



MMI Clinician Scientist ANNUAL MEETING 2011

**Science Gallery, Trinity College Dublin
Friday 1 July**



- **Keynote Address by Professor Garret FitzGerald (University of Pennsylvania)**
- **MMI Clinician Scientist Fellows present their research as short talks**
- **Other Medical Graduates present their PhD research as posters**
- **Opportunities to discuss the activities of MMI in facilitating clinical and translational research nationally**

The meeting has Continuing Medical Education (CME) Credits from the Royal College of Physicians of Ireland (5 Credits)



MMI Clinician Scientist Annual Meeting 2011

The third Annual Scientific Meeting of the MMI Clinician Scientist Fellowship Programme (CSFP) will take place on Friday 1 July 2011 (Science Gallery, Trinity College Dublin) and will also be part of the Tercentenary of the foundation of the Trinity College Dublin School of Medicine. This year we are broadening participation and we are keen to attract those with an interest in clinical and translation research and in developing careers as clinician scientists.

MMI Clinician Scientist Fellows present their research as short talks

The meeting features MMI Clinician Scientist Fellows presenting their research as short talks, with the best presentation awarded the MMI CSFP Medal 2011. This will be the final CSFP Annual Scientific Meeting for the first cohort of MMI Fellows, as they are soon to complete their PhD studies. It therefore represents a milestone in their careers and the last opportunity for them to present their research as a group with their supervisors, leading principal investigators in five academic institutions, in the audience. A number of the MMI Clinician Scientist Fellows presenting their research as short talks during the meeting have published high impact research findings and/or received prestigious awards during their fellowships.

Call for Posters from other medical graduates undertaking PhDs

This year we are inviting other medical graduates undertaking PhDs in the MMI partner institutions to present posters on their research. An easy online registration process on the MMI website has been set up for this purpose. There will be prizes for the best posters.

Demonstration of the MMI CSFP Curriculum Web-Portal

There will be hands-on demonstrations of the MMI Clinician Scientist Curriculum Web Portal. The aim is to attract more users in its pilot phase by demonstrating the importance of this collaborative resource currently hosting information on and facilitating participation in 69 Graduate Education Modules taking place in five academic institutions, all aligned with a curriculum developed for clinician scientist trainees.

Keynote Address

We are delighted to welcome Professor Garret FitzGerald (Professor of Medicine & Pharmacology at the University of Pennsylvania and Director of the Institute for Translational Medicine & Therapeutics) to give the keynote address: *The Divided Self: a Science of Uncertainty and an Art of Probability*. As well as considering the role of the Clinician Scientist in the 21st century, Prof FitzGerald will adjudicate the awards for best presentations.

The event will be an excellent opportunity for Clinicians and GPs currently involved in research at any level, and those not yet involved but contemplating it, to learn more about patient-focused research facilitated nationally by MMI. Please note we have applied for CPD credits for this meeting.

MMI Clinician Scientist Annual Meeting 2011

Date: Friday 1 July 2011		Venue: Science Gallery, Trinity College Dublin	
0930	Tea / Coffee		
1000	Welcome and Opening Remarks Professor Michael Gill (Head of Department of Psychiatry, School of Medicine, TCD)		
Session 1			
Chair: Dr Jane McGrath (TCD)			
1015	Dr Mark Coyne (NUI Galway) <i>Targeting and Stratifying High Risk Myeloma: Reasons to Target Cell Division Cycle 7</i>		
1030	Dr Fionnuala Ni Áinle (TCD) <i>Enhancing the Therapeutic Potential of Activated Protein C</i>		
1045	Dr Brian Walsh (UCC) <i>Umbilical Cord Blood Biomarkers of Neonatal Hypoxic Ischaemic Encephalopathy</i>		
1100	Dr Gerard Curley (NUI Galway) <i>Mesenchymal Stem Cells Enhance Repair from Ventilator Induced Lung Injury by A Paracrine Secreted Mediator Mechanism</i>		
1115	Tea / Coffee + Poster Viewing		
Session 2			
Chair: Dr Eoin Feeney (UCD)			
1145	Dr Daniel Schmidt (UCC) <i>Intensive Temporal Mapping of Hepatitis C HVR1 Sequences – Are there Window in the Envelope?</i>		
1200	Dr David Prichard (TCD) <i>Integrin Expression is Modulated by Deoxycholic Acid in Squamous Oesophageal Epithelium and May Have a Role in the Aetiology of Barrett's Oesophagus</i>		
1215	Dr Damian McCartan (RCSI) <i>Global Characterisation of Transcriptional Impact of Src-1 Identifies an ER Independent Mediator of Endocrine Resistant Breast Cancer</i>		
1230	<i>MMI Clinician Scientist Structured PhD Curriculum Web Portal Demonstration</i>		
1240	Lunch		
1330 - 1430	<ul style="list-style-type: none"> • Computers available to access the MMI Clinician Scientist Structured PhD Curriculum Web Portal • Poster Session (adjudicated) • Representative of the Irish Clinical Research Infrastructure Network (ICRIN) and the Dublin Centre for Clinical Research (DCCR) will be available to discuss the activities of MMI in facilitating clinical and translational research nationally • Opportunities to discuss the other MMI Education & Training initiatives 		
Session 3			
Chair: Dr Mark Coyne (NUI Galway)			
1430	Dr Fergus McCarthy (UCC) <i>Peroxisome Proliferator Activated Receptor Gamma Critically Regulates the Risk of Pre-Eclampsia</i>		
1445	Dr Mazen Al-alawi (RCSI) <i>Regulation of Ion Transporters and Airways Surface Dynamics by Lipoxin in Cystic Fibrosis Bronchial Epithelium</i>		
1500	Dr Niall Conlon (TCD) <i>CD32A R131 is Associated with a Relative Phagocytic Defect In Vitro and with the Development and Clinical Course of Bronchiectasis in an Irish Cohort</i>		

1515	Dr James Ryan (UCC) <i>Altered Adipocyte Differentiation due to the R482W LMNA Gene Mutation and Correlation with the Clinical Phenotype in Dunnigan-type Lipodystrophy (FPLD)</i>
1530	Tea / Coffee + Poster Viewing
Session 4	
Chair: Dr James Ryan (UCC)	
1600	Dr Sanjay Chotirmall (RCSI) <i>Estrogen in Cystic Fibrosis (CF): Inflammatory, Immune & Infectious Consequences</i>
1615	Dr Eoin Feeney (UCD) <i>Correlations Between Low HDL-c and Monocyte Intracellular Cholesterol Accumulation in HIV-Infected Patients Reflect Disturbances in Reverse Cholesterol Transport</i>
1630	Dr Jane McGrath (TCD) <i>Neural Connectivity in Autism Spectrum Disorders</i>
1645	Dr John O'Sullivan (UCC) <i>Novel Therapies for Myocardial Infarction and its Consequences</i>
Clinician Scientist Keynote Lecture	
Chair: Thomas Lynch (Chair, Molecular Medicine Ireland)	
1700	Professor Garret Fitzgerald (Professor of Medicine & Pharmacology at the University of Pennsylvania and Director of the Institute of Translational Medicine & Therapeutics) <i>The Divided Self: a Science of Uncertainty and an Art of Probability</i>
1800	Closing Remarks Dr Ruth Barrington (Chief Executive, Molecular Medicine Ireland)
1815	Presentation of Prizes Professor Dermot Kelleher (Head of School of Medicine, TCD)
1830	Wine Reception

MMI Fellows' presentations judging panel:

- Professor Garret Fitzgerald (Professor of Medicine & Pharmacology at the University of Pennsylvania and Director of the Institute of Translational Medicine & Therapeutics)
- Professor Anita Maguire (VP for Research and Innovation, UCC)

Posters judging panel:

- Dr Ross McManus (Senior Lecturer & Director of the PhD in Molecular Medicine, TCD)
- Dr Clare O'Connor (Senior Lecturer & Director of the Life Sciences Graduate School, UCD)
- Dr Geraldine Boylan (Senior Lecturer, Department of Paediatrics & Child Health, UCC)



MMI Fellows Presentations Abstracts

Session 1

Dr Mark Coyne (NUI Galway)

Targeting and Stratifying High Risk Myeloma: Reasons to Target Cell Division Cycle 7

Myeloma remains an incurable cancer. Although the majority of myeloma is not proliferative at diagnosis, one of the strongest predictors of progression and poor outcome is increased proliferation. This feature of myelomagenesis makes risk and treatment stratification essential and requires the development of novel, tailored treatments. This presentation suggests ways in which these objectives might be met. Cdc7 is an essential kinase required for initiation of DNA replication and cell cycle progression. This presentation will build on previous presentations at this forum highlighting the pre-clinical work supporting Cdc7 as a potential novel target in treating myeloma. Additionally, this presentation will explore the sequelae of Cdc7 inhibition and the utility of using the active kinase as a method of predicting high-risk myeloma in comparison with both traditional and more contemporary tools of stratification.

