of rapidly progressive idiopathic pulmonary fibrosis (IPF) and pinpointed a defective molecular function as a potential therapeutic target.

IPF is a fatal progressive interstitial pneumonia that leads to the breakdown of normal lung architecture and the loss of lung function as a result.

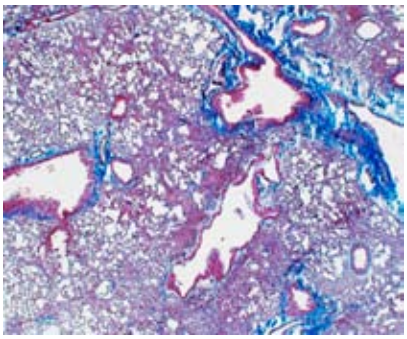
In humans, the innate immune system is responsible for recognising tissue injury and infection. Toll-like receptor 3 (TLR3) is an innate immune system receptor involved in this process of identifying pathogens and defending against them.

The Donnelly group investigated whether a particular genetic defect in the TLR3 gene might disrupt the normal inflammatory response in IPF and accelerate the progression of the disease. This specific genetic variation in one of the component DNA building blocks of the TLR3 gene is named L412F single-nucleotide polymorphism (SNP).

The UCD team in collaboration with colleagues internationally examined the impact of defective TLR3 function in the lung and on the progression of IPF using lung fibroblasts from patients with and without TLR3 L412F SNP and in a laboratory disease model.

Commenting on the results, Dr Gordon Cooke, senior postdoctoral research fellow and an author on this publication said, "This study identifies the TLR3 L412F polymorphism as a potential marker of rapidly progressive disease and defective TLR3 function represents a potential therapeutic target in IPF."

Reference
The Toll-like Receptor 3 L412F Polymorphism and Disease Progression in Idiopathic Pulmonary Fibrosis. Dwyer DN et al. American Journal of Respiratory & Critical Care Medicine. 188; 12, 1442-1450. December 15, 2013.



Masson-trichrome staining of lung sections from TLR3-/- mice shows increased collagen deposition

'Molecular fossil' identified in fungi

All but a few eukaryotes die without oxygen, and they respond dynamically to changes in the level of oxygen available to them. One example of ancient oxygen-requiring biochemical pathway in eukaryotes is the biosynthesis of sterols, producing cholesterol in animals and ergosterol in fungi.

The mechanism regulating the sterol pathway is widely conserved between animals and fungi and centres on a protein family of transcription activators named the sterol regulatory element binding proteins (SREBPs), which form part of a sterol-sensing complex.

However, in one group of fungi; the Saccharomycotina, control of the sterol pathway has been taken over by an unrelated regulatory protein, Upc2.

The Butler group used comparative genomic analysis to investigate the timing of the evolutionary switch from one regulatory mechanism to another; from SREBPs to Upc2. They found that one yeast species, Yarrowia lipolytica is unique as it contains both SREBP and Upc2 genes.

Using genetic and biochemical analysis, the group showed that Upc2 is the main regulator of the hypoxic response in Y. lipolytica, and regulates the levels of sterols in the membrane, while SREBP appears to be a 'molecular fossil' that has lost its role as a sterol regulator.

The SREBP gene retains some role in the hypoxic response of Y. lipolytica however, and is required for maximal growth when oxygen levels are low. Derivatives of SREBPs are also required for the growth of several yeast species as filamentous forms, which is important for virulence.

Conway Fellow, Prof Geraldine Butler says, "We found that the evolutionary switch from SREBP to Upc2 was a two-step process in which Upc2 appeared in an ancestor of Saccharomycotina, and SREBP subsequently lost its sterol-regulatory function while retaining an ancient role in filamentation.

The findings are exciting from an evolutionary perspective but also have tremendous potential for clinical use if they can be applied to the development of more effective anti-fungal therapies".

Reference
Zinc finger transcription factors displaced SREBP proteins as the major sterol regulators during Saccharomycotina evolution. Maguire SL et al. PLoS Genetics. doi/pgen.1004076

Targeting monocyte function to reverse atherosclerosis

The Belton group recently published findings describing a novel mechanism through which a dietary fatty acid alters monocyte function inducing regression of pre-established atherosclerosis.

