APRIL
2016
NEWSLETTER

SCHOOL OF
Biochemistry & Immunology

Trinity College Dublin
The University of Dublin

2015 has seen some major biochemical research discoveries in the School typified by publications of the highest quality, particularly in some of our core research areas of inflammation, neurodegeneration and structural biochemistry. The importance of the collaborative and multidisciplinary approach taken in the School was demonstrated by the success of projects ranging from issues of global clinical importance such as antibiotic resistance to an innovative multidisciplinary approach to the deciphering and prediction of patterns of protein glycosylation in health and disease. Some of this research is described below.

The appointment of five new academics from places like the Massachusetts Institute of Technology and Harvard Medical School highlight the international reputation the School has developed over the years and will ensure the continuation of excellent research and teaching in the School in years to come.

Our Chair of Biochemistry, Professor Luke O'Neill, has just been elected a Fellow of the Royal Society which is made up of the UK's most eminent scientists. Congratulations to Luke!

Hope you have an enjoyable summer,

Gavin Davey

Professor Gavin Davey
Head of School

Trinity Researchers Lead €2.5 million Project to Tackle Autoimmune Diseases

Researchers from the School of Biochemistry & Immunology have been awarded €2.5 million to work on biomarkers and drug targets for autoimmune and other immune-mediated diseases. This funding has been provided by Science Foundation Ireland (SFI) and AbbVie, to support four new research positions over the next three years. Professor Kingston Mills said: "Inflammation is a vital process in fighting infection. However, if uncontrolled, it can contribute to the development of autoimmune diseases, such as rheumatoid arthritis, psoriasis, Crohn's disease and multiple sclerosis. This collaborative research project with AbbVie, a major biopharmaceutical company, will focus on identifying and building our understanding of the cellular and molecular mechanisms that cause inflammation to assist in developing new disease markers and drug targets for the treatment of a range of inflammatory diseases." Jim Sullivan, Ph.D., Vice President, Pharmaceutical Discovery, AbbVie, and Ph.D. graduate of the School of Biochemistry, said: "AbbVie has a long history in Ireland and the country has contributed greatly to our global success. Combined with our existing manufacturing operations, these new research collaborations will foster continued innovation in the treatment of Crohn's disease, one of our most important therapeutic areas. We hope to unlock the potential for significant advancements for patients with serious disease."

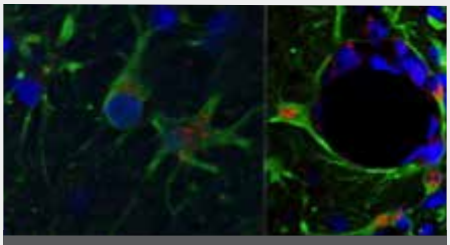
(Left to right): Dr Ken Nally, APC Microbiome Institute Project Leader, Professor Mark Ferguson, Director General Science Foundation Ireland & Chief Scientific Adviser to the Government of Ireland, Mr Richard Bruton TD, Minister for Jobs, Dr Jim Sullivan,Vice President of Pharmaceutical Discovery at AbbVie, Mr Todd Manning, General Manager, AbbVie Ireland, Professor Jean Fletcher, School of Biochemistry and Immunology, TCD and Professor Fergus Shanahan, Director, APC Microbiome Institute, University College Cork.

Immunologists Unearth Key Piece of MRSA Vaccine Puzzle

Professor Rachel McLoughlin's group has unearthed a key piece of the MRSA vaccine puzzle by identifying specific 'helper' cells whose role in the immune response is critical in infection outcomes. Anti-microbial resistance is a global crisis and the development of alternatives to antibiotics such as vaccines is imperative as the World Health Organisation warns of an impending "post-antibiotic era," with the potential to undermine modern medicine. Traditional approaches to vaccine development have failed to develop an effective weapon against MRSA, methicillin resistant S. *aureus*, a major cause of healthcare-associated infections and mortality. Eight promising candidate vaccines have failed in clinical trials, despite showing promise in pre-clinical models. Professor McLoughlin's group found that 'T-helper type 1 cells' were elevated in patients following *S. aureus* infection. Their model vaccine, which jolted these cells into action, improved infection outcomes. Dr McLoughlin said: "This study demonstrates the importance of translational research. Using pre-clinical models we identified an immune mechanism important for protection against *S. aureus* infection, but it was via collaboration with clinicians at three Dublin teaching hospitals that we were able to translate these findings to show the same mechanism of immunity is relevant in human infection. Our findings will directly inform the design of next-generation anti *S. aureus* vaccines and could significantly increase our chances of realising an effective vaccine to protect patients from MRSA."