Dr Fionnuala Ni Áinle (TCD)

Enhancing the Therapeutic Potential of Activated Protein C

Severe sepsis results in a massive morbidity and mortality burden. Activated protein C (APC), a natural anticoagulant, is licensed for use in severe sepsis. APC possess anti-inflammatory signalling properties which are thought to mediate its beneficial effects.

I have characterized the role of APC glycosylation in modulating protective signalling and generated a novel recombinant APC variant with enhanced protective signalling but no undesirable anticoagulant properties [1]. I have also identified that protamine sulphate, widely used to reverse heparin anticoagulation, ablates APC substrate generation [2], highlighting the need to address potential bleeding side effects during clinical use. Moreover, I have recently identified a potential novel natural cofactor for APC protective signalling.

1. Ni Ainle, F., et al., *Activated protein C N-linked glycans modulate cytoprotective signaling function on endothelial cells*. J Biol Chem, 2011. **286**(2): p. 1323-30.
2. Ni Ainle, F., et al., *Protamine sulfate down-regulates thrombin generation by inhibiting factor V activation*. Blood, 2009. **114**(8): p. 1658-65.

Dr Brian Walsh (UCC)

Umbilical Cord Blood Biomarkers of Neonatal Hypoxic Ischaemic Encephalopathy

Hypoxic ischaemic encephalopathy (HIE) is among the commonest causes of neonatal mortality and morbidity. Until recently there was no treatment available, but with the advent of therapeutic hypothermia this is changing. Hypothermia is used for those with moderate to severe HIE, and to be effective must be initiated in the first 5.5 hours of life. Clinically it is difficult to grade HIE within this period, resulting in some who do not require treatment being cooled and others being missed. The aim of this PhD is to better categorise the disease mechanism of HIE, and to develop an early serum biomarker, to predict its severity.



Dr Gerard Curley (NUI Galway)

Mesenchymal Stem Cells Enhance Repair from Ventilator Induced Lung Injury by A Paracrine Secreted Mediator Mechanism

Mechanical ventilation, while necessary to sustain life during critical illness, can exacerbate the disease process. We have utilized the reparative effects of mesenchymal stem cells to focus on repair after lung stretch injury. We developed a novel animal model of mechanical ventilation induced injury and repair in the rat. We successfully administered systemic MSC therapy to enhance recovery from stretch induced lung injury in this model, illustrating that these beneficial effects were mediated through a paracrine secreted mediator rather than by the cells themselves. These effects were replicated in an in vitro study of a wound scratch model in alveolar epithelial cells.

Session 2

Dr Daniel Schmidt (UCC)

Intensive Temporal Mapping of Hepatitis C HVR1 Sequences – Are there Window in the Envelope?

Hepatitis C exists as a swarm of closely related variants called quasispecies. These are generated as a result of a lack of fidelity of the RNA polymerase with new variants replacing predecessors by merit of increased fitness or immune selection and this process is thought central to the establishment of chronic infection. Recent analysis suggests that complexity and diversity of the sequences in the hypervariable region 1 may predict treatment response. We investigate the natural history of these variables in chronic infection and our results demonstrate that potential windows of increased treatment efficacy exist. These results have important implications for the individualisation of treatment at a molecular level.

Dr David Prichard (TCD)

Integrin Expression is Modulated by Deoxycholic Acid in Squamous Oesophageal Epithelium and May Have a Role in the Aetiology of Barrett's Oesophagus

Barrett's Oesophagus (BO) represents a pre-malignant lesion for oesophageal adenocarcinoma. Severe erosion of squamous epithelium is required to allow re-epithelialization with columnar BO. Increasing exposure of the oesophagus to bile acids (BAs) has been shown to correlate with increasing likelihood of erosive oesophagitis and increasing risk of Barrett's oesophagus. This has been presumed to be because of the lethal effects of BAs and low pH on squamous epithelium. Here we demonstrate that Deoxycholic Acid (DCA) induces a loss of adherence hours prior to the onset of apoptosis. Oesophageal cells which had lost adherence were able to re-adhere and to continue growing after removal of the DCA. Using flow cytometry we demonstrated that DCA induced a reduction in integrins αV , $\alpha 5$ and $\alpha 6$, but not $\alpha 3$. Other BAs did not elicit a reduction in expression of ITGAV. Our findings suggest that DCA mediated loss of cell adhesion and apoptosis may be discreetly regulated entities, and indicate a new mechanistic understanding of the aetiology of erosive reflux disease and the genesis of BO.



Dr Damian McCartan (RCSI)

Global Characterisation of Transcriptional Impact of Src-1 Identifies an ER Independent Mediator of Endocrine Resistant Breast Cancer

Endocrine Oncology Research Group, RCSI,

SRC-1 mediates breast cancer metastasis as a transcription factor coactivator yet its complete transcriptional impact is unknown.

SRC-1 CHIP sequencing and RNAi knockdown of SRC-1 in endocrine resistant breast cancer cells with subsequent whole genome cDNA expression array analysis identified a total of 244 genes downregulated ($p < 0.05$) following SRC-1 knockdown that harboured a high confidence SRC-1 peak in the promoter region.

The most novel target selected for further validation is a transmembrane disintegrin protein identified in 49% of breast cancer patients. Expression of the protein associated with an almost two fold increase in rate of disease relapse at follow up.

Session 3

Dr Fergus McCarthy (UCC)

Peroxisome Proliferator Activated Receptor Gamma Critically Regulates the Risk of Pre-Eclampsia

Pre-eclampsia is a major cause of maternal mortality and morbidity world-wide. Peroxisome proliferator activated receptors (PPARs) are ligand activated transcription factors expressed in placental tissue. Healthy pregnant rats treated with a PPAR- γ antagonist developed key features of pre-eclampsia including hypertension, endothelial dysfunction, proteinuria, increased platelet aggregation and altered angiogenic factors. Administration of the PPAR- γ agonist, rosiglitazone, to pregnant rats with surgically induced pre-eclampsia ameliorated hypertension, vascular dysfunction and abnormally elevated microalbumin creatinine ratios, effects that were abrogated in the presence of a heme-oxygenase 1 inhibitor. These findings have important implications regarding the underlying etiology of pre-eclampsia and potential therapeutic targets.

Dr Mazen Al-alawi (RCSI)

Regulation of Ion Transporters and Airways Surface Dynamics by Lipoxin in Cystic Fibrosis Bronchial Epithelium

Lipoxin A4 is produced at inflammatory sites, and exerts anti-inflammatory effects and has been reported to be reduced in cystic fibrosis airways. The altered Cl⁻ secretion and Na⁺ hyperabsorption in CF affects the ASL height and leads to a defective mucociliary clearance, chronic infection, inflammation and progressive lung destruction. The role of LXA4 in modulating ion transport and ASL height in CF and non-CF airway epithelia was investigated. Novel findings provide evidence for an effect of LXA4 involving the FPR2/ALX receptor, apical ATP release and purinoreceptor activation, inhibition of Na⁺ absorption and stimulation of Cl⁻ secretion in CF and non-CF epithelia to finally increase ASL height. These effects open up a new therapeutic avenue in the treatment of CF.

Dr Niall Conlon (TCD)

CD32A R131 is Associated with a Relative Phagocytic Defect In Vitro and with the Development and Clinical Course of Bronchiectasis in an Irish Cohort

We identified an excess of an R131 polymorphic variant of CD32A, an IgG receptor, in a cohort of 101 Irish patients with HRCT proven idiopathic bronchiectasis compared with controls ($p < 0.01$). Patients with the R131 variant had more severe disease ($p < 0.05$), more frequent infective exacerbations ($p < 0.05$) and increased frequency of hospitalisation ($p < 0.001$). Further investigation demonstrated that CD32A R131 bearing neutrophils ($p < 0.01$) and monocytes ($p < 0.05$) are relatively less able to phagocytose pneumococcal targets and generate less oxidative burst ($p < 0.05$) than phagocytes bearing other receptor variants. CD32A R131 neutrophils also produce less elastase ($p < 0.05$). We suggest that this relative defect in phagocytosis predisposes to infection with encapsulated bacteria and is an important contributing factor to the development and course of bronchiectasis in this cohort.

