2014 Annual Symposium, Friday 9th May 2014
‘Research at the Interface’

Prof. Stanley Appel, Professor of Neurology, Weill Cornell Medical College of Cornell University
Prof. Kevin Shakesheff, Professor of Advanced Drug Delivery and Tissue Engineering, University of Nottingham.
Prof. Hidde Ploegh, Professor of Biology, MIT
Prof. Dennis McGonagle, Professor of Regenerative Medicine, University of Leeds

A selection of PhD students and Postdoctoral Researchers from TBSI will also present at the symposium

‘Investing in your future’
Programme
8.50 am – 9.10 am – Opening of Symposium – Prof. Luke O’Neill and Prof. Clive Williams

Session 1 – Chair – Prof. Cliona O’Farrelly
9.10 am – 10 am – Prof. Hidde Ploegh, Professor of Biology, MIT
“Immune engineering using sortases and single domain antibodies”
10.00 am – 10.40 am – PhD Session 1
Catherine Byrne – “Teicoplanin dosing in haematological malignancy: Is it time to reconsider?”
Henrique Almeida – “Extracellular matrix derived scaffolds for cartilage regeneration”
Andrew Byrne – “The synthesis of novel compounds to target Burkitt’s lymphoma”
Gisela Vaz – “3D oesophageal cancer models for PDT”
10.40 am – 11.00 am – Coffee (Knowledge Exchange)

Session 2 – Chair – Prof. Daniel Kelly
11.00 am – 11.50 am – Prof. Kevin Shakesheff, Professor of Advanced Drug Delivery and Tissue Engineering, University of Nottingham. “Materials for cell and protein delivery”
11.50 am – 12.40 pm – PhD Session 2
Jason Gavin – “Colonial drug metabolism: Friend or foe?”
Tariq Mesallati – “Tissue engineering scaled-up, anatomically accurate osteochondral constructs for joint resurfacing”
Sarah Edwards – “The role of Vγ4 T cells in EAE, a model for multiple sclerosis”
Gillian Gunning – “Cardiovascular research: How to mend a broken heart”
Roisin Loftus – “mTORC1 dependent metabolic reprogramming is a prerequisite for NK cell effector function”
12.40 pm – 1.40 pm – Lunch (Knowledge Exchange)

Session 3 – Chair – Prof. Conor Buckley
1.40 pm – 2.30 pm – Prof. Dennis McGonagle, Professor of Regenerative Medicine, University of Leeds. “Mesenchymal Stem Cells in vivo”
2.30 pm – 3.20 pm – Postdoctoral Researcher Session
Dr Grainne Cunniffe – “Regenerating large bone defects”
Dr Russell McLaughlin – “The genetics of amyotrophic lateral sclerosis in Ireland”
Dr Francesco Manoni – “Coaxing electrophilic anhydrides to become nucleophiles”
Dr Eva Palsson – “Pyruvate Kinase M2 as a key regulator of the Warburg Effect in macrophages”
3.20 pm – 3.50 pm – Coffee (Knowledge Exchange)

Session 4 – Chair – Prof. Orla Hardiman
3.50 pm – 4.40 pm – Prof. Stanley Appel, Professor of Neurology, Weill Cornell Medical College of Cornell University. “Neuroinflammation Fans the Flames of Neurodegeneration: Lessons from Amyotrophic Lateral Sclerosis”
4.40 pm – 5.20 pm – PhD Session 3
Sharee Basdeo – “Pathogenic T-cell plasticity; CD161 the new therapeutic target for RA?”
Susan Breslin – “The effects of acquired neratinib-resistance on HER2-overexpressing breast cancer cells”
Martin Holmes – “Using acoustics to objectively assess inhaler use”
Ryan McGarrigle
5.20 pm – 5.30 pm – Closing Remarks and Prizes – Prof. Luke O’Neill - TCD
5.30 pm – Reception (Knowledge Exchange)
Invited Speakers

Prof. Hidde Ploegh, Professor of Biology, MIT

Title: "Immune engineering using sortases and single domain antibodies"