Dark Stars in Inflammation: Astrocytes in the Neurodegenerating Brain

Researchers from the School discovered that specialised astrocytes abandon their posts as protectors and repairers of the brain when primed by the neurodegeneration of cells around them. Astrocytes, named as a result of their star-shaped appearance, function in healthy brains to assist with normal brain function and metabolism. However, the researchers from the School of Biochemistry & Immunology demonstrated that these cells play a major role in the inflammatory hypersensitivity of the degenerating brain, by responding in an inappropriate and exaggerated fashion when stimulated by inflammation around them. This discovery has important implications for the management of neurodegenerative conditions such as stroke and Parkinson's and Alzheimer's diseases.



(Left) Astrocytes (green) express abundant chemokine CCL2 (red) after acute IL-1 insult and this chemokine is also expressed at the surface of brain blood vessels (right) to attract immune cells to the tissue.

In findings just published in the *Journal of Neuroscience*, the research group of Wellcome Trust Research Professor, Colm Cunningham, showed that stimulated astrocytes produce exaggerated amounts of molecules known as chemokines, which mobilise and recruit large numbers of inflammatory cells from the periphery to the brain. Normally, this process is tightly regulated in the young, healthy brain. The chemokines CCL2 and CXCL1 are synthesised when the brain is exposed to acute pro-inflammatory cytokines, such as those produced during acute injury to the brain or during neurodegeneration. Professor Cunningham is funded through a Wellcome Trust Senior Research Fellowship, while Edel Hennessy, a PhD student who performed much of the research, was supported by a Trinity Foundation College Award.

A New Language for Cells

In a ground-breaking study that merges linguistics, biochemistry, computer science and mathematics, Professor Gavin Davey's group has written a formal language that enables deciphering of the complex process of glycosylation whereby proteins are modified by sugar molecules .

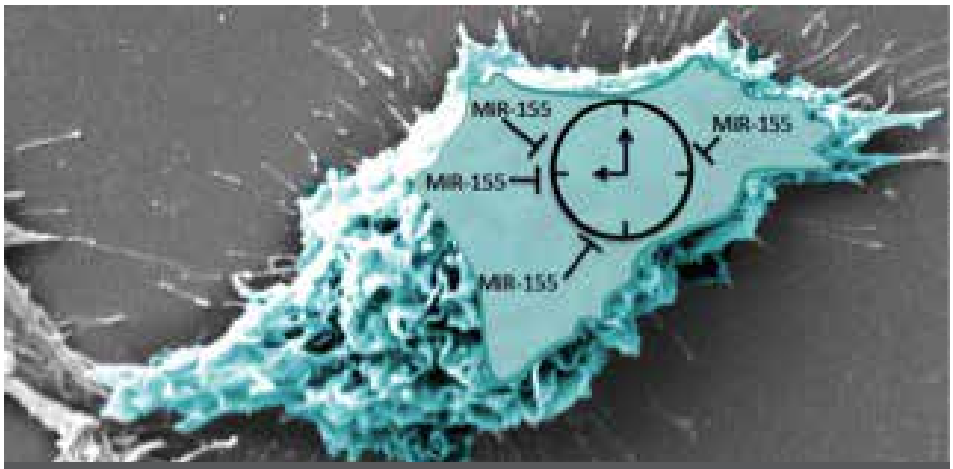
In the study published in world-leading systems biology journal, *PLOS Computational Biology*, a computer-based language and computational model are presented, along with a web application.

Professor Davey said: "The majority of proteins are modified with millions of sugar molecules. This is extremely important to physiological processes like blood typing. However, we still do not understand how cells control these glycosylation events. This has enormous ramifications for cancer cells, neurons, immune cells and any other cell type whose surface is enriched with glycoproteins."

Andrew McDonald, the inventor of the language, said: "We took our lead from the linguist Noam Chomsky who described the formal properties of grammar in 1959. We assigned a letter-based grammar that allows the simple representation of millions of glycoforms."

"We constructed a method for their graphical interpretation and a pattern-matching algorithm that generates networks of enzyme-catalysed reactions. This system can predict millions of possible glycoforms and the control points that generate much of the complexity in normal and cancerous cells."

This will greatly facilitate the study of how cancer cells, immune cells and neurons change their surface glycosylation during disease states.



The microRNA MiR-155 can target the clock in macrophages, leading to enhanced inflammation.

Inflammation Stops the Clock

Dr Annie Curtis, Senior Research Fellow in Professor Luke O'Neill's lab is the lead author of a paper published in *Proceedings of the National Academy of Sciences USA*, which uncovered a link between the body clock and the immune system that is relevant to the treatment of inflammatory and infectious diseases. The study shows how the biological clocks in important white blood cells (macrophages) stop when they are exposed to bacteria. This exposure causes the destruction of a key cog in the clock's mechanism called BMAL1 and results in the cell becoming active and inflamed. The macrophage begins to make a number of inflammatory proteins that effectively wake up and activate the immune system.

€2 Million Award for Inflammation Research


Professor Luke O'Neill with Dr Eva Palsson McDermott and Dr Beth Kelly.