Dr James Ryan (UCC)

Altered Adipocyte Differentiation due to the R482W LMNA Gene Mutation and Correlation with the Clinical Phenotype in Dunnigan-type Lipodystrophy (FPLD)

FPLD is a rare and severe form of mono-genic insulin resistance (IR), due to autosomal dominant inheritance of mutations in the LMNA or PPAR γ genes. We have demonstrated altered differentiation in 3T3-L1 adipocytes transfected to over-express the R482W LMNA mutation, the most common genetic mutation reported in FPLD. Altered SREBP-1 activation, followed by a reduction of PPAR γ expression, leads to a reduction in the ability of adipocytes to store triglycerides. We developed a novel technique to radiologically measure areas of adipose tissue deposits in patients with FPLD. We subsequently demonstrated changes in these deposits in association with PPAR γ agonist treatment via whole body MRI. We also demonstrated reduced IR in these patients. Our on-going research involves identifying key targets in the adipocyte differentiation process in order to develop new treatment modalities for FPLD.

Session 4

Dr Sanjay Chotirmall (RCSI)

Estrogen in Cystic Fibrosis (CF): Inflammatory, Immune & Infectious Consequences

Chotirmall SH¹, Cosgrove S¹, Oglesby IK¹, Smith SG², Thomas W³, O'Neill SJ¹, Harvey BJ³, *Greene CM¹, *McElvaney NG¹.

¹Respiratory Research Division, Department of Medicine, Royal College of Surgeons in Ireland

²Department of Clinical Microbiology, School of Medicine, Trinity College Dublin

³Department of Molecular Medicine, Royal College of Surgeons in Ireland

An unexplained 'gender gap' is observed in cystic fibrosis (CF). Females have poorer lung function, decreased survival and earlier *Pseudomonas aeruginosa* colonization. We evaluated the inflammatory and immune consequences of 17 β -estradiol (E2) on cystic fibrosis bronchial epithelial cells in vitro and vivo and the effect of E2 exposure on microbial pathogens within the CF airway.

E2 inhibits IL-8 release via ER β in CF bronchial epithelial cells through up-regulation of SLPI, inhibition of NF- κ B and IL-8 gene expression. Additionally, E2 and its major metabolite estriol (E3) are implicated in the mucoid conversion of *Pseudomonas aeruginosa* in vitro and vivo. These data implicate novel mechanisms for E2 in females with CF, which predisposes to infection, colonization and early mucoid *Pseudomonas* conversion which could in part, account for the observed gender dichotomy in CF.

Dr Eoin Feeney (UCD)

Correlations between Low HDL-c and Monocyte Intracellular Cholesterol Accumulation in HIV-Infected Patients Reflect Disturbances in Reverse Cholesterol Transport

ER Feeney^{1,2}, N McAuley¹, JA O'Halloran², C Rock², J Low², CS Satchell², PWG Mallon^{1,2}.

1. HIV Molecular Research Group, UCD School of Medicine and Medical Sciences, UCD, Dublin 4.

2. Department of Infectious Diseases, Mater Misericordiae University Hospital, Dublin 7.

HIV infection is associated with low levels of high density lipoprotein cholesterol (HDL-c) and an elevated risk of cardiovascular disease (CVD). In vitro data suggests HIV can interfere with genes involved in reverse cholesterol transport (RCT). These effects have not been demonstrated in vivo. We examined intracellular cholesterol (ICC) and expression of genes involved in RCT in vivo in circulating monocytes from HIV-infected subjects and HIV-negative controls. We demonstrate novel findings in relation to RCT gene expression, and show associations between ICC and circulating lipoproteins which have potential implications for the pathogenesis of atherosclerosis and CVD in HIV infection.

Dr Jane McGrath (TCD)

Neural Connectivity in Autism Spectrum Disorders

Abnormal neural connectivity may underpin core deficits of autism spectrum disorders (ASDs). The aim of this project is to investigate and relate structural and functional connectivity in the brain in ASD.

Functional MRI and functional connectivity analyses have revealed numerous brain regions that show reduced activation and connectivity in ASD. Structural MRI using diffusion tensor imaging has revealed interesting white matter abnormalities in ASD. The abnormal brain activity and connectivity in the autism group may be secondary to this anatomical abnormality in white matter.

Linking brain structure to function is complex, but this approach is crucial in improving our insight into the pathogenesis of this devastating condition.

Dr John O'Sullivan (UCC)

Novel Therapies for Myocardial Infarction and its Consequences

1. Delivering 600pg of IGF-1 post myocardial infarction (MI), we demonstrate acute activation of pro-survival kinases (Akt, ERK, and GSK-3beta), reduction in apoptosis, and long-term improvements in infarct size, LV function, regional wall function, and local and global LV remodeling.

2. Post MI, we demonstrate that nitrite increases regional blood flow in the infarct territory by fluorescent microsphere quantitation, but does not affect CT contrast patterns within the infarct zone. This has implications for interpretation of CT and MRI contrast definitions of infarct size and microvascular obstruction.

Keynote Address

Professor Garret Fitzgerald (Professor of Medicine & Pharmacology at the University of Pennsylvania and Director of the Institute of Translational Medicine & Therapeutics)

The Divided Self: a Science of Uncertainty and an Art of Probability

Physicians pursue the art of medicine in a highly personalized manner, yet their practice is based on a science designed to detect large average effects of therapeutics in potentially unrepresentative populations. The particular challenge of this century is to develop the science to inform progressively therapeutic decisions based on an individual's characteristics, such that they derive benefit and avoid harm.

Physician scientists are well placed to integrate the advances of science with the practice of medicine, yet they are a disappearing breed. The challenges of training, the economic disparities with clinically active peers and the uncertainty of success are often articulated. Less frequently discussed are the attractions and fulfillment of this choice; the possibility to impact the public health at scale, the continuous intellectual challenge, the global reach of friendship, the clash of the new, the eroticism of ambiguity. There is even, if you wish, the possibility of great wealth.

Physician scientists are crucial to solving the impasse in the development of new therapeutics. As the large vertically integrated pharmaceutical companies disintegrate, we are moving to a more globalized, modular approach to drug discovery and development. Along the way from discovery and rationalization of a target to the impact of an approved drug on clinical outcomes and its adoption in practice, the heterogeneous skills necessary to ensure success will increasingly be assembled from Pharma, Biotech and Academia as the rules of intellectual property are redrawn.

The focus on Translational Medicine and Therapeutics (TMAT), as exemplified by the proliferation of such institutes in developed countries and the proposed new center in the NIH, is designed to enhance the ability of academia to play in this space. Central to this endeavor is the need to address the deficiency in human capital – the absence of scientists, especially physician scientists – whose own research experience spans the divide between basic and clinical research and who have an understanding of pharmacology. Such physician scientists will be fundamental to our hope to reduce the art of personalized medicine to a science and to realize the potential of novel therapeutics.