Abstract: Methods for the visualization of proteins often rely on fusions with fluorescent proteins such as GFP, but not all such constructs tolerate the presence of these bulky substituents without loss of function. Sortases are bacterial transacylases with the remarkable property of having very short recognition motifs in their substrates, and capable of accepting a sheer limitless number of modified peptides that may then be installed on the protein of interest. The sortagging reaction is exquisitely specific and often proceeds with quantitative yields. These methods have been used to install fluorophores on antibodies and antibody fragments, as well as isotopes suitable for in vivo PET imaging. Importantly, entire classes of surface proteins, such as type II membrane proteins (N-terminus inside, C-terminus outside) are refractory to labelling with GFP, for example because the fusion product fails to properly insert in the membrane, or does not properly display its ligand binding site(s). Sortagging of type II membrane proteins can often overcome these shortcomings. We have used this approach also to equip antibodies with payloads destined for antigen presentation, as a means to elicit a robust immune response. More recently we have begun to generate panels of camelid-derived single domain antibodies, not only as a more convenient source of well-behaved antibody fragments for delivery of sortase-installed antigenic payloads, but also as crystallization chaperones. Structural biologists are well aware of the impact of inclusion of such single domain antibody fragments in obtaining crystals of proteins that are otherwise difficult to crystallize.

Bio: Hidde L. Ploegh is a biochemist who received his training in the Netherlands and at Harvard University. After group leader positions at the University of Cologne (1980), Germany, and the Netherlands Cancer Institute, Amsterdam (1984), he moved his laboratory to the Center for Cancer Research at MIT (1992) where he continued his studies of the antigen processing and presentation pathways that feed MHC products with the peptides presented to T cells. In 1997 he assumed the directorship of the graduate program in immunology at Harvard Medical School. In 2005 he joined the Whitehead Institute for Biomedical Research, where he is also a Professor of Biology in the Department of Biology at MIT. His current work is focused on the development and application of protein engineering methods and genetic tools to manipulate the immune response.
Prof. Kevin Shakesheff, Professor of Advanced Drug Delivery and Tissue Engineering, University of Nottingham.

Title: Materials for cell and protein delivery

Abstract: This talk will review the work of the UK Regenerative Medicine Platform Hub in Acellular Technologies. Materials can play an important role in orchestrating regenerative signals at sites of injury within the body. Highly porous injectable materials have been developed that allow cell-to-material interactions to be controlled and co-delivery of cells and drugs within a mechanically tailored environment. Applications in orthopaedics, cardiology and neurology will be highlight.

Bio: Professor Kevin Shakesheff is Director of the Wolfson Centre for Stem Cells, Tissue Engineering and Modelling (STEM). His independent scientific career began at the Massachusetts Institute of Technology under a NATO fellowship following a PhD and his qualification as a register pharmacist. His inventions and scientific breakthroughs have resulted in over 170 peer-reviewed full papers that have been cited more than 5500 times to date, the establishment of 2 successful companies, the submission of 13 patent application families and numerous international awards. He currently holds a prestigious European Research Council Advanced Grant within an active research portfolio of more than £7 million. In addition, he has taken a leading role in shaping interdisciplinary research in the UK through continued membership of senior policy and grant awarding committees. In 1997 he founded, with Dame Julia Polak, the Tissue and Cell Engineering Society (TCES). In 2013 he became a Royal Society Wolfson Merit Award Holder. He is a member of the Medicines and Healthcare Products Regulatory Authority (MHRA) Biologicals and Vaccines Expert Advisory Group, co-Director of the EPSRC Centre for Innovative Manufacturing Centre in Regenerative Medicine, Lead of the Research Councils UK India Science Bridge in Biopharmaceuticals and a Member of the Department of Health’s Modernising Pharmacy Careers Programme. He is a Sub-Panel Member for the UK’s Research Excellence Framework (REF) for 2014. In 2011 he was made a Fellow of the Royal Pharmaceutical Society. Throughout his career he has demonstrated a commitment to communicating his science and his field to non-specialist audiences. For many years he has worked with the Royal Institution initially as part of their Scientists for the New Century series and then by taking Royal Institution presentations to Schools across the UK. He has presented his work on Channel 4 as part of the Animal Farm series in which he discussed the potential of tissue engineering and stem cell technologies.
**Prof. Dennis McGonagle, Professor of Regenerative Medicine, University of Leeds.**