Atherosclerosis, the underlying cause of heart disease and stroke, is a complex progressive disease involving multiple genetic and environmental factors.

One contributing factor to the development of atherosclerotic plaque is the continual recruitment of circulating pro-inflammatory monocytes to the damaged blood vessel and their subsequent migration through the activated endothelial where they rapidly differentiate into macrophages.

The recruitment of monocytes is a highly orchestrated process. Transmembrane proteins called integrins play a central role in this by mediating rolling and adhesion of leukocytes that causes them to adhere to the developing plaque.

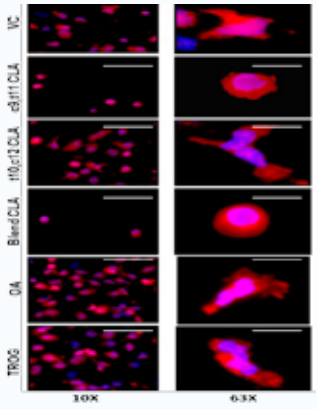
The Belton group have previously shown in a murine model of atherosclerosis that conjugated linoleic acid (CLA), alters monocyte/macrophage function causing regression of the disease.

Dr Orina Belton said, "We are trying to define the mechanisms through which CLA mediates its atheroprotective effect so as to identify novel pathways that limit or ultimately reverse atherosclerosis.

In this study, we have been able to clearly demonstrate that CLA targets integrin gene expression so as to suppress the ability of monocytes to adhere to endothelial cells. We also show that CLA modulates monocytes toward an anti-inflammatory phenoype resulting in impaired monocyte migration."

The data presented by the Belton group describe a novel functional role for CLA in the regulation of monocyte adhesion, polarisation, and migration.

Reference
Conjugated Linoleic Acid Targets b2 Integrin Expression to Suppress Monocyte Adhesion. de Gaetano, M; Dempsey E et al. The Journal of Immunology, 2013, 191: 4326–4336.



Confocal microscopy of human peripheral blood monocytes treated with CLA isomers, vehicle (VC), control lipids (OA) and positive control (TROG). CLA inhibits migratory response of HPBMCs

Ministerial launch of Systems Biology Ireland

On December 5th 2013, Minister for Research and Innovation, Seán Sherlock TD launched the dedicated research facility for Systems Biology Ireland (SBI) and highlighted its potential for breakthroughs in personalised medicine.

Minister Sherlock said, "This magnificent new facility is a major step that will enable SBI to lead in the advancement of personalised medicine on a global scale, and in a key area prioritised for investment under Horizon 2020."

Combining the power of computers and modern biology to understand diseases such as cancer, SBI develops diagnostics and therapies that are tailored to the individual patient. Finding the right drug for the right patient is a major problem and SBI aim to double the number of patients that cancer drugs work for by 2020.

"To really take advantage of the new drugs becoming available for targeted therapies, we urgently need the telescopic sights that will allow us to take each patient's cancer into the crosshairs individually. SBI is developing these sights" says Prof Walter Kolch, SBI Director.

Prof Walter Kolch (Director, Systems Biology Ireland), Sean Sherlock TD (Minister of State for Research and Innovation) Hugh Brady (President UCD) Prof Boris Kholodenko (Associate Director, Systems Biology Ireland)

Welcoming new Conway Fellow

Following his successful application, Dr Brian Rodrigues, UCD School of Physics has been awarded Conway fellowship. His research is focused on functional biological materials and advanced scanning probe microscopy-based characterisation techniques of biological materials.

A recent *Nature Communications* article in collaboration with Prof Abhay Pandit at NUI, Galway demonstrates the possibilities of atomic force microscopy (AFM). Dr Rodrigues and PhD candidate Liam Collins utilised very high-aspect ratio probes to navigate the complex architecture of microscopic algae (diatoms) and show that nano-scale architectural features of the frustule remained after chemical modification.

"Atomic force microscopy is a versatile tool applicable to many of the Conway research themes, and I look forward to developing productive collaborations with fellow Conway researchers in the years to come", said Dr Rodrigues.

Reference
Thiol-functionalization of the living diatom- tailoring the chemistry of the frustule during synthesis. Lang,Y et al. Nature Communications 2013: 4, 3683..

Investing in Your Future

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