Posters

No	Presenting Author	Poster Title
1	John Baugh	Getting to the Heart of Cardiac Remodelling: How Collagen Subtypes May Contribute to Phenotype
2	Peter Bede	Neuroimaging Biomarkers in Amyotrophic Lateral Sclerosis
3	Karen Boland	RPT4 as A Potential Therapeutic Target in Colorectal Cancer
4	Claire Donohoe	Establishing a Role for Targeted Therapies in Oesophageal Adenocarcinoma
5	Fred English	Blocking Poly(adp-ribose) Polymerase in Animal Models of Pre-Eclampsia Protects against the Hallmarks of Pre-Eclampsia
6	Caoimhe Fahy	A Murine Model of Atopic Dermatitis: Variation in Phenotype Development in Skin Barrier Deficiency
7	Alan Gaffney	Carbon Nanotube Surface Modification Increases Blood-Surface Interactions in Cardiopulmonary Bypass
8	Stephen Horgan	What does Brain Natriuretic Peptide tell us about Progressive Left Ventricular Diastolic Dysfunction?
9	Evonne Low	Correlation of Cardiac Output with Cerebral Oxygenation in Sick Preterm Infants During the Transitional Period.
10 - 11	Niamh Lynch	<ul style="list-style-type: none"> • Comparison of Seizure Characteristics in Full Term Newborns with Stroke and Hypoxic Ischemic Encephalopathy • The Temporal Evolution of Electrographic Seizure Burden in Neonatal Hypoxic Ischemic Encephalopathy
12	Cliona Ni Cheallaigh	Latent Tuberculosis Prevalence in Irish-Born Individuals: An Assessment by Interferon Gamma Release Assays
13	Sarah O'Beirne	Mechanisms of the Inhibitory Effects of Cxcl9 on Tgf-b Induced EMT
14	Stephen Paul	Quantum Dots Interactions with Vascular Microenvironment: The Influence of Particle Size, Human Plasma and Shear Forces
15	Nathan Stevenson	Automated Neonatal Seizure Detection using Machine Learning
16 - 17	Carol Stone	<ul style="list-style-type: none"> • Falls: Is this Geriatric Giant an Even Bigger Issue in Palliative Oncology? • Vitamin D Deficiency in Advanced Cancer; the Prevalence and its Relevance
18	Frederick Sundram	White Matter Microstructural Abnormalities in Antisocial Personality Disorder: A Pilot Diffusion Tensor Imaging Study
19	Chris Watson	Profiling Serum Markers of Inflammation and Fibrosis across the Spectrum of Hypertensive Heart Disease; TIMP1 and MMP9 Identify an At-Risk Asymptomatic Group

See following pages for abstracts



No	Presenting Author	Poster Title
1	John Baugh	Getting to the Heart of Cardiac Remodelling: How Collagen Subtypes May Contribute to Phenotype

Patrick Collier, Chris Watson, Maarten Van Es, Dermot Phelan, Catherine McGorrian, Michael Tolan, Mark Ledwidge, Kenneth McDonald, **John Baugh**

Conway Institute of Biomolecular and Biomedical Research, University College Dublin

Background

Targeting cardiac interstitial abnormalities is likely to become a major focus of future preventative strategies with regard to the management of cardiac dysfunction. Recent biomarker studies have attached particular pathological importance to accumulation of myocardial collagen subtype 3. These data are at odds with conventional wisdom which states that collagen subtypes 1&3 are inextricably linked within supra-molecular structures. Current knowledge regarding the component structures of myocardial collagen networks (often derived from non-human or even noncardiac tissue) is limited, further delineation of which will require application of more innovative technologies.

Methods

Using ex-vivo right atrial tissue from patients undergoing coronary bypass, methodology involved immunohistochemical and immuno-fluorescent staining in addition to combined confocal laser scanning and atomic force microscopy.

Results

We show for the first time, that collagen fibers within the human heart are subtype specific, with disparate anatomical locations and differential biomechanical properties. Specifically, compared to collagen 1 fibers, collagen 3 fibers tend to delineate myocytes, are less stiff, more likely to undergo plastic deformation and are less energy efficient. In atrial biopsies taken from patients in permanent atrial fibrillation versus sinus rhythm, stiffness of both collagen fiber subtypes was augmented.

Conclusions

In conclusion, we demonstrate that the two major collagen subtypes within the human heart form discrete fibers, have preferential anatomical locations within the extra-cellular compartment and exhibit significantly different biomechanical properties. We describe altered collagen quality (in addition to increased quantity) in chronic atrial fibrillation. A more complete understanding of the pathophysiology of the human cardiac collagen network may ultimately allow fibrosis to become a generalised modifiable risk factor that can be targeted in order to improve prognosis. In particular, therapies aimed at preventing atrial fibrillation must address collagen quality in addition to collagen quantity.



No	Presenting Author	Poster Title
2	Peter Bede	Neuroimaging Biomarkers in Amyotrophic Lateral Sclerosis

Bede P^{1,3}, Bokde A¹, Fagan A², Elamin M^{1,3}, Jordan N³, Byrne S^{1,3}, Hampel H¹, Hardiman O^{1,3}
¹Trinity College Dublin, ²Centre For Advanced Medical Imaging, ³Beaumont Hospital Dublin

Background

Amyotrophic lateral sclerosis(ALS) is an incurable, relentlessly progressive neurodegenerative condition. While previous imaging studies in ALS have focused primarily on the motor cortex, ALS is now recognized as a complex multisystem disorder with non-motor manifestations: neuropsychological and behavioural deficits [1]. Cognitive and behavioural deficits in ALS may precede motor symptoms, are challenging to manage and have a significant impact on survival and quality of life.

Objectives

The aim of this study is to determine the extent of frontotemporal pathology in different ALS phenotypes.

Results & Discussion

48 ALS patients and 48 age-matched healthy controls were assessed by a comprehensive battery of neuropsychological tests and underwent 3 Tesla MRI neuroimaging. 5 ALS patients demonstrated executive dysfunction, 10 ALS patients fulfilled the Neary Criteria for Frontotemporal dementia(ALS-FTD) and 33 ALS patients had no cognitive deficits. Voxel based morphometry(VBM) analysis revealed considerable differences in grey matter volumes between ALS-FTD and ALS patients with no cognitive deficits in the left anterior temporal lobe, ventral medial frontal lobe and parahippocampal regions. ALS patients with no cognitive deficits showed grey matter volume changes in the hippocampus, left dorsolateral prefrontal cortex, cerebellum, posterior cingulate and in the in right superior temporal gyrus when compared to healthy controls.

Conclusions

The results underscore the heterogeneity of extra motor involvement within the ALS spectrum. The study demonstrates the unique radiological attributes of the ALS-FTD complex. However, ALS patients with no cognitive or behavioural deficits on formal neuropsychological testing also show signs of extensive extra motor cortex atrophy.

References

[1] Phukan J, Pender NP, Hardiman O. Cognitive impairment in amyotrophic lateral sclerosis.Lancet Neurol. 2007 Nov;6(11):994-1003.



No	Presenting Author	Poster Title
3	Karen Boland	RPT4 as A Potential Therapeutic Target in Colorectal Cancer

Boland K¹, Concannon CG¹, Murray FE², Prehn JH¹

¹ Centre for Human Proteomics and Medical Systems Analysis, Department of Physiology and Medical Physics, RCSI, Dublin 2

²Department of Gastroenterology and Hepatology, Beaumont Hospital, Dublin 9

Background

Colorectal cancer is one of Irelands commonest cancers, with 2271 cases in 2009. The proteasome is a complex responsible for the degradation of intracellular proteins, playing key roles in cell cycle regulation and apoptosis. Malignant cells have higher vulnerability to the cytotoxic effects of proteasomal inhibition through greater dependence on proliferative and anti-apoptotic pathways^[1]. Rpt4 is one of 6 ATPases forming part of the 19S regulatory subunit, involved in proteasome substrate recognition and entry into the catalytic core. While its role in the ubiquitin-proteasome system has not been clearly characterized to date, yeast models have demonstrated proteasome independent roles in protein translocation and telomeric gene silencing^[2].

Results and Discussion

We have shown that Rpt4 expression is increased in tumour tissue from CRC patients compared to patient matched normal mucosa. Furthermore, we have demonstrated that colorectal cancer cells have elevated expression of Rpt4 relative to a non-transformed colorectal epithelial cell line. Rpt4 knockdown in HCT116 colorectal cancer cell lines using siRNA leads to increased cell death and reduced clonogenic survival; whilst CRL1807 non-transformed cells remained relatively unaffected. Analysis of protein expression in HCT116WT cells following knockdown of Rpt4 demonstrated increased expression of markers of ER (Endoplasmic Reticulum) stress including KDEL. We also demonstrated decreased proteasome activity following Rpt4 inhibition. Western blotting revealed increased expression of poly-ubiquitinated proteins and Hsp70 upon silencing of Rpt4. We are developing a subcutaneous tumour model in nude mice to investigate whether Rpt4 inhibition modulates tumour growth. Tumour progression will be monitored on a longitudinal basis using bioluminescence imaging^[3].