**Title: Mesenchymal Stem Cells in vivo**

**Abstract:** A pre requisite for the optimal exploitation of Mesenchymal Stem Cell (MSC) therapy is a better understanding of the biology of MSCs in vivo and their function in health and disease. Historically such studies have been hampered by a paucity of useful phenotypic markers and by the notion that MSCs were so incredibly rare, that therapeutic exploitation would only be feasible following prolonged “bulking up” utilising cell culture. Having recognized a close relationship between bone marrow (BM) MSCs and bone marrow resident fibroblasts, we developed a procedure based on microbead pre-enrichment/FACS sorting and purified characteristic stellate cells that could differentiate into three mesenchymal lineages following culture expansion that is based on MSC expression of the CD271 (LNGFR marker).

Comparisons between freshly sorted and expanded BM MSCs revealed quantitative changes in the expression of both molecular and surface markers, suggesting loss of some in vivo settings that maybe directly controlled by BM microenvironment. The function of MSCs also changes with ageing and the aspirated CD271 fraction and sister CFU-F formation in vitro falls off. Furthermore, the microarchitecture of the bone marrow environment hinders the procurement of MSCs compared to the more mobile HSCs. Upon defining the in vivo niche of marrow MSCs it is possible to liberate large quantities using enzymes or physical disaggregation. In man MSCs are quite abundant at sites of rapid skeletal regeneration and produce several molecules including BMPs and SDF-1 that may play important roles in orchestrating tissue repair.

Armed with the knowledge of the marrow MSC phenotype and topography, we subsequently discovered synovial fluid resident MSCs. Surprisingly the numbers of these are elevated in Osteoarthritis which was unexpected since the OA joint is generally thought not to be capable of good intrinsic repair. However, situations can arise in vivo where fluid resident MSCs, that appear to be derived from the adjacent synovium based on comparable molecular profiling, can adhere to injured cartilage. This opens open novel “in situ tissue engineering” strategies aimed at bolstering resident MSC function. To summarise, the knowledge of native skeletal and joint resident MSCs is still in its infancy but holds great promise for the development of cost effective and efficient regenerative medicine applications.

**Bio:** Dennis McGonagle FRCPI, PhD trained in medicine at University College Dublin and graduated in 1990. He trained in General Medicine and Rheumatology at St James University Teaching Hospital in Dublin and at the Leeds General Infirmary UK. He is currently Professor of Investigative Rheumatology at the NIHR funded Academic Unit for the Musculoskeletal Diseases and Leeds Teaching Hospitals NHS Trust. His major interest is the use of
unmanipulated mesenchymal stem cells for arthritis therapy development where seminal papers on the in vivo phenotype of adult mesenchymal stem cells in collaboration with Dr Elena Jones at the University of Leeds have been published. The group also discovered synovial fluid stem cells in 2004. His second major interests include the use of imaging to understand pathogenic mechanisms of arthritis in man, tissue microanatomy studies and laboratory studies into mechanisms of therapeutic responses to drugs. He has published several articles relevant to understanding disease mechanisms and a pathological oriented classification of psoriatic arthritis and has developed a new mechanistic classification of inflammatory disease. In Spondyloarthritis his work has helped elucidate the central role of the enthesis in disease and has shown how the enthesis anchors the nail to the skeleton. In osteoarthritis (OA) his work has shown the emerging role of collateral ligaments/entheses in early hand OA and he has also developed new mechanistic classifications for OA. In RA his MRI work showed the primacy of synovitis. His funding sources include or have included the Wellcome Trust-EPSRC, UK NIHR, ARUK, MRC UK and EU FP7 programme. He has published over 240 articles and has a Google Scholar H factor of 61.
Title: Neuroinflammation Fans the Flames of Neurodegeneration: Lessons from Amyotrophic Lateral Sclerosis.

