Improving Psoriasis with GLP-1 Analogue Therapy

UCD clinician scientists and researchers from NUI Maynooth and Trinity College led by Conway Fellow, Professor Donal O'Shea have reported an improvement in the severity of psoriasis in patients following glucagon-like peptide-1 (GLP-1) analogue therapy. Their findings, published in Diabetologia raise the possibility of therapeutic applications for GLP-1 in inflammatory conditions due to the direct impact on innate natural killer T (iNKT) cells.

Psoriasis is an inflammatory skin condition causing scaling, itching, redness and plaque formation to varying degrees of severity. Associated with obesity and other metabolic diseases such as diabetes, it carries an increased risk of cardiovascular disease. iNKT cells are implicated in the development of psoriasis and obese people have lower iNKT cells in comparison to lean individuals.

The clinical team based in St Vincent's University Hospital found an unexpected improvement in the severity of psoriasis in a patient with type 2 diabetes within days of starting GLP-1 analogue therapy. They surmised this was due to the direct action of GLP-1 on iNKT cells.

The team began treating two obese patients with type 2 diabetes and psoriasis with the GLP-1 analogue, liraglutide. Both patients experienced relief from their psoriasis symptoms within days of starting treatment and the psoriasis area and severity index (PASI) decreased in both.

Describing the laboratory findings, Dr. Andrew E. Hogan, UCD Newman Scholar and senior scientist said, "There was an alteration in iNKT cell number before and after commencing treatment; an increased number in the circulation and decreased number in psoriatic plaques. We also found that iNKT cells expressed GLP-1 receptor and modulated cytokine production".

Professor Donal O'Shea believes that "Although extensive research will be required to investigate GLP-1 immune cell interactions, the potential benefit for inflammatory conditions such as psoriasis is promising".

Reference:

Hogan AE et al. Glucagon-like peptide-1 (GLP-1) and the regulation of human invariant natural killer T cells: lessons from obesity, diabetes and psoriasis. Diabetologia (2011) 54:2745–2754 doi:10.1007/s00125-011-2232-3

Drucker DJ & Rosen CF. Glucagon-like peptide-1 (GLP-1) receptor agonists, obesity and psoriasis: diabetes meets dermatology. Diabetologia (2011) 54:2741–2744 DOI 10.1007/s00125-011-2297-z

Conway Successes at SSRA and MGA Awards

More than 10 Conway Fellows supervised undergraduate medical students for laboratory or clinical research projects during the summer. The students presented their results as part of the summer student research awards (SSRA) scheme organised by UCD School of Medicine & Medical Science.

Valerie Toh received the Research Excellence Silver medal for her project entitled, "The Fate of Chemoresistance in Epithelial Ovarian Carcinoma (EOC)". Jointly supervised by Dr Amanda McCann and Dr Fiona Furlong, Valerie looked at the epigenetic regulation of two proteins overexpressed in EOC and their impact on chemoresistance.

Dr Len Harty received the UCD Medical Graduate Association (MGA) O'Connell Research Medal for his work entitled "Early TNF Inhibition Therapy Greatly Reduces the Impact of Inflammatory Arthritis on Personal Productivity over Time". Len works with Professor Doug Veale and Dr Ursula Fearon in the Education Research Centre, St Vincent's University Hospital. His study of early arthritis patients suggests that the impact of arthritis on patient productivity may be used as a predictor when considering early TNFi therapy.

Pictured at the SSRA ceremony (L-R) Mary Anne Kenny (Irish Medical Times), Valerie Toh (Research Excellance Silver awardee), Professor Michael Keane, Chair, research adjudication panel

Profiling Enzyme Active Site Characteristics

UCD researchers, Nicole Howe and Mariangela Ceruso, led by Professor J. Paul G. Malthouse recently published findings in Biochimia et Biophysica Acta (BBA) Proteins & Proteomics on their investigation of the pH stability of the stromelysin-1 catalytic domain and its mechanism of interaction with a glyoxal inhibitor using nuclear magnetic resonance (NMR) studies.