References

1. Proteasome inhibitors in cancer therapy. Crawford LJ, Walker B. J. Cell Commun. Signal. (2011) 5:101-110
2. Proteasomal ATPases link ubiquitylation of histone H2B to methylation of histone H3. Mol Cell. 2004 Feb 13;13(3):435-42
3. Bioluminescent Imaging: a critical tool in pre-clinical oncology research. O'Neill, Lyons et al. J Pathol;220(3):317-327



No	Presenting Author	Poster Title
4	Claire Donohoe	Establishing a Role for Targeted Therapies in Oesophageal Adenocarcinoma

Claire L Donohoe¹, MC Cathcart¹, E Daly², J Lysaght¹, GP Pidgeon¹, JV Reynolds¹
1Dept of Surgery, Trinity College Dublin/St James' Hospital, ²Dept of Pathology, Beaumont Hospital

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Background

Despite recent improvements in disease-specific survival following curative treatment for oesophageal adenocarcinoma (OAC), long-term outcomes remain poor with an overall 5 year survival rate of less than 40%. Therapies specific to highly expressed receptors may hold promise for increasing treatment responses. To prevent resistance developing, downstream signalling of the receptor must be inhibited.

Objectives

To assess OAC tumours for IGF1R, KDR and VEGF expression and assess the impact of *in vitro* IGF1R inhibition on cell survival.

Results

Tumours positive for IGFIR (n=161, by immunohistochemistry) had a significantly shorter median survival (23.4 months) than IGFIR negative (60.0 months, $p < 0.027$) with a corresponding decrease in 5 year survival from 52% to 32%. IGFIR positivity achieved borderline significance a predictor of poor prognosis on multivariate analysis ($p = 0.055$). IGFIR inhibition *in vitro* reduced the viability (MTT assay) and proliferation (BrdU) of OAC lines with increasing apoptosis (Annexin/PI and high content screening). Despite inhibition of IGFIR, there was no decrease in signalling via PI3K pathway (Western blot: pAKT, STMN1). Inhibition of IGFIR led to a significant increase in VEGF production by treated cells (ELISA). 95.6% of tumours from patients positive for IGFIR expressed KDR and patients with high VEGF expression and IGF1R positive tumours had poorer prognosis than those with low VEGF and no IGF1R.

Conclusion

Inhibition of IGFIR is a promising target for treatment in OAC. Co-targeting of IGFIR and KDR may prevent resistance developing.

No	Presenting Author	Poster Title
5	Fred English	Blocking Poly(adp-ribose) Polymerase in Animal Models of Pre-Eclampsia Protects against the Hallmarks of Pre-Eclampsia

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Introduction

Pre-eclampsia is a major cause of maternal and perinatal mortality and morbidity world-wide. The condition is characterised by intra-uterine growth restriction, widespread vascular dysfunction and maternal hypertension. Poly(ADP-ribose) polymerase (PARP) is a nuclear enzyme which mediates repair to damaged DNA. Overactivity of this enzyme may be associated with the pathogenesis of pre-eclampsia. We show here that PARP overactivity critically regulates the risk of pre-eclampsia in two animal models of the disease.

Materials and methods

Two distinct animal models of pre-eclampsia were utilised; the reduced uterine perfusion pressure (RUPP) rodent model of pre-eclampsiaⁱ and the eNOS^{-/-} murine modelⁱⁱ of the condition. The PARP inhibitor PJ34 was administered (30mg/kg/day in drinking water) to the above animals, and healthy relevant controls (HPC), on gestational days (GD) 12-18 of a 19 day gestation. Blood pressure (BP) was measured GD17. On GD18 the animals were culled. Pups were weighed. Resistance arteries were mounted on a wire myograph and endothelial function was assessed by measuring relaxation responses to bradykinin (BK).

Results

Pups born to vehicle treated RUPP and eNOS^{-/-} animals displayed significant growth restriction which was not impacted by inhibition of PARP (P<.001 vs. HPC). Vehicle treated RUPP and eNOS^{-/-} animals exhibited significantly raised maternal blood pressure (P<0.001 vs. HPC). PJ34 administration significantly prevented the development of maternal hypertension in both the rodent and murine models (P<0.001 vs. RUPP and eNOS^{-/-}). Both RUPP and eNOS^{-/-} animals were characterised by significant vascular dysfunction (P<0.01 vs. HPC). Administration of the PARP inhibitor PJ34 prevented this dysfunction (P<0.01 vs. RUPP and eNOS^{-/-}).

Conclusion

PARP over activity contributes to the development of a pre-eclampsia like state in the RUPP and eNOS^{-/-} models. Inhibition of PARP may be a potential therapeutic target in pre-eclampsia.

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No	Presenting Author	Poster Title
6	Caoimhe Fahy	A Murine Model of Atopic Dermatitis: Variation in Phenotype Development in Skin Barrier Deficiency

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Background

Atopic dermatitis (AD) is a chronic inflammatory skin disease. Aetiology was associated with immunologic dysregulation, however, many reports highlight how a defective epidermal barrier has a key aetiological role in AD, rather than just a result of immune disruption [1]. Filaggrin is a vital structural epidermal barrier protein. Loss-of-function mutations in the filaggrin gene cause the skin disorder ichthyosis vulgaris and convey strong genetic risk for AD [2,3,4]. The flaky tail (*maflg^{ft}/maflg^{ft}*) mouse is a model of ichthyosis vulgaris and skin barrier deficiency [5].

Objectives

To examine the effects of environments on skin barrier deficiency. Populations of *maflg^{ft}/maflg^{ft}* and *wt/wt* mice were bred in 2 specific pathogen-free housings; individually ventilated (IVC), and conventional (OPEN), boxes. Sealed caging in IVC was the only housing difference. Samples were taken at weeks 1, 4, 8, 20 and 32 of age. Dermatitis-like skin disease was scored. Serum IgE was investigated via ELISA. Histopathology assessed skin and lung tissue changes.

Results and Discussion

Clinical scoring showed increased levels of cutaneous inflammation in OPEN *maflg^{ft}/maflg^{ft}* mice compared to IVC *maflg^{ft}/maflg^{ft}* mice ($p=0.0103$). Elevated cutaneous inflammatory infiltrates were found in OPEN *maflg^{ft}/maflg^{ft}* mice compared to IVC *maflg^{ft}/maflg^{ft}* subjects (wk 4 $p=0.0002$, and wks 8, 20, 32 ns). Total serum IgE levels were higher in OPEN *maflg^{ft}/maflg^{ft}* mice from 8 weeks, significantly so from 20 weeks ($p<0.0006$).

Conclusions

This study suggests that such alterations are key in the emergence of inflammation and dermatitic-like disease, in skin barrier deficiency. Also highlighted is that initiation and severity of inflammation can be altered by environment.

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No	Presenting Author	Poster Title
7	Alan Gaffney	Carbon Nanotube Surface Modification Increases Blood-Surface Interactions in Cardiopulmonary Bypass

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Background

Blood-surface interaction in extracorporeal circuits requires the infusion of a systemic anticoagulant to prevent devastating clot formation. Bleeding and thrombosis are the most common serious complications of extracorporeal circulation[1]. Platelet activation upon contact with proteins adsorbed to foreign surfaces is the primary mechanism underlying clot formation[2].

Objectives

The general hypothesis driving our research is that surface modification of the extracorporeal circuit using carbon nanotubes, functionalised with antiplatelet agents, could decrease blood-surface interactions, thus attenuating systemic complications. The aim of the current research was to investigate interactions between non-functionalised, carbon nanotube-modified surfaces of extracorporeal circuits and blood *in vitro* and in a rabbit model of extracorporeal circulation *in vivo*.

Results & Discussion

Polyvinylchloride was coated with a surface layer of immobilised multi-walled carbon nanotubes using a swelling and ultrasonification technique. Platelet-surface interaction in a dynamic *in vitro* flow model of circulation was assessed using the Q-Sense® nanobalance system[3]. A rabbit model of extracorporeal circulation was used to test blood-surface interaction *in-vivo*. [1]

Significantly increased platelet aggregation was observed in *in-vitro* testing (n=8, p<0.05). Significantly increased clot formation was observed in *in-vivo* testing (n=8, p<0.05).

Conclusion

Surface-immobilised multi-walled carbon nanotubes, non-functionalised with antiplatelet drugs, cause platelet aggregation and increased clot formation *in-vitro* and *in-vivo*.

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No	Presenting Author	Poster Title
8	Stephen Horgan	What does Brain Natriuretic Peptide tell us about Progressive Left Ventricular Diastolic Dysfunction?