Abstract: Neuroinflammation is a prominent pathological feature of neurodegeneration in Alzheimer Disease, Parkinson Disease, and Amyotrophic Lateral Sclerosis, and characterized by activated microglia and infiltrating T cells at sites of injury. These diseases present predominantly as sporadic, and to a lesser extent, inheritable disorders. Although the etiology of the sporadic forms is unknown, specific mutations in inheritable forms of ALS have revealed the central role of misfolded proteins. In experimental models dysfunction of multiple molecular pathways has been implicated in neuronal injury including alterations in RNA, autophagy, the ubiquitin-proteasome, and mitochondria, increasing reactive oxygen species and impairing axonal transport. The key question is whether compromise of any or all of these pathways within neurons is sufficient to cause neuronal death. In mouse models of ALS, expression of the genetic defect and accumulation of misfolded proteins in motor neurons, microglia, or astrocytes alone do not lead to clinical disease. Neurons do not die alone; neuronal injury is non-cell autonomous and depends on a well-orchestrated dialogue involving neurons, glia, and T cells that actively influences the balance of neuroprotection and neurotoxicity, and mediates neuronal viability and neuronal injury. In early stages neuroprotection predominates with M2 microglia and Treg lymphocytes. In later stages, misfolded proteins such as SOD1, TDP-43, and FUS amplify neuronal injury and neuroinflammation, activating M1 microglia to kill motor neurons and promote self-propagating neurodegeneration. T cells and monocytes/macrophages/microglia appear to mediate similar functions in ALS patients: circulating monocytes are predominantly M1 pro-inflammatory phenotypes, and T regulatory cells are dramatically decreased and dysfunctional leading to rapid deterioration and early death. Thus neuroinflammation is the sine qua non of neurodegeneration. Quelling inflammation by upregulating neuroprotective Treg/M2 cells and downregulating Th1/M1 provide potentially meaningful therapeutic interventions in human ALS.

Bio: Stanley H. Appel, M.D. is the Director of the Houston Methodist Neurological Institute, Chair of the Department of Neurology, and the Edwards Distinguished Endowed Chair for ALS at Houston Methodist Hospital in Houston, TX. He is also Professor of Neurology at Weill Cornell Medical College.

Dr. Appel is a native of Massachusetts and received his Bachelor Degree at Harvard University and his Medical Degree from Columbia College of Physicians and Surgeons. He was previously Chair of the Department of Neurology at Baylor College of Medicine as well as Chief of the Neurology Division and the James B. Duke Professor of Medicine at Duke University Medical Center. Dr. Appel has served on a number of MDA advisory committees.
Research in Dr. Appel’s laboratory has focused on developing new insights into neurodegenerative diseases with primary emphasis on ALS. His studies of mutant SOD transgenic mice have documented that neuroinflammation and activated microglia are neuroprotective during early stages of disease and cytotoxic during late stages of disease. These two stages appear to be modulated by peripheral T-cells that enter the CNS at sites of neuronal injury; Th2 and regulatory T-cells are increased in early stages and appear to provide neuroprotection, while Th1 T-cells are increased in later stages and mediate cytotoxicity. Comparable studies in human ALS have employed PCR techniques to confirm the presence of activated microglia and to demonstrate the presence of CD4 T-cells as well as immature and mature dendritic cells and enhanced chemokine signaling.

His laboratory was the first to document that regulatory T lymphocytes modulate disease progression in ALS patients. More specifically, regulatory T lymphocytes are decreased in ALS patients that progress at a faster rate; the levels of Treg may thus serve as a biomarker of rates of disease progression. His current efforts are focused on enhancing the protective immunity of Treg cells and anti-inflammatory microglia, and decreasing the proinflammatory immunity of Th1 effector lymphocytes and proinflammatory microglia.

Dr. Appel is a member of numerous professional societies and committees, and is the author of 15 published books and over 400 articles on topics such as Amyotrophic Lateral Sclerosis (ALS), neuromuscular disease, Alzheimer Disease, and Parkinson Disease. He has received a number of awards for his accomplishments in Neurology and Biochemistry, including the 1997 Gold Medal for Excellence in Biomedical Research from Columbia College of Physicians and Surgeons, the 2003 Sheila Essey Award for ALS Research, 2004 MDA’s Wings Over Wall Street Diamond Award, 2005 Texas Neurological Society Lifetime Achievement Award and the 2008 John P. McGovern Compleat Physician Award.