The stromelysins are metalloproteases and, as all metalloproteases have similar active sites, the team believe that their findings should provide insights into the interaction of glyoxal inhibitors with the catalytic domains of other similar metalloproteases.

In advance of their experiments, the team looked at the pH stability of stomelysin over a range of values so as to ensure no significant irreversible denaturation of the enzyme during experiments. They concluded that the stromelysin-1 catalytic domain (SCD) is stable in the pH range 6.0-8.4 for at least 16 hours. From their experiments using ^{13}C NMR to determine if there is oxyanion stabilisation and 1H NMR to detect the presence of low barrier hydrogen bonds, they concluded that the inhibitor glyoxal group is not directly coordinated to the catalytic zinc atom of the SCD. SFI, PRTLI4 and UCD funded this research.

Reference:

Howe N, Ceruso M et al. pH stability of the stromelysin-1 catalytic domain and its mechanism of interaction with a glyoxal inhibitor. BBA Proteins & Proteomics (2011) 1394–1403

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Investing in Your Future

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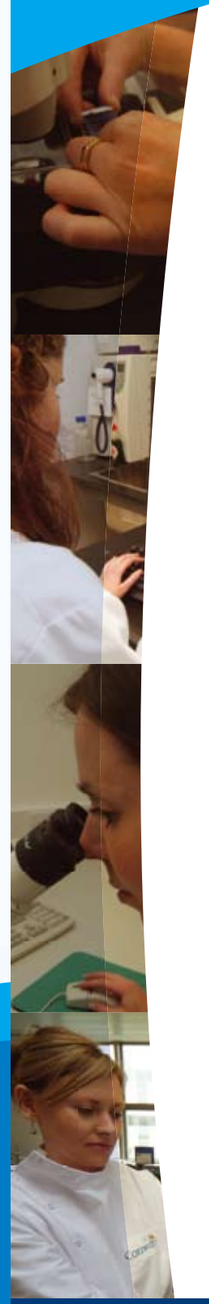
conway focus



Creating the Tree of Life

Imagine the wealth of information that would be at our fingertips if we could understand the genetic basis and evolutionary history that underlies the vast diversity in form and function seen within mammals.

An international collaboration including Conway Fellow, Dr Emma Teeling has created a phylogenetic framework using large genetic datasets to better understand the evolutionary history of mammalian families and the role of the environment and events in earth history in promoting living biodiversity.

Recently published in the journal Science, the findings of the Tree of Life consortium are the culmination of a five year project led by scientists at the University of California, Riverside (Prof. Mark Springer) and Texas A&M, USA (Prof. William Murphy).

The study generated the largest DNA sequence alignment from more than 99% of mammalian families to build evolutionary trees that depict how different groups of mammals are related to each other and when they diverged from each other.

Dr Emma Teeling's research group, a Science Foundation Ireland funded team and members of the Tree of Life consortium, produced the majority of bat data in the project.

Explaining how the team produced reliable time estimates of when different mammal groups split, she said, "We used a 'relaxed clock' approach that enables rates of DNA to change across the tree of mammals. We used a large collection of well established fossil mammals to estimate rates of change on different branches of the tree. This allowed us to convert the phylogentic tree of evolutionary relationships into a time-tree, in which the branches are scaled in proportion to time.

Using the time-tree, we were able to examine when different groups of mammals originated and diversified, and then associate factors that might have been responsible for these diversification events. For example, we observed a distinct pulse of diversification near the end of the Cretaceous Terrestrial Revolution (80-82 million years ago) when flowering plants started to diversify and when most of the mammalian orders began diverging from one another".

This phylogeny also serves as a framework to understand the history of the unique changes in the genome underlying the vast morphological diversity observed in more than 5400 living species of mammals. Co-lead author on the publication, Professor Mark Springer from the University of California, Riverside said, "When you understand how taxa are related to each other…you can pinpoint key molecular changes that are associated with key morphological changes".

For Emma Teeling's research, this equates to changes at genomic level underpinning morphological and molecular changes associated with flight and echolocation in bats. "I personally will use this phylogeny to explore in more detail the evolution and genetic control of vision and hearing and how this relates to human disease", she said.