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Background

Heart failure with preserved ejection fraction is commonly preceded by a prolonged asymptomatic phase during which progressive left ventricular diastolic dysfunction (LVDD) develops. The purpose of this study was to assess whether B-type natriuretic peptide (BNP) could distinguish those with progressive LVDD from those whose diastology remained stable.

Methods

This was a retrospective cohort substudy of the STOP-HF trial [NCT00921960] an ongoing randomised controlled study involving patients with risk factors for heart failure that are being serially followed with clinical and echocardiographic assessment. We defined LVDD progression using changes in left atrial volume index (LAVI), a robust continuous echocardiographic measure of LVDD whereby progressors had a LAVI increase of greater than 3.5mls/m^2 from an initial LAVI between $20\text{--}34\text{mls/m}^2$. From 518 patients that underwent serial clinical and echocardiographic assessment, 228 patients fulfilled these criteria and were included in the analysis.

Results

34 (15%) patients displayed evidence of LVDD progression and were compared to the remaining population. Mean follow up was 14 ± 5 months. At baseline, progressors were older [68 ± 8 versus 65 ± 10 yrs; $p<0.05$], were more likely to be treated with beta-blockers [$17(50\%)$ versus $49(25\%)$; $p<0.05$], had higher levels of BNP [$28(14:44)$ versus $17(9:34)$; $p<0.05$] and had higher left ventricular mass indices [105 ± 27 versus 95 ± 23 ; $p<0.05$]. No significant gender difference or difference in rates of hypertension, diabetes mellitus, coronary artery disease, obesity or smoking was noted between cohorts. Although BNP correlated with LAVI at both timepoint1&2 ($p<0.001$), linear regression analysis revealed that even significant increases in LAVI would anticipate just small increases in BNP of a magnitude within biological variability.

Conclusions

Clinically, changes in BNP appear to be relatively indifferent to LVDD progression and pronounced changes in LAVI. Given the emerging epidemic of heart failure, more accurate biomarkers are urgently needed to aid detection of those at high risk of LVDD progression.



No	Presenting Author	Poster Title
9	Evonne Low	Correlation of Cardiac Output with Cerebral Oxygenation in Sick Preterm Infants During the Transitional Period.

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Background

Preterm infants are at increased risk of brain injury. Low superior vena cava (SVC) flow in the first 24 hours is associated with cerebral hemorrhage and adverse long term neurodevelopmental outcome. Regional cerebral oxygenation can be routinely measured at the bedside.

Objective

To investigate the relationship between cardiac function and regional cerebral oxygenation in sick preterm infants during the first 48 hours.

Design/Methods

Neonates less than 32 weeks gestation, without significant cardiac malformations, were enrolled. Echocardiographic evaluation included assessment of left ventricular output (LVO), right ventricular output (RVO), superior vena cava (SVC) flow and presence of a patent ductus arteriosus (PDA) during the first 24 hrs and at 48 hrs of life. Regional cerebral oxygenation (rSO₂) was measured continuously during the first 48 hrs utilising near infrared spectroscopy (NIRS, INVOS 5100C) and peripheral oxygen saturation (SpO₂) was simultaneously recorded. The cerebral fractionated oxygen extraction [CFOE= (SpO₂ - rSO₂) / SpO₂] was calculated. Cranial ultrasound imaging was performed between 7 and 14 days of life and at discharge.

Results

Seventeen neonates were enrolled. The median (range) for gestational age was 28+3 (23+4-32) weeks, birthweight was 1.04 (0.53-1.88) kg. Fifteen neonates survived to discharge, three of whom had abnormal cranial ultrasounds. No infant died within the first 48 hours of life. Low SVC flow occurred in 23.5% of cases, all on day 1. There was a significant increase in mean SVC flow (sem) from 83.5(11) ml/kg/min on day 1 to 95.3 (12.5) ml/kg/min day 2. SVC flow was significantly lower in the presence of a large PDA (79 vs 120mls/kg/min), pvalue<0.05).

There was a poor correlation between all cardiac output measurements and CFOE on day one (RVO: r.= 0.078, p=0.774; SVC: r= 0.064, p=0.81; LVO: r= 0.358, p=0.46) and similarly on day 2 (RVO: r.= 0.224, p=0.059; SVC: r= 0.242, p=0.45; LVO: r= 0.034, p=0.90). There was no difference in CFOE in patients with a large PDA (0.2258) compared to a small PDA(0.224).

Conclusions

There was a poor correlation between all measures of cardiac output and cerebral fractionated oxygen extraction. This reflects the inadequacy of each cardiac output measurement as a surrogate marker of cerebral blood flow and highlights the complex process of cerebral autoregulation in the preterm infant.



No	Presenting Author	Poster Title
10	Niamh Lynch	Comparison of Seizure Characteristics in Full Term Newborns with Stroke and Hypoxic Ischemic Encephalopathy

Niamh Lynch MB¹, Evonne Low MB¹, Janet Rennie MD², Geraldine Boylan PhD¹

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Aims

Up to 20% of neonatal seizures are secondary to perinatal stroke. Diagnosis relies largely on neuroimaging which is often delayed. The aim of this study was to describe the clinical and electrographic characteristics of seizures in full term newborns with perinatal stroke and to compare with seizures due to hypoxic ischaemic encephalopathy (HIE).

Methods

Continuous multichannel EEG recordings of ≥ 24 hours in neonates with evidence of stroke or HIE were reviewed. Electrographic seizures were annotated and defined as sudden repetitive stereotyped discharges lasting for at least 10 seconds on at least one EEG channel. Background EEG grade, seizure duration, frequency, location and morphology were measured. The median seizure duration and overall seizure burden were also measured.

Results

Six term neonates were identified with MRI or CT confirmation of unilateral stroke in arterial distribution between 2003 and 2010. The EEGs of these babies were compared with those of 14 term neonates, born during the same period, with HIE.

Background EEG in infants with stroke showed continuous mixed frequency activity with evidence of sleep cycling over the unaffected side. All neonates in the HIE group showed background abnormalities consistent with grade 2 or 3 HIE and sleep cycling was absent. All seizures in stroke cases were focal and accompanied by clonic seizures prior to AED administration. Seizures also showed a characteristic spike or polyspike morphology over the affected side in contrast to a predominantly diffuse sharp wave morphology in HIE.

Conclusions

This is the first study to compare long term multi channel EEGs obtained from neonates with a subsequent confirmed diagnosis of stroke, and EEG from neonates with HIE. It has identified clear differences between the EEG background activity and electrographic seizures in neonates with stroke and HIE which may aid diagnosis in the early newborn period.



No	Presenting Author	Poster Title
11	Niamh Lynch	The Temporal Evolution of Electrographic Seizure Burden in Neonatal Hypoxic Ischemic Encephalopathy

Niamh Lynch MB, Nathan Stevenson PhD, Vicki Livingstone PhD, Janet Rennie MD, Geraldine Boylan PhD

Purpose

Hypoxic ischemic encephalopathy (HIE) accounts for 60% of all neonatal seizures. There is emerging evidence that seizures cause additional injury to the developing brain that has sustained hypoxic ischemic injury. Temporal evolution of clinical seizure burden in HIE has been characterised, with maximum clinical seizure burden being observed between 24 and 48 hours of age. Continuous multi-channel video EEG is the gold standard for detection of neonatal seizures. The purpose of our study was to analyse electrographic seizures in infants with HIE, to investigate the distribution of seizure burden over time, following the initial hypoxic ischemic insult.

Methods

Full term newborns with HIE and seizures, and a minimum of 48 hours of continuous video EEG, were included in the study. Infants who received therapeutic hypothermia were excluded. Medical records of the infants were reviewed and details of clinical seizures and anti-epileptic drugs were recorded. EEGs were annotated by two electroencephalographers. Seizure annotations were converted into a time series, and the seizure period was identified. The degree of temporal evolution of seizure burden within this period was tested using skewness. Maximum seizure burden was defined as the mid-point of an hour long window, shifted in time by 1s across the full EEG recording, which contained the maximum duration of seizures. Temporal evolution was further analysed by segmenting the time series into two periods; the time between the first recorded seizure and the maximum seizure burden (T1), and the time between the maximum seizure burden and the last recorded seizure (T2). Seizure burden, duration and number of seizures per hour were analysed within each time period.