Arthritis, inflammatory bowel syndrome, Multiple Sclerosis and Alzheimer's disease all have one thing in common: inflammation. Understanding what causes it is crucial to developing new treatments for these chronic illnesses. Professor of Biochemistry at Trinity, Luke O'Neill, is a global pioneer in inflammation research.

He has secured a €2 million Investigator Award through the Science Foundation Ireland-Health Research Board-Wellcome Trust partnership to investigate new theories that consider how certain cells behave and cause inflammation. His goal is to find new therapies.

Public Engagement


Renuka with her project at BT Young Scientist Exhibition 2016.

An important part of the School remit is engagement with the public, outreach to primary and secondary students and the encouragement of young scientists. Professor James Murray is justly proud of his work mentoring Renuka Chintapalli from Loreto Secondary School, Balbriggan, who was the individual runner up at this year's BT young scientist competition, held in the RDS, Dublin. Renuka developed a predictive tool for identifying FLNc-associated biomarkers of oesophageal cancer metastasis. Renuka also won the Perrigo student award for best project in the Biological & Ecological Science category at the Young Scientist competition and the RCSI Special Award for the project with the "Best Impact on Human Health". So impressed was Professor Murray with Renuka's work that he submitted the research results to the journal Nutrition and Cancer where it has been accepted for publication. Quite an achievement for a secondary school student and a wonderful example of the importance of outreach and the potential of young scientists. Renuka also spent a week in the School in 2015 as part of a TY group who spend a week learning about and engaging in research. Mol an óige agus tiocfaidh sí!

Winner — Best Partnership Alliance of the Year Award (2015 Pharma Award)

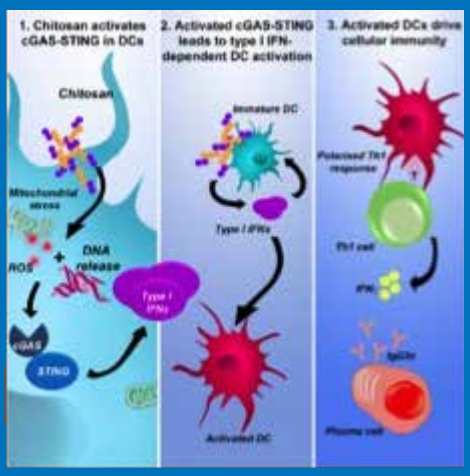
Tom Tobin, Logistics Manager, Micro Bio Ireland, presents the Partnership Alliance of the Year award to the team from the Biopharmaceutical Industry Technical Group which includes industry members and Professor Gavin Davey, School of Biochemistry and Immunology, TCD.

A group led by Professor Gavin Davey was the winner of the Best Partnership Alliance of the Year Award (2015 Pharma Awards). This award recognises innovative collaborations, both internally and externally, in Ireland's pharma industry that have a strong strategic partnership involving commercial inputs from both partners. The SFI-funded Spokes Project 'Advanced Biopharmaceutical Technologies' involves scientists from the National Institute of Bioprocessing Research and Training (NIBRT), Dublin City University, Trinity College Dublin and Solid State Pharmaceutical Centre (SSPC) who, along with seven pharma partners will investigate new methods for bioprocessing immunotherapeutics and controlling post-translational modifications of biotherapeutics. The project relies on the use of the Nuclear Magnetic Resonance (NMR) centre in Trinity Biomedical Sciences Institute for quantitative metabolomics and protein structure determination.

The Lavelle Group Publish Two Papers in the Cell Press Journal *Immunity*

The Lavelle group and the O'Neill group recently reported a novel role for the adaptor protein Mal. The role of Mal as an adaptor protein in toll like receptor signalling was identified by Prof O'Neill in 2001. In a recent paper Dr Cliona Ní Cheallaigh *et al* demonstrate a new role for Mal in interferon-γ signalling and find that it is required to kill intracellular *Mycobacterium tuberculosis*. The common human Mal S180L polymorphism attenuates IFN-γ signalling and impairs responses to tuberculosis infection. This discovery has potential implications in the treatment of TB patients and opens up new avenues to address the role of Mal in other conditions, including cancer, where interferon gamma either plays pathogenic or protective roles.

In the second paper from the team, Elizabeth Carroll *et al* demonstrate a novel mode of action by which the vaccine adjuvant chitosan promotes cellular immune responses. Adjuvants are essential in many vaccines to promote innate and adaptive immunity. However, our limited understanding of their mode(s) of action is an obstacle to progress. Carroll *et al* demonstrate that the cationic polysaccharide chitosan activates dendritic cells and promotes Th1 responses by engaging the DNA sensor cGAS-STING pathway. This work provides new insights into adjuvanticity and may lead to improved vaccine adjuvants for diseases including TB, malaria and cancer.



Save the Dates

26-28 August 2016
Alumni Weekend at TCD
For more information please visit
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