She is excited about the possibilities that the framework offers biologists for comparative research in biomedicine, physiology and immunology. "Although the Tree of Life is currently a work in progress, it provides a benchmark that we can use into the future to decipher how our genome functions and has evolved".

Reference:

Meredith et al. Impacts of the Cretaceous Terrestrial Revolution and KPg Extinction on Mammal Diversification. www.sciencexpress.org/22 September 2011/Page 1/ doi:10.1126/science.1211028

Tree of Life: http://mammaltree.informatics.sunysb.edu/investigators.htm

Plecotus Auritus: the brown long-eared bat found all over Ireland

Director's Message

Welcome!

This issue follows the tremendous success of the 11th annual UCD Conway Festival of Research & Innovation, which celebrated the outstanding achievements of our researchers in the past year. The moderated poster sessions highlighted how basic research findings are being translated into clinical and industrial applications that will positively impact our society into the future. Arising from his UCD Conway Festival Medal award, Dr Mark Pickering will now represent UCD in the Roche 'National Researcher of the Year' competition in November. We wish him every success in the event!

As we enter the second decade since the establishment of the Institute, we are consolidating our research expertise in order to dynamically respond to the prevailing funding environment and to proactively engage with stakeholders to shape the research funding landscape into the future. I look forward to working within our research community in this new academic year to harness our collective strengths and strive to achieve our strategic goals.

Professor Walter Kolch
Director

conway focus

Neurotherapeutic Research Scoops Conway Festival Medal

Dr Mark Pickering was awarded the 2011 UCD Conway Festival of Research & Innovation gold medal, sponsored by Roche, for his research to identify a novel class of remyelinating agent with potential therapeutic use in myelination disorders such as multiple sclerosis. He will now represent UCD in the Roche 'National Researcher of the Year' competition, which takes place on November 8th in the Radisson Blu Hotel, Golden Lane, Dublin.

A postdoctoral researcher in the Neurotherapeutics Research Group led by Conway Fellow, Dr Keith Murphy, Dr Pickering staved off his competitors and impressed the judging panel with a concise overview of this research project and its innovative potential.

He explained that although therapeutic agents currently on the market, such as interferon beta and natalizumab, produce significant benefits in multiple sclerosis, they are limited in targeting inflammation and immune-mediated damage, and are ineffective in progressive disease types. The Neurotherapeutics Research Group has instead focused on finding an agent that can induce remyelination.

Using an in-vitro system, the team screened for potential remyelinating agents before progressing to validate results in-vivo. Outlining their findings, Mark said, "We saw that UCD-MS1 accelerated myelin repair after cuprizone-induced, non-inflammatory demyelination in murine models. The pro- myelin properties of UCD-MS1 may not be unique to this compound as we have identified three structurally related compounds that display similar efficacy in vitro."

He believes that UCD-MS1 may be useful as a single therapy in myelination disorders, or synergistically with an immunomodulatory agent. Additionally, UCD-MS1 might be deployed in non-inflammatory myelinopathies for which no therapies currently exist.

In total, thirty abstracts were shortlisted for presentation to judging panels in the six moderated poster sessions held over the course of the one-day event. Each of the six category winners were then given ninety seconds in which to persuade the judges of the importance of their research. The six category winners were Drs Mark Pickering, Jens Rauch, Fiona Furlong, Luis Alvarez, Alex Cheong, Emma Börgeson.

Dr Hugh Brady, UCD President (left) and Dr Mark Pickering, UCD Conway Festival gold medal winner.

HRB Fellowship Award for Translational Kidney Disease Research

Dr Debra Higgins, UCD School of Medicine & Medical Science, has been awarded a 4-year Postdoctoral Fellowship in Translational Medicine from the Health Research Board. This will allow her to further investigate lysyl oxidase (LOX) proteins as potential biomarkers for early stage kidney disease and as a therapeutic target for treatment of chronic kidney disease (CKD).

