UCC
University College Cork, Ireland
Coláiste na hOllscoile Corcaigh

# Irish Association of Pharmacologists

# Annual Meeting

## Friday, 16th October 2015

### Hosted by

## The Department of Pharmacology & Therapeutics

## University College Cork

### Brookfield Health Sciences Complex

IRISH ASSOCIATION OF PHARMACOLOGISTS

BRITISH PHARMACOLOGICAL SOCIETY

# *Welcome*

On behalf of the Conference Committee, I am delighted to welcome you to the 16th Annual Meeting of the Irish Association of Pharmacologists.

This year's programme is an excellent mixture of lectures by leading researchers in their field and young scientists presenting their findings in transational pharmacology, as well as clinical trials and observational studies.

This meeting – the only one of its kind in Ireland, is a unique and valuable forum, where clinical and basic pharmacologists can meet to exchange new results, discuss new therapeutic strategies and to lobby.

With presentations by six world-class researchers who are presenting their latest results in topics ranging from cancer to Alzheimer's and vaccine and drug delivery, there should be plenty of opportunities for fruitful discussion.

We hope you enjoy the day.

***Professor Thomas Walther, Conference Chair***

**Conference Committee:**

**Conference Chair:** Professor Thomas Walther, Head of Department, Pharmacology & Therapeutics, University College Cork
Dr Anne Marie Liddy, School of Medicine, Trinity College Dublin
Dr Christian Waeber, Department of Pharmacology & Therapeutics, University College Cork
**Conference Office:** Mary O'Donovan

# *Irish Association of Pharmacologists Annual Conference Programme*

***Friday, 16th October 2015 12:00 Noon to 5.00pm***

| Contributor | Title | Time |
|---|---|---|
| Professor Thomas Walther | ***Welcome address from Meeting Chair &Head of Department of Pharmacology & Therapeutics, UCC*** | **12.00 Noon** |
| Professor Brian Lawlor | *"Through the looking glass: seeing clinical trials in dementia from a different perspective"* | **12.10** |
| Mr Chris Brown | ***"Effect of drug class on association of beta-blocker with ovarian cancer survival"*** | **12.34** |
| Dr Kinga Gebolys | *"The G protein-coupled receptor Mas encoded by the Mas proto-oncogene mediates its mitogenic properties through constitutive activity"* | **12.44** |
| Ms Clare Butler | ***"Phenotype based development of novel therapies for the treatment of colorectal cancer"*** | **12.54** |
| Professor Seamas Donnelly | *"Targeting of macrophage migration inhibitory factor (MIF) as a new therapeutic option for the treatment of cancer"* | **13.04** |
| **LUNCH & POSTER SESSION 13.45-14.30** | | |
| Professor Timothy O'Brien | ***"Therapeutic potential of mesenchymal stromal cells in peripheral artery disease"*** | **14.30** |
| Dr Mortimer O'Connor | *"Osteoporosis management following teriparatide therapy for vertebral fractures: Are patients on correct maintenance therapy"* | **14.54** |
| Ms Anna Connolly | ***"Investigating novel crosstalk between the Ghrelin 1α and Serotonin 2C receptors in hedonic feeding"*** | **15.04** |
| Dr Alice O'Farrell | *"Cardiac Metabolic Pathway Remodelling in Response to Sunitinib Malate"* | **15.14** |
| Professor Therese Kinsella | ***"Thromboxane Receptors: A tale of two receptors cut from the same cloth??"*** | **15.24** |
| **COFFEE BREAK & POSTER SESSION 15.25-16.05** | | |
| Professor Geraldine Boylan | *"Neonatal seizures – measuring treatment efficacy"* | **16.06** |
| Dr Anne Moore | ***"Dissolvable Microneedle Technologies for Drug and Vaccine Delivery"*** | **16.30** |
| **Closing Remarks and Prize Giving*** *1st Prize for Best Oral Presentation – 250 euro (Sponsored by the British Pharmacological Society) 2nd Prize for Best Poster – 200 euro (Sponsored by the Department of Pharmacology & Therapeutics, UCC) | | |

## *List of Posters*

| Contributor | Title |
|---|---|
| **Evin Allen** | *"The Administration and Biodistribution of Vaccines using Dissolvable Microneedle Patches"* |
| **Kathleen Fitzgerald** | *"Anisamide-targeted Gold Nanoparticles for Prostate Cancer Therapy"* |
| **Anirudh Jaisimha** | *"Use of GPN-mediated lysosomal rupture to identify a unique pool of amyloid precursor protein (APP) metabolites in cultured cortical neurons."* |
| **Dr Mortimer O'Connor** | *"Vaccine status of a group of elite international rugby players in Ireland"* |
| **Dr Mortimer O'Connor** | *"Fracture risk assessment of patients with inflammatory joint disease receiving biological agents attending a rheumatology service in a university affiliated teaching hospital"* |
| **Dr Adel Ali Shelfah** | *"Consultant geriatricians' attitude and their usage of new oral anticoagulants in patients with non-valvular atrial fibrillation"* |