Key Findings

This study included continuous multi-channel video EEG from 15 babies. EEG was commenced at a median of 13.9 hours of age. The median seizure period was 36.6 hours (IQR: 17.8 to 52.7). Median seizure burden was 8.9 minutes per hours (IQR: 4.1 to 14.6) and median seizure duration was 206 seconds (IQR: 98 to 331). There was a median of 2.7 seizures per hour (IQR: 1.9 to 4.0). The median of the skewness coefficients was positive and statistically significant (coefficient=0.62, $p=0.015$), indicating an accumulation of seizures near the first recorded seizure. Maximum electrographic seizure burden was reached at a median age of 22.7 hours. Time from first recorded seizure to maximum seizure burden (T1) was significantly shorter than time from maximum seizure burden to last recorded seizure (T2) (p -value=0.007). Median seizure burden during T1 was significantly higher than during T2 (p -value=0.007). This study provides evidence that there is temporal evolution of electrographic seizure burden in full-term newborns with HIE. There is a short period of high seizure burden (T1) followed by a longer period of lower seizure burden (T2).

Significance

Understanding of the temporal evolution of seizure burden in HIE contributes further to our understanding of neonatal seizures, helps identify an optimal therapeutic window for seizure treatment, and provides a benchmark against which to measure the efficacy of new and innovative forms of neuroprotection and anti-epileptic medication on evolution of seizure burden.



No	Presenting Author	Poster Title
12	Cliona Ni Cheallaigh	Latent Tuberculosis Prevalence in Irish-Born Individuals: An Assessment by Interferon Gamma Release Assays

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Background

There is limited data on the prevalence of LTBI in Irish-born individuals.

Objective

We sought to assess the prevalence of latent tuberculosis using the two commercially available interferon gamma release assays (IGRAs).

Results

Quantiferon 3G® ELISA assays, incorporating ESAT-6, CFP-10 and TB7.7, and T-SPOT.TB® ELISPOT assays, incorporating ESAT-6 and CFP-10, were performed in a convenience sample of individuals of Irish origin attending the STI clinic. HIV and active TB were excluded. SPSS was used for statistical analysis. 294 patients were recruited. 195 (66%) were male, the median age was 26. 49(17%) reported travel >2 months to a country of high TB prevalence. 34 (12%) reported contact with active TB.

Test results:

	ELISA	ELISPOT
Total number of individuals	294	102
Positive n (%)	16 (5.4%, 95% CI: 2.5-7.7%)	6 (5.8%, 95% CI 0.5-6.9%)
Negative n (%)	278 (94.6%)	100 (98%)
Indeterminate	0 (0%)	0 (0%)

On multivariate regression analysis, age (OR 1.1/year, p=0.005) and travel (OR 3.8, p=0.03) were independent predictors of results.

Conclusions

The relatively high prevalence of TB risk factors and positive IGRA results in young Irish-born individuals reinforces the importance of LTBI screening of all patients when indicated, e.g. before use of biological therapies.

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No	Presenting Author	Poster Title
13	Sarah O'Beirne	Mechanisms of the Inhibitory Effects of Cxcl9 on Tgf-b Induced EMT

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Background

Idiopathic pulmonary fibrosis is the most common of the idiopathic interstitial pneumonias and is associated with a poor prognosis. Its aetiology remains poorly understood. Epithelial cell to mesenchymal cell transition (EMT) whereby fully differentiated epithelial cells transition to a mesenchymal phenotype, giving rise to fibroblasts and myofibroblasts has been implicated in its pathogenesis. Transforming Growth Factor- β (TGF)- β induces EMT in vitro and in vivo. We have previously demonstrated that CXCL9 abrogates TGF- β induced EMT via the CXCR3 receptor.

Objectives

To investigate the regulation by CXCL9 of the expression of genes involved in signaling and downstream effects of TGF- β in EMT.

Results and Discussion

Human alveolar epithelial cells (A549) were stimulated with TGF- β alone or in combination with CXCL9. Changes in the expression of a panel of TGF- β target genes at 24 hours was determined by Real Time Polymerase Chain Reaction (RT-PCR). Stimulation with TGF- β resulted in a significant increase in the expression of EMT related genes including collagen 1 α 1 and α -smooth muscle actin. Expression of these genes was abrogated by the addition of CXCL9. TGF- β stimulation resulted in the up-regulation of genes related to downstream signaling of TGF- β including Bone Morphogenetic Protein 2 (BMP2) and Bone Morphogenetic Protein Receptor type-2 (BMPR2), and the transcription factors jun and jun-B. CXCL9 inhibited the expression of these genes. CXCL9 increased the expression of Lefty, a negative regulator of Receptor-Smad phosphorylation.

Conclusions

This suggests a novel mechanism for the inhibitory effects of CXCL9 on EMT and the subsequent development of fibrosis.

No	Presenting Author	Poster Title
14	Stephen Paul	Quantum Dots Interactions with Vascular Microenvironment: The Influence of Particle Size, Human Plasma and Shear Forces

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Background

Nanomedicine approaches, many of which utilize engineered nanoparticles designed for systemic administration, have the potential to interact with platelets and endothelial cells if delivered via systemic routes [1]. Platelets play a critical role in haemostasis and thrombosis [2]. Endothelial cells line the inner surface of blood vessels and provide the surface for coagulation cascade. Hemodynamic forces generated by the flow of blood along the endothelial surface regulate both the morphology and function of endothelial cells [3]. Quantum dots (QDs) represent one of the most interesting nanotechnology-based platforms, and their unique optoelectronic properties make them a potentially versatile tool for biomedical applications [4].

Objectives

The aim of this study was to investigate possible interactions of cadmium telluride QDs with human platelets and endothelial cells.

Methods

Human platelets and platelet rich plasma were isolated from peripheral blood of healthy volunteers. Their interactions with QDs were analyzed by aggregometry, immunofluorescence and zymography. Cellular uptake and localization of QDs under various shear stresses in human umbilical vein endothelial cells and their toxicity were investigated utilizing Cellix biochips, immunofluorescence imaging and high content analysis approach. Shear-induced alterations in endothelial cell morphology were studied using confocal and atomic force microscopy.

Results

QDs were found to induce significant aggregation of platelets which was abrogated in the presence of plasma. In the absence of plasma, QDs increased the surface expression of GPIIb-IIIa and P-selectin receptors on platelets, and release of a pro-coagulant enzyme matrix metalloproteinase-2. Stimulation of endothelial cells with tumour necrosis factor- α did not cause significant difference in the uptake of QDs, however a decrease in uptake was observed at higher shear stress rates. Shear stress induced membrane ruffling and was critical for cellular uptake of nanoparticles which were localized mostly in the cytoplasm.

Conclusions

Our study demonstrates that the presence of plasma prevents human platelets from undergoing QD induced aggregation. Vascular endothelium could be effectively targeted for short term drug delivery and imaging by fine tuning the shear stress. The micro fluidics enabling platform used here could pave the way to establish a flow system in the future to study the influence of QDs on coagulation system components, and to develop new nano-scale drug delivery systems targeting vascular endothelium in an experimental setting closer to the physiological microenvironment.

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No	Presenting Author	Poster Title
15	Nathan Stevenson	Automated Neonatal Seizure Detection using Machine Learning

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Background

Neonatal seizures are associated with poor neurodevelopmental outcome. The identification of newborns with seizure and subsequent estimation of the seizure burden (the accumulated duration of seizure) are, therefore, of clinical importance. EEG is the only reliable method available for detecting seizures in the sick newborn. Unfortunately, neonatal EEG interpretation is difficult, time-consuming and requires specialised skills that are not readily available in the neonatal intensive care unit. Automation of the decision making process, using the computer, has the potential to simplify the task of seizure recognition in the EEG. The simplification of EEG analysis can assist the neonatologist when no specialist support is available.

Aim

To validate the performance of a neonatal seizure detection algorithm (SDA) based on machine learning techniques.

Methods

Multi-channel video EEGs were recorded in full term newborns with hypoxic ischaemic encephalopathy admitted to the Cork University Maternity Hospital. Seizures were annotated, blindly and independently, by 2 experienced neonatal EEG specialists. The performance of the SDA was assessed using the sensitivity/specificity via a receiver operating characteristic (ROC). Several additional metrics were developed in an attempt to translate the engineering performance for clinical interpretation.

Results

The test database consisted of EEG recordings from 41 newborns. This database was 1345 hours in length and contained 377 seizures in 7/41 newborns. Median seizure duration was 108s (IQR, 40 to 173s). The SDA produced an area under the ROC of 0.954. The accuracy of the SDA when discriminating seizure from nonseizure newborns was 40/41 (98%). All newborns with seizure were correctly classified. The detection threshold used in these calculations was based on a threshold that minimises the error of an estimate of seizure burden. This threshold results in a seizure detection rate of 60%, a false alarm rate of 0.1/hr (the results are averaged across the cohort).

Conclusion

Automated detection of seizure in newborn EEG is approaching a level of accuracy that is sufficient for clinical implementation. The process of translating from benchtop to bedside continues.



No	Presenting Author	Poster Title
16	Carol Stone	Falls: Is this Geriatric Giant an Even Bigger Issue in Palliative Oncology?

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Background

The small number of reports that describe fall rates in inpatient palliative care and oncology settings report incidences that greatly exceed average fall rates in acute and community hospitals. However, there have been no prospective studies of the epidemiology of falls in patients with cancer over longer time periods or in community-dwelling patients.¹

Objectives

(1) Identify incidence of falls in people with advanced cancer (2) test hypothesis that patients aged ≥ 65 years have a greater risk of falling than those aged < 65 years.

Results/Discussion

Consecutive admissions to community-based and inpatient palliative care services, with a diagnosis of advanced cancer, who were able to sit-to-stand and mobilize unassisted, were recruited. Demographic data was verified by patient interview and participants followed-up weekly for 6 months, or until the time of fall or death, if within 6 months. Descriptive analyses of falls were conducted. Incidence density of falls was calculated and time to fall examined using survival analysis methods.

Of 185 patients recruited, 174 have completed recruitment to date, of whom 89(51%) experienced a fall. The incidence density of falls was 2477 per 1000 person-years. Thirty-six percent of patients were aged < 65 yrs; median time to fall for persons < 65 yrs was 85 days (95% CI; 61-109) and median time to fall for persons ≥ 65 years was 96 days (95% CI; 43-150), $\chi^2=0.26$, $p=0.6$.

Conclusions

The observed incidence density of falls is more than double that reported for healthy older persons.² Our findings suggest that the exceptionally high incidence of falls observed is related to factors other than the demographic profile of cancer.

References

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2. Allan LM, Ballard CG, Rowan EN, Kenny RA. Incidence and Prediction of Falls in Dementia: A Prospective Study in Older People. *PLoS ONE.* 2009;4(5):e5521.



No	Presenting Author	Poster Title
17	Carol Stone	Vitamin D Deficiency in Advanced Cancer; the Prevalence and its Relevance

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Background

In addition to its role in bone health, vitamin D has been shown to be important for muscle strength and function and falls prevention in older persons; serum concentrations of 90-100nmol/L are associated with optimal lower limb function.¹

Objectives

To identify the prevalence of vitamin D deficiency (serum concentrations of <50 nmol/L) and vitamin D insufficiency (serum concentrations of 50-74nmol/L) in patients with cancer admitted to the Palliative Care Inpatient Unit at Our Lady's Hospice and Care Services.

Results/Discussion

From 27/07/10, consecutive adult patients with a diagnosis of cancer, admitted to the Palliative Care Unit have been invited to participate. Patients who provide consent have a blood sample drawn for analysis of serum vitamin D, at the time of phlebotomy, should this occur during the course of routine care. Descriptive statistics and results of Mann-Whitney U testing were generated using SPSSv18. We report interim findings, on patients who have participated up to 09/03/11.

From 27/07/10- 09/03/11 there were 268 admission episodes involving 227 patients; 117/155 eligible patients participated. Mean age of participants 69±12 years, 54% female, 10/117 taking vitamin D supplements. Median vitamin D 21.5 (range 0-113). Median vitamin D in non-supplemented group 20nmol/L versus 70.1nmol/L in supplemented group (p<0.0001).

Conclusions

Eighty-two percent of patients with advanced cancer had vitamin D deficiency; 94% had vitamin D insufficiency and levels below that required for optimal lower limb function. As an additional risk factor for osteoporosis and suboptimal muscle function, vitamin D deficiency may have a detrimental effect on pain control, functioning and quality of life in patients with advanced cancer.

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No	Presenting Author	Poster Title
18	Frederick Sundram	White Matter Microstructural Abnormalities in Antisocial Personality Disorder: A Pilot Diffusion Tensor Imaging Study

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Background

Antisocial personality disorder (ASPD) and psychopathy involve significant interpersonal and behavioural impairments. However, little is known about their underlying neurobiology and in particular, abnormalities in white matter (WM) microstructure. A preliminary diffusion tensor magnetic resonance imaging (DT-MRI) study of adult psychopaths employing tractography revealed abnormalities in the right uncinate fasciculus (UF) [1], indicating fronto-limbic disconnectivity. However, it is not clear whether WM abnormalities are restricted to this tract or are more widespread, including other tracts which are involved in connectivity with the frontal lobe.

Objectives

We performed whole brain voxel-based analyses on WM fractional anisotropy (FA) and mean diffusivity (MD) maps acquired with DT-MRI to compare 15 adults with ASPD and healthy age, handedness and IQ-matched controls. Also, within ASPD subjects we related differences in FA and MD to measures of psychopathy.

Results

Significant WM FA reduction and MD increases were found respectively in ASPD subjects relative to controls. FA was bilaterally reduced in the anterior corpus callosum while in the right frontal lobe FA reduction was found in the UF, inferior fronto-occipital fasciculus (IFOF), anterior corona radiata and anterior limb and genu of the internal capsule. These differences negatively correlated with measures of psychopathy. Also in the right frontal lobe, increased MD was found in the IFOF and UF, and the corpus callosum and anterior corona radiata. There was a significant positive correlation between MD and psychopathy scores.

Conclusions

The present study confirms a previous report of reduced FA in the UF. Additionally, we report for the first time, FA deficits in tracts involved in inter-hemispheric as well as frontal lobe connectivity in conjunction with MD increases in the frontal lobe. Hence, we provide evidence of significant WM microstructural abnormalities in frontal brain regions in ASPD and psychopathy.

References

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No	Presenting Author	Poster Title
19	Chris Watson	Profiling Serum Markers of Inflammation and Fibrosis across the Spectrum of Hypertensive Heart Disease; TIMP1 and MMP9 Identify an At-Risk Asymptomatic Group

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Background

Hypertension is one of the main drivers of the heart failure epidemic. This study profiled the biochemical natural history of hypertension across different stages of the hypertensive heart disease spectrum and also examined whether a particular fibro-inflammatory profile in patients with asymptomatic hypertension could identify those at higher risk of evolution to heart failure.

Methods

This was a cross-sectional observational study involving a population of 275 stable hypertensive patients divided into two different cohorts: Group 1: Diastolic Heart Failure [n=181]; Group 2: Asymptomatic Hypertension [n=94]. Asymptomatic patients were subdivided by left atrial volume index ≥ 34 mls/m² [n=30] and <34 mls/m² [n=64]. Study assays involved markers of inflammation [IL6, MCP1, IL8, TNFalpha], markers of collagen 1&3 metabolism [P1CP, P1NP, P3NP, C1TP], markers of extra-cellular matrix turnover [MMP2, MMP9, TIMP1] and the natriuretic peptide, BNP. Data were adjusted for age, sex, systolic blood pressure and creatinine.

Results

The presence of heart failure was associated with significantly higher levels of inflammatory markers (IL6, $p<0.001$; MCP1, $p=0.028$; IL8, $p<0.001$). Increased levels of collagen3 were also observed in heart failure patients (P3NP, $p<0.001$) with no increased concentration of collagen1 (P1CP, $p=NS$; P1NP, $p=NS$) despite evidence of heightened turnover of this protein (C1TP, $p<0.001$). Within an asymptomatic hypertensive population, we demonstrated that increased levels of MMP9 and reduced levels of TIMP1 identified patients with significant abnormalities in left atrial volume index ($p=0.041$, $p=0.007$ respectively).

Conclusions

These data define varying fibro-inflammatory profiles throughout the natural history of . In particular, the observations on MMP9 and TIMP1 may help identify a subgroup of patients with hypertension at high risk for progressive hypertensive heart disease and thereby facilitate focused preventative strategies.



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