Chronic kidney disease is associated with poor health outcomes and high economic cost. There is a significant lack of reliable biomarkers to identify early stage renal injury and to predict those patients likely to progress to chronic and end-stage kidney disease.

The degree of tubulointerstitial fibrosis correlates with progression of the disease and decline in renal function. Dr Higgins has shown that hypoxia occurs early in kidney injury and promotes disease progression through up-regulation of a number of pro-fibrogenic processes.

LOX proteins are involved in cross-linking collagen fibres in the extracellular matrix, thus enhancing fibrotic scarring and contributing to loss of renal function. Dr Higgins identified that these hypoxia-inducible targets are up-regulated early in kidney disease and pivotal for disease development.

Debra Higgins proposes to devise novel diagnostic products for renal disease by analysing LOX expression in human blood, urine and biopsy samples from patients with acute and chronic kidney injury.

"By correlating expression levels of LOX and hypoxia regulated proteins with degree of kidney damage in acute kidney injury or chronic kidney disease, I aim to validate LOX as an early biomarker of renal injury and develop an appropriate detection strategy for point of care use in the clinic", she said.

Dr Higgins has already shown that inhibiting LOX activity in the body can protect against development of renal disease. She now proposes to evaluate LOX inhibition as a therapeutic strategy for early treatment of renal disease through use of a number of complementary and appropriate in vivo models.

"My collaborators on this project will provide vital expertise in the process of translating my basic research findings into the clinical setting and industrial application".

They include consultant nephrologists, Dr Denise Sadlier, Mater Misericordiae University Hospital and Dr John Holian, St. Vincent's University Hospital; UCD academic sponsor and Conway Fellow, Prof Catherine Godson, UCD School of Medicine & Medical Science; international academic partners, Prof Barbara Murphy, Mount Sinai, New York and Prof Amato Giaccia, Stanford University; and industrial partner, Dr Cormac Kilty, CEO of Argutus Medical, a company involved in the development of renal injury biomarkers.

Comparing Effectiveness in Rheumatoid Arthritis Therapeutics

In head-to head comparisons of the five therapeutic agents currently licensed in Europe for the treatment of rheumatoid arthritis (RA), differences in efficacy have been highlighted in findings published in the Annals of the Rheumatic Diseases.

Researchers at St Vincent's University Hospital, the National Centre of Pharmacoeconomics and the Department of Statistics, Trinity College Dublin led by Conway Fellow, Professor Oliver Fitzgerald analysed 16 published trials using a Bayesian mixed treatment comparison (MTC) model.

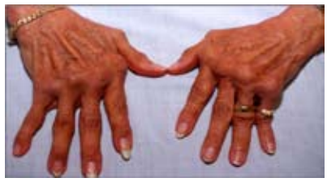
Each of the five tumour necrosis factor-α (TNFα)antagonists; adalimumab, certolizumab, etanercept, golimumub and infliximab have shown considerable efficacy compared to a placebo control in randomised controlled trials with patients who show an inadequate response to conventional disease-modifying anti-rheumatic drugs such as methotrexate. However, with little comparative information of the relative efficacy between the anti-TNFα agents, it is difficult for clinicians to make an informed choice of agent.

The Bayesian MTC model was chosen for the flexibility to include more data and handle more complex modelling structures. The trials measured the response to treatment using either the American College of Rheumatology (ACR) response criteria or the Health Assessment Questionnaire (HAQ). ACR measures the relative improvement in a defined set of criteria while HAQ looks at the extent of functional disability in the disease.

The study found that the rank order of efficacy when using the HAQ score is etanercept, certolizumab, adalimumab, golimumub and infliximab. The most effective agents throughout the trials were etanercept and certolizumab. This may be due to the fact that they are less likely to stimulate the body's immune response than antibody therapies.