## *Invited Speaker: Professor Brian Lawlor, Conolly Norman Professor of Old Age Psychiatry, Trinity College Dublin*

## *"Through the looking glass: seeing clinical trials in dementia from a different perspective"*


### Abstract:

Alzheimer's disease is the commonest cause of dementia worldwide and is a major societal challenge. There have been no new drug treatments since 2002 and there are no disease modifying agents available to treat Alzheimers diseases This paper will review the landscape of clinical trials in dementia and discuss current and future trends. The rationale for a new investigator driven clinical trial of a potential disease modifying drug in mild to moderate Alzheimers disease called NILVAD ( www.nilvad.eu) will be described. NILVAD is the first clinical trial of its kind in Alzheimer's disease being coordinated out of Ireland and may offer a different model of clinical trial prosecution in dementia.


### Biography:

Professor Lawlor is Conolly Norman Professor of Old Age Psychiatry at TCD, consultant psychiatrist and Director of the Memory Clinic at St.. James's Hospital, Dublin. His research interests are in the early detection, diagnosis and treatment of Alzheimer's disease, the neurobiology and treatment of behavioural and psychological symptoms in dementia and the study of mental disorders in the community dwelling elderly. The overarching aims of his research programmes are to develop clinical, neuropsychological and biological markers of Alzheimer's disease at the earliest possible stage and to test promising new interventions in clinical populations. His research involves collaborative partnership with disciplines from basic science (developing animal models of Alzheimer's disease) through to health service development, clinical trials and implementation.

His current research activity is focused on CSF biomarkers for Alzheimer's disease as part of BiomarkAPD, coordinating NILVAD (www.nilvad.eu), a major investigator driven clinical trial of nilvadipine in Alzheimer's disease and an exercise intervention trial in mild cognitive impairment. In addition, as Clinical Director of the NEIL Research Programme at Trinity College Institute of Neuroscience, he is involved in studying hearing impairment and cognitive reserve in older people at the Memory Research Unit and in developing scalable interventions to prevent dementia.

*Chris Brown, National Cancer Registry*

## *"Effect of drug class on association of beta-blocker with ovarian cancer survival"*

(Chris Brown, Thomas Ian Barron, Kathleen Bennett, Linda Sharp)

## Abstract:

**Background:** There is evidence in breast, colorectal and prostate cancer that patients who use beta-blocker (BB) medication have better cancer outcomes. There is conflicting evidence of similar benefits in ovarian tumours. We investigated whether type of drug effected association between BB use and survival within Irish ovarian cancer patients.

**Method:** Women diagnosed with invasive ovarian cancer (ICD code: C56) between 2001-2011 were identified from the National Cancer Registry Ireland. Those with continuous eligibility for a (means-tested) medical card in the year immediately prior to diagnosis were identified and linked to pharmacy claim records. Any BB exposure (WHO ATC: C07) in the year prior to diagnosis was determined. Associations between exposure and ovarian cause-specific survival (OvCSS) and all other causes was estimated using Cox regression (until follow-up 31/12/2012) adjusted for age, smoking, marital status, diagnosis year, urban/rural residence, deprivation, stage, grade, and surgery at diagnosis. Adjusted hazard ratios (AHR) and 95% CI are presented. Class of medication (selective, non-selective) was a pre-planned subgroup and patients were classified as having one, neither or both.

**Results:** Of 3097 invasive ovarian cancers diagnosed 2001-2011, 1823 (59%) had a medical card for at least one year prior to diagnosis. Of these, 432 (24%) had some BB exposure in that year. 78% of women in the cohort had died by 31/12/2012 (median follow-up 5.8 years). Pre-diagnostic use was not associated with improved OvCCS (AHR=1.08, 95%CI 0.93,1.23) or other-cause survival. Exposure to selective drugs (AHR=1.11, 95%CI 0.95,1.30) was not significantly different to that of non-selective drugs (AHR=0.88, 95%CI 0.56,1.38), interaction p=0.55.

**Conclusions:** In this large study of beta-blocker use in ovarian cancer, we observed no modification of association by drug class on cancer-specific survival.

**Dr Kinga Gebolys, Department of Pharmacology & Therapeutics, University College Cork**

## *"The G protein-coupled receptor Mas encoded by the Mas proto-oncogene mediates its mitogenic properties through constitutive activity"*

Anja Tetzner[a*], Kinga Gebolys[a*], Florian Gembardt[b], Thomas Wieland[c], Susanne Lutz[c,d], Thomas Walther[a,e]
[*]Both authors contributed equally to the work

[a]Department of Pharmacology and Therapeutics, University College Cork (UCC), Cork, Ireland;

[b]Department Nephrology–MK3, University Hospital Dresden, Dresden, Germany;

[c]Institute for Experimental and Clinical Pharmacology and Toxicology, Mannheim Medical Faculty, University Heidelberg, Mannheim, Germany;
[d]Department Pharmacology, Universitätsmedizin, Georg-August-Universität, Göttingen, Germany;

[e]Center for Perinatal Medicine, Department of Obstetrics, University of Leipzig, Leipzig, Germany

## Abstract:

The *Mas* proto-oncogene was first detected through its tumourigenic activity in tumour assays and encodes a G protein-coupled receptor (GPCR). Recently, we identified the receptor Mas to be associated with angiotensin-(1-7)-stimulated signalling.
In *Mas* over-expressing cells, we quantified transcriptional activity and focus formation to investigate Mas-dependent signalling mechanisms.

In these cells, we found an agonist/antagonist-independent RhoA activation by constitutively active Mas signalling via $G_{aq/11}$ proteins. Mas thereby induced the activation of different transcription factors (NFAT, NFkB, SMAD, and SRF) and consequently stimulated transformation of NIH 3T3 cells as demonstrated by significantly enhanced focus formation.
This is the first demonstration that a GPCR mediates its mitogenic properties through constitutive activity. Consequently, Mas could be a promising target for pharmacological/biochemical intervention in tumour therapy.

*Ms Clare Butler, Conway Institute, University College Dublin*

## *"Phenotype based development of novel therapies for the treatment of colorectal cancer"*

**(Clare Butler[1],** Adrian Murphy[1], Emer Conroy[1], William M. Gallagher[2], Jacintha O'Sullivan[2], & Breandán Kennedy[1])

## Abstract:

**Background:** Colorectal cancer (CRC) is the third most commonly diagnosed cancer in the world. The treatment of late stage CRC using Bevacizumab®, a targeted anti-VEGF therapy, produces insufficient response rates among patients and inevitable acquired tumour resistance. There is a clinical need for development of improved treatment options.

**Method:** Previously, anti-angiogenic screens in [Tg]*fli1*:EGFP zebrafish identified Quininib, a small molecule drug shown to be more effective than Bevacizumab® at reducing tumour volume *in vivo* and which can reduce tumour CD31 expression in xenografted mice. Here, structural analogues of Quininib were synthesised to identify novel chemical entities with higher anti-angiogenic and anti-inflammatory efficacy. Analogues were examined for anti-angiogenic effects in the [Tg]*fli1*:EGFP zebrafish intersegmental-vessel assay. Hits were then progressed for analysis of safety in cytotoxic assays, anti-angiogenic efficacy in aortic explants, and for effects on cell proliferation and tubule formation using HT29_Luc2 and HMEC cells. Leads were then tested in *ex vivo* human CRC tumour explants to determine effects on angiogenic and inflammatory factor secretion. A study was carried out to determine the maximum tolerated dose (MTD) of our highest ranking analogue in mice by i/p injection. A CRC-specific murine xenograft model was created by subcutaneous injection of HT29_Luc2 cells for anti-tumorigenic analysis of the Quininib analogues

**Results:** Five out of 12 drug candidates (CC16_HCl, CC12_HCl, Z_HCl, CC8_HCl & OS_1) reduced developmental angiogenesis in [Tg]*fli1*:EGFP zebrafish significantly more than Quininib (***P<0.01). These analogues were well tolerated in human endothelial and CRC cell cytotoxic assays and were more effective than Quininib at reducing tubule formation and angiogenic factor secretion in HMEC cells. Two analogues reduced aortic ring vessel sprouting equally or more effectively than Quininib. Some analogues can reduce inflammatory and angiogenic factor secretion from *ex vivo* human CRC explants more significantly than Quininib. Using a ranking efficacy table, we chose the highest ranking analogue and determined its safety via a maximum tolerated dose study (MTD) using balb/c wild type mice. We will analyse the anti-tumorigenic and anti-metastatic effects of our highest ranking analogue by i/p injection of an optimised model of HT29_Luc2-CRC tumourigenesis in Balb/c nude mice.

**Conclusion:** We identified 5 analogues which are significantly more effective than Quininib within *in vitro* and *ex vivo* models of inflammation and angiogenesis. Our highest ranking analogue can be administered by i/p injection in mice up to 50 mg/kg with no obvious adverse effects. Our highest ranking analogue will be tested in murine xenografts to determine effects on tumour burden and metastasis.

***Keynote Address: Professor Seamas Donnelly,***
***Professor of Medicine, Trinity College, Dublin.***

## *"Targeting of macrophage migration inhibitory factor (MIF) as a new therapeutic option for the treatment of cancer"*

### The Donnelly Laboratory:

The Donnelly Laboratory works encompasses three defined areas:

- Defining key regulatory pathways which drive chronic inflammation
- Personalised Medicine and how genetic expression profiles predict prognosis and response to therapy in disease.
- Enhancing our understanding of how pathogens evade the host's immune defences.


### Abstract:

This talk will illustrate these research interests via our work over the years in defining the key regulatory roles for the pro-inflammatory cytokine, Macrophage Migration Inhibitory Factor (MIF). This body of work defines the important role for this protein in a variety of key cellular processes translating to a variety of diseases and presents persuasive data supporting academia and industries current interest in targeting this cytokine as an anti-inflammatory and anti- cancer therapeutic agent.


### Biography:

Seamas Donnelly is Professor of Medicine at TCD. He is an international leader in Translational Medicine whose research encompasses defining key regulatory processes driving disease to how pathogens evade the host immune response. He is a medical graduate of University College Galway and was funded via the Wellcome Trust to undertake postgraduate studies at the University of Edinburgh and the Picower institute, New York. Returning to Ireland in 2001, he has generated > €35 million grant funding either as PI or CoPI. He was recently awarded an honorary Professorship by the University of Edinburgh for international leadership in Translational Medicine. He is currently Editor-in-Chief of the Quarterly Journal of Medicine (QJM).

***Invited Speaker: Timothy O'Brien, MD, PhD, FRCPI. Regenerative Medicine Institute, CURAM, NUI Galway and Saolta University Healthcare Group.***

## *"Therapeutic potential of mesenchymal stromal cells in peripheral artery disease"*


## Abstract:

Critical limb ischemia is a condition of high prevalence which often results in the need for amputation. While revascularization represents the optimal treatment approach approximately 30% of patients who present with this condition are not suitable and amputation remains the only option. Stem cell therapeutics has been proposed as a potential approach to this condition of unmet medical need. My group is interested in the use of mesenchymal stromal cells (MSCs) as a therapeutic approach to patients with no option critical limb ischemia. This approach requires a consideration of the use of cells as drugs. It is now believed that the mechanism of action of MSCs in inducing angiogenesis is via paracrine secretion of angiogenic factors. The cells may be considered as "factories" which produce therapeutic products. Our group has demonstrated the angiogenic potential and safety of MSCs in pre-clinical models and has recently received approval to undertake a phase 1b clinical trial of autologous MSC transplantation in patients with no option critical limb ischemia. The regulatory pathway to this approval will be described and the challenges associated with MSC manufacture under GMP will be discussed. The use of cells as drugs will be reviewed in the context of critical limb ischemia.


## Biography:

Professor Timothy O'Brien trained in internal medicine and endocrinology in Cork, Milwaukee, Rochester and San Francisco. He was elected to Fellowship of the Royal College of Physicians of Ireland in 1995, the Royal College of Physicians of UK in 1997, the American College of Physicians in 1995 and the American College of Endocrinology in 1996. He was awarded MD (1993) and PhD (1997) degrees from the National University of Ireland. In 2001 he was appointed as Head of Medicine at NUI Galway and Consultant Endocrinologist at Galway University Hospital. In 2004 he established the Regenerative Medicine Institute (REMEDI) at NUI Galway with funding in excess of €19 million from Science Foundation Ireland and holds the position of Director. He has been a principal or co-applicant on grants worth in excess of €73 million. He has published 249 original papers and is an author on 375 abstracts presented at National and International meetings.

Research interests include gene therapy approaches to vascular disease using nitric oxide synthase and the translation of basic research findings in stem cell biology to regenerative approaches to peripheral vascular disease and diabetic complications in partnership with industry and the health service.

## *Dr Mortimer O'Connor, Mercy University Hospital, Cork*

## *"Osteoporosis management following teriparatide therapy for vertebral fractures: Are patients on correct maintenance therapy?"*

Daniel Gilmartin[1,2], Mortimer B. O'Connor[1,2,3], Siobhan Scanlon[1,2], Ursula Bond[1], Mark J. Phelan[1,2].

1. The Department of Rheumatology, South Infirmary Victoria University Hospital, Cork, Ireland.
2. The Department of Medicine, Mercy University Hospital, Cork, Ireland.
3. The Doctor John Walsh Research Foundation, South Infirmary Victoria University Hospital, Cork, Ireland.

## Abstract:

**Background:** Teriparatide is used as a daily subcutaneous therapy for severely osteoporotic patients, with therapy duration of 18 to 24 months. It functions as an anabolic agent, and demonstrates increases in cortical thickness and reduces fracture risk. For the benefits of teriparatide to be sustained anti-reabsorbative therapy, in combination with calcium/vitamin D supplementation, should be initiated/restarted long-term after teiparatide therapy.

**Methods:** All patients prescribed teriparatide therapy from 2009 to 2012 were identified from departmental prescription records. Contact information was identified from local hospital databases. Patients were sent a pre-study letter outlining the nature of the study and the questions. This was followed by a telephone call, within two weeks, from the investigators. Three telephone attempts were made to contact participants after which they were excluded from the study. Participants were asked to list their current medications, background diagnoses and if they sustained a fracture since completing teriparatide therapy.

**Results:** 113 patients were identified from records. 42 were contacted and consented to participate in the study, 16 were deceased and 55 were uncontactable despite three attempts. Of the 42 enrolled, 45.2% (n=19) were no longer on a calcium or vitamin D supplementation and 57.1% (n=24) were no longer on an anti-reabsorbative, despite it being prescribed at their post-teriparatide Rheumatology assessment prior to discharge to GP care.

**Conclusions:** Despite being prescribed an anti-reabsorbative osteoporosis medication and calcium/Vitamin D supplementation on completion of teriparatide therapy there was a significant number of patients who no longer took these medications. The reasons for discontinuation are undocumented. This leaves them exposed to a submaximal benefit from therapy and an increased future fracture risk. This care-gap needs to be tackled.

*Anna Connolly, Department of Anatomy & Neuroscience,*
*University College Cork*

## *"Investigating novel crosstalk between the Ghrelin 1α and Serotonin 2C receptors in hedonic feeding"*

**Anna C. Connolly[1] ,** Dalia Kandil[1,3], Wesley E.P.A van Oeffelen[1], John F. Cryan[1,2], Harriët Schellekens[1,2,3]

[1]Department of Anatomy & Neuroscience, School of Medicine, University College Cork, College Road, Cork, Ireland, [2]Alimentary Pharmabiotic Centre, University College Cork, College Road, Cork, Ireland, Food for Health, Ireland. [3]Food for Health, Ireland.

## Abstract:

Lorcaserin is a 5-$HT_{2C}$ agonist which has been used clinically to treat obesity since 2012. Our lab has previously demonstated that lorcaserin can decrease ghrelin-mediated food intake (Schellekens et al., 2015). Ghrelin is an endogenous orexigenic hormone which is produced peripherally, and can signal centrally via the GHS-R1α, to regulate energy homeostasis. Accumulating evidence indicates that ghrelin can modulate hedonic feeding behaviour, or motivated behaviour, in addition to homeostatic feeding behaviour (Schellekens et al., 2012). Hedonic feeding behaviour describes the consumption of food beyond the body's caloric needs and is typically associated with foods high in fat / sugar. The aim of this research is to identify if lorcaserin can modulate hedonic feeding, in addition to homeostatic feeding behaviour. To accomplish this, we conducted a sucrose preference test – a measure of hedonic behaviour, in which mice were presented with a choice between a 2% sucrose solution and water. Sucrose consumption was measured over 24 hours following treatment with either vehicle, ghrelin, lorcaserin, or ghrelin-lorcaserin combination. We found that ghrelin significantly increased sucrose consumption (g) over 24 hours, and that lorcaserin could significantly attenuate this ghrelin-enhanced preference for sucrose. We also demonstrated that these findings were not confounded by any alterations in mobility, as measured in a 100 minute locomotor assay. Finally, we will also investigate the effect of lorcaserin on GHS-R1α internalization, and GHS-R1α-mediated intracellular calcium signalling, in order to better understand the ghrelin-serotonin interaction. In summary, our data shows that ghrelin increases consumption of a sucrose solution, and that lorcaserin can attenuate a ghrelin-enhanced preference for sucrose. We show, for the first time (to our knowledge), that hedonic behaviours mediated by GHS-R1α, can be modulated by 5-$HT_{2C}$ signalling. This novel finding uncovers new avenues for pharmacotherapies targeting eating disorders, and potentially for addictive disorders in which the ghrelinergic system is involved.

## *Dr Alice O'Farrell, Royal College of Surgeons in Ireland*

## *"Cardiac Metabolic Pathway Remodelling in Response to Sunitinib Malate"*

Alice C. O'Farrell 1*, R. Evans 1, J.M.U. Silvola 2, I.S. Miller 1, E. Conroy 3, S. Hector 1,4, M. Cary 5, D. Murray 1,6, M.A. Jarzabek 1,4, A. Maratha 6, M. Alamanou 6, G. Mallya Udupi 6, L. Shiels 1, C. Pallaud 4, A. Saraste 2,7, H. Liljenbäck 2, M. Jauhiainen 8, V. Oikonen 2 , A. Ducret 4, P. Cutler 4, F.M. McAuliffe 9, J.A. Rousseau 10, R. Lecomte 10, S. Gascon 10, B. Ky 11, T. Force 12, J. Knuuti 2, W. Gallagher 3,6, A. Roivainen 2, and A.T. Byrne 1

1 Royal College of Surgeons in Ireland, Dublin, Ireland
2 Turku PET Centre, University of Turku, Turku University Hospital and Åbo Akademi University, Turku, Finland
3 University College Dublin, Dublin, Ireland
4 Roche Innovation Center Basel, F Hoffman La Roche, Basel, Switzerland
5 Pathology Experts GmbH, Basel, Switzerland
6 Oncomark Ltd, Dublin, Ireland
7 Heart Center, Turku University Hospital and University of Turku, Turku, Finland
8 Public Health Genomics Unit, National Institute for Health and Welfare, Helsinki, Finland
9 UCD Obstetrics and Gynaecology, School of Medicine and Medical Science, University College Dublin, National Maternity Hospital, Dublin, Ireland
10 Université de Sherbrooke, Québec, Canada
11 Department of Medicine, Hospital of the University of Pennsylvania, Philadelphia, PA, USA
12 Vanderbilt University School of Medicine, Nashville, USA

## Abstract:

Sunitinib is a tyrosine kinase inhibitor approved in the oncology setting. Despite widespread clinical approval, cardiovascular toxicity sequelae are of concern. Hypertension, decreased left ventricular ejection fraction (LVEF) and congestive heart failure are reported. High-grade toxicities lead to dose reduction, interruption or discontinuation of treatment, significantly impacting patient outcome. Pathophysiologic molecular pathways and kinases implicated include those related to cardiac energy metabolism. We hypothesised that plasticity in cardiac energy substrate usage could represent a novel early cardiotoxicity biomarker. We have developed clinically relevant rodent models to interrogate pathophysiologic mechanisms using positron emission tomography (PET).

Balb/CJ mice or Sprague-Dawley rats were treated daily via oral gavage for 4 weeks with clinically relevant doses (40/20 mg/kg) of sunitinib. Blood pressure and LVEF were assessed via tail-cuff monitoring/ echocardiography. Cardiac PET was implemented to interrogate alterations in myocardial glucose and oxidative metabolism, using [$^{18}$F]-fluorodeoxyglucose ([$^{18}$F]FDG), and [$^{11}$C]acetate tracers respectively. [$^{11}$C]Acetate-PET was additionally implemented to investigate myocardial perfusion. Tissue was collected following treatment and snap-frozen or formalin fixed for subsequent analyses.

In both models following treatment, blood pressure increased significantly, whilst left ventricular ejection fraction decreased. In mice, cardiac [$^{18}$F]FDG-PET revealed significantly increased glucose uptake after 48 hours. Electron microscopy indicated increased lipid storage in the myocardium. In rats, myocardial perfusion was significantly reduced following 5 days of treatment. Proteomic analyses revealed that oxidative metabolism, fatty acid β-oxidation and mitochondrial dysfunction were among the top myocardial signalling pathways perturbed.

Our data demonstrates that sunitinib treatment results in an increased cardiac reliance on glycolysis, increased myocardial lipid deposition and perturbed mitochondrial function which may underpin a fundamental energy crisis resulting in compromised myocardial energy metabolism and function. Cardiac PET may represent a potential clinical approach to monitor metabolic pathway remodelling following sunitinib treatment in the oncology setting.

## *Invited Speaker: Professor Therese Kinsella, School of Biomolecular and Biomed Science, Conway Institute, University College Dublin*

## *"Thromboxane Receptors: A tale of two receptors cut from the same cloth??"*


## Abstract:

The cyclooxygenase-derived prostanoid thromboxane (TX)$A_2$ plays a central role in the vasculature, dynamically regulating haemostasis and vessel tone, and is widely implicated in various inflammatory and cardiovascular diseases (CVDs). More recently, $TXA_2$ and its **T P**rostanoid receptor/**TP** have been implicated in several prevalent cancers, including bladder, prostate and breast cancers, as evidenced in part by the prophylactic benefits of Aspirin in reducing their overall incidence, while lowering $TXA_2$ levels. However, due to its lack of efficacy & associated side-effects, Aspirin is a less-than ideal drug and it has been proposed that more targeted ***TP antagonists*** may be more efficacious in treating such diseases involving $TXA_2$.

Critically, in humans $TXA_2$ actually signals through 2 receptor isoforms, namely **TPα and TPβ**, that are encoded by the same gene but differentially expressed, and functionally distinct including in the vasculature. Whilst the biologic significance of two TP isoforms in humans/primates is not fully understood, they greatly add to the complexity of $TXA_2$ responses and there is substantial evidence that they have distinct (patho)physiologic roles. For example, based on our recent discoveries, we propose that TPα and TPβ may play distinct roles in cancer and in immunity & inflammation, processes central to the role of $TXA_2$ in both neoplastic growth and CVD. In this presentation, I will describe of our recent findings regarding the expression of the individual TPα and TPβ isoforms in the clinical setting of prostate cancer. Furthermore, I will outline some of our work on (i) the transcriptional regulation of the TP gene (the TBXA2R) and (ii) on our identification of novel signalling pathways regulated by TP/TP that might account, at least in part, for their common but also divergent roles in prostate cancer.


## Biography:

B. Therese Kinsella, B.Sc (Hons), PhD, MRIA completed her B.Sc (Hons) and PhD degrees in Biochemistry at University College Cork, before taking up a postdoctoral position at UCC and the Howard Hughes Medical Institute, Salt Lake City, USA. From there, she held posts as Senior Molecular Biologist, Guinness Worldwide Research Centre, Dublin (1986-1989) and as Senior Scientist, Weis Center for Cardiovascular Medicine, Geisinger Clinic, PA, USA, affiliated with Hershey Medical School (1989-1992).

In 1992, she returned to Ireland to take up an academic post at University College Dublin (UCD), where she is Associate Professor of Biochemistry, and runs a highly successful research program at the Conway Institute for Biomolecular & Biomedical Research. A major focus of her research is in the role of the prostanoids thromboxane A2 and prostacyclin in the vasculature and, more recently, in neoplastic disease. In this, Therese has gained international recognition for her work in the field, having published extensively in leading peer-reviewed journals and secured funding in excess of €7M. In recognition of her research achievements, she was awarded the Royal Irish Academy medal for Biochemistry in 2000 and elected Member of the Royal Irish Academy (MRIA) in 2006. In 2008, she received the Gold Medal from the Biochemical Society (Irish area section).

## *Invited Speaker: Professor Geraldine Boylan, Director, Irish Centre for Fetal and Neonatal Translational Research INFANT*

## *"Neonatal Seizures – measuring treatment efficacy"*


### Abstract:

Despite the fact that neonatal seizures are a neurological emergency and prompt treatment is required they still represent a considerable diagnostic and therapeutic challenge to clinicians worldwide. Due to their subtle nature, clinical diagnosis is challenging, and without diagnostic tools such as electroencephalography (EEG), up to 80% of seizures can be missed. Interpretation of neonatal EEG is a highly specialised skill and rarely available out of office hours, if at all. Consequently, many newborn infants with seizures may go undiagnosed and untreated. Seizures are associated with detrimental effects on child neurodevelopment: up to 50% of those with seizures in the neonatal period may have serious adverse sequelae.

Phenobarbitone is the first line drug for treatment of neonatal seizures despite having only around 50% efficacy. There is little consensus about the best second-line treatment for neonatal seizures and there is considerable off-licence use of other antiepileptic medications without efficacy data in the neonatal period. Despite the fact the seizures are more common in the neonatal period than at any other time of life, there have been no adequately powered randomised trials of antiepileptic drugs in this population. Thus, there is an urgent need to improve the detection of seizures (for diagnosis and monitoring), and to develop effective age-specific therapeutic interventions with robust outcome measures. This talk will review currently available treatments for neonatal seizures and discuss innovative ways of measuring treatment efficacy in this population.


### Biography:

Geraldine Boylan is Professor of Neonatal Physiology at University College Cork. Together with Louise Kenny, Geraldine led the successful Science Foundation Ireland Research Centre bid, which underpins INFANT, and is a founding Director.

Geraldine has a career long track record in clinical neurophysiology and since 1996 has worked exclusively in the field of neonatal neurophysiology. Her PhD thesis from Kings College London focused on EEG and cerebral blood flow velocity during neonatal seizures. She is a Science Foundation Ireland and Wellcome Trust funded Principal Investigator and as an INFANT PI, Geraldine leads the thematic research areas related to the neonatal brain. Geraldine's group comprise a multidisciplinary research team that have established an international reputation in the area of neurological monitoring in the neonatal intensive care unit, particularly in seizure detection and early diagnosis of brain injury. Researchers in Geraldine's group are developing automated algorithms for monitoring brain activity and remote monitoring tools for physiological data acquisition in the neonatal intensive care unit. One such innovation, an automated seizure detection algorithm for newborn babies, is the focus of a large multicentre trial, ANSeR funded by a Strategic Translational Award from the Wellcome Trust and led by INFANT. Geraldine is co-coordinator of the FP7 funded NEMO study, Europe's first multicentred dose finding and safety study of Bumetanide for the treatment of seizures in newborn babies.

## *Invited Speaker: Dr Anne Moore, Department of Pharmacology, & School of Pharmacy University College Cork*

## *"Dissolvable Microneedle Technologies for Drug and Vaccine Delivery"*


### Abstract:

ImmuPatch is a microneedle patch platform technology for vaccine delivery to the skin that aims to address current financial and logistic obstacles in immunization programmes. We briefly discuss the development of stabilised vaccines in dissolvable microneedle patches and designs that induce immune responses in murine models. We demonstrate the significant enhancement of long-term stability of clinically available influenza vaccine in dissolvable ImmuPatch and its associated immunogenicity in mice and larger animals. Finally, we discuss the use of clinically relevant adjuvants and vaccines in these patches and their effects on mucosal, serological and B cell responses to antigens in mice. In contrast to traditional immunization approaches, ImmuPatch represents a tailored strategy for the development of more potent live and subunit vaccines through enhanced immunity and it provides potential solutions to logistic obstacles of immunization programmes by stabilising vaccines out of cold chain conditions.


### Biography:

Dr Anne Moore graduated with a degree in Biochemistry University College Cork. She completed a PhD in HIV vaccine immunology with Professor Kingston Mills. Dr Moore subsequently embarked upon post-doctoral work on defects in immune responses in HIV-infected individuals in the Wistar Institute in Philadelphia and further work on recombinant vaccines against viruses such as HIV and Ebola virus in Dr Gary Nabel's lab then at the University of Michigan. As a senior immunologist in Professor Adrian Hill's group in the University of Oxford, she developed several T cell inducing vaccine candidates against malaria and TB and was involved in clinical trials of these and other vaccine candidates in Oxford and malaria endemic areas in Africa. She took up a position as a Lecturer in Pharmacology, based in the School of Pharmacy, UCC in early 2007.

# POSTER PRESENTATIONS

***Evin Allen, School of Pharmacy, University College Cork***

## *"The Administration and Biodistribution of Vaccines using Dissolvable Microneedle Patches"*

**E. Allen[1]**, S. Vučen[1], S. McInerney[1], O. Flynn[1] A. Crean[1] and **A. Moore[1, 2]**

[1]School of Pharmacy, [2]Dept. of Pharmacology and Therapeutics University College Cork, Cork, Ireland

## Abstract:

**Introduction:** Percutaneous vaccine and drug delivery is constrained by the lipophilic nature of the skin. Dissolvable microneedle (DMN) patches circumvent this by penetrating the epidermis and dermis, realising active material allowing for lymphatic and systemic drainage. However skin is a viscoelastic tissue that can resist penetration, resulting in some recoil of microneedles and partial skin penetration. This necessitates the appropriate design of microneedles to ensure maximum delivery of drugs and vaccines into the skin. Here we hypothesised that concentrating the vaccine to the microneedle tip would enhance vaccine delivery.

**Methods:** Dissolvable microneedle patches containing a model protein labelled to a fluorescent marker, FITC-BSA or a subunit influenza vaccine were fabricated with a 15% w/w trehalose formulation with and without a backing-layer. Delivery of FITC-BSA was assessed in a full thickness *ex vivo* pig skin model using fluoresence to quantify delivery.

**Results:** Bi-layered DMN with antigen localised in the microneedle tip were successfully fabricated with both BSA and influenza antigens. This process was shown not to affect vaccine integrity as determined by SRID. A significantly higher amount of antigen was delivered to the epidermis with a bi-layer microneedle rather than a single layer needle.

**Discussion:** Bi-layered DMN successfully delivered greater levels of antigen to the skin compared to first generation single layer DMN proving our hypothesis. Approximately one third of antigen incorporated in microneedle was delivered to the immunologically relevant skin sections. This represents a large improvement on coated microneedle systems where less 10% is delivered.

**Conclusion:** Bi-layered DMN designs should be advanced further with optimisation of mechanical strength and subsequent penetration to increase the antigen payload delivered.

*Kathleen Fitzgerald, School of Pharmacy, University College Cork*

## *"Anisamide-targeted Gold Nanoparticles for Prostate Cancer Therapy"*

Kathleen A. Fitzgerald[1], Kamil Rahme[2,3,4], Jianfeng Guo[1], Justin D. Holmes[2,3] and Caitriona M. O' Driscoll[1]

[1]Pharmacodelivery Group, School of Pharmacy, University College Cork, Ireland. [2]Materials Chemistry and Analysis Group, Department of Chemistry and the Tyndall National Institute, University College Cork, Cork, Ireland. [3]AMBER (Advanced Materials and Biological Engineering Research Centre), CRANN (Centre for Research on Adaptive Nanostructures and Nanodevices), Trinity College Dublin, Dublin, Ireland [4]Department of Sciences, Faculty of Natural and Applied Science, Notre Dame University (Louaize), Lebanon

## Abstract:

**Introduction**: Prostate cancer is expected to be the second-leading cause of cancer-related death in men in the United States in 2015. Hence new and improved treatments are urgently needed. RNA interference (RNAi) has emerged as a potential therapeutic option for prostate cancer; however, successful delivery remains a barrier. Gold nanoparticles (NPs) possess a number of favourable attributes for RNAi delivery including low toxicity and ease of chemical modification. The aim of this work was to synthesize and characterise cationic gold NPs targeted with anisamide. Anisamide is