Commenting on the significance of the study, Professor Oliver FitzGerald said, "This comparative effectiveness estimate for anti-TNFα agents may be a useful tool when cost-effectiveness is a consideration in the choice of drugs. It could be used within the clinical setting as part of a matrix of decision-making tools"

Reference
Schmitz S et al. A mixed treatment comparison of the efficacy of anti-TNF agents in rheumatoid arthritis for methotrexate non-responders demonstrates differences between treatments: a Bayesian approach. Ann Rheum Dis (2011) doi:10.1136/annrheumdis-2011-200228



Patient with rheumatoid arthritis

Clustal Omega: The Ultimate Alignment Programme?

How would you compare the sequence of a histone protein across 10,000 different species? Until now the question was partly an abstract one because the technology for generating sequences was slow and expensive.

Today, rapid advances in technology and the falling cost of genome sequencing are facilitating proposals to sequence 1000 human genomes (http://www.1000genomes.org) and 10,000 vertebrate genomes (http://www.genome10k.org). Future scientific studies may have to compare 100,000s of sequences and databases will house millions of genome sequences.

Modern approaches to aligning very large numbers of sequences are starting to become a bottleneck when facing such large data sets. They are either fast yet generate unacceptably poor quality alignments or they are accurate yet prohibitively intensive of computing power.

UCD researchers led by Professor Des Higgins and their collaborators in Europe, Asia and the USA have addressed these issues using Clustal Omega, a new programme recently described in Molecular Systems Biology, a scientific journal produced jointly by Nature and EMBO.

Clustal Omega can align virtually any number of protein sequences quickly and delivers accurate alignments. One novel aspect is the use of vectors to reduce the complexity of a key step in the algorithm, dramatically reducing the processing time. Currently, the programme is designed to align protein sequences (not nucleic acids) but can run on a personal computer or over a server and is available at http://www.clustal.org. Science Foundation Ireland funded this research.

Des Higgins developed the original Clustal programme for aligning protein sequences in 1988, which has become one of the most highly cited bioinformatics papers ever. One of the innovations of that programme was that the algorithm was designed to work on personal computers, which greatly increased its use among scientists.

Reference
Sievers F et al. (2011) Fast, scalable generation of high-quality protein multiple sequence alignments using Clustal Omega. Molecular Systems Biology, Vol. 7, No. 1 msb.2011.75.

Higgins DG, Sharp PM (1988). "CLUSTAL: a package for performing multiple sequence alignment on a microcomputer". Gene 73 (1): 237–244

Helicobacter Pylori Target Key Regulator of Actin Cytoskeleton

Cell migration and invasion are critical aspects of disease development whose actions can be sabotaged by bacteria and viruses for their own benefit.

By targeting signalling factor proteins tasked with regulating changes to the scaffolding or cytoskeleton of the cell, bacteria and viruses can promote their uptake into cells and sustain the infective process by spreading further.

A study led by Professor Steffen Backert, UCD School of Biomolecular & Biomedical Science and involving researchers in Germany, Austria and Spain proposes that the type-1 carcinogen Helicobacter pylori (Hp) targets the protein, cortactin in order to protect the gastric epithelium from excessive cell lifting and ensure sustained infection in the stomach.

Cortactin is a key regulator of the actin cytoskeleton but often described as its Achilles heel because it seems prone to hijack by pathogens keen to attack the very structure of the cell.

The findings of this study, published recently in the journal Cell Host & Microbe, describe how Hp targets cortactin by two independent signalling pathways in order to regulate gastric epithelial cell scattering and adhesion.

Professor Backert explains, "When Hp targets cortactin, it leads to tyrosine dephosphorylation and serine phosphorylation. The phosphorylation status of cortactin dictates its subcellular localisation and signal transduction partners. These changes to the amino acid structure of the protein consequently impact on the regulation of gastric epithelial cell scattering and adhesion."

The gene encoding cortactin is amplified in some human cancers and scientists suspect that the protein plays a major role in tumour invasion. Backert and his team hope to investigate in future studies how Hp-mediated disruption of signalling to cortactin could contribute to the onset of gastric cancer.

Reference
Tegtmeye N et al. Serine Phosphorylation of Cortactin Controls Focal Adhesion Kinase Activity and Cell Scattering Induced by Helicobacter pylori. Cell Host & Microbe 9,520–531,June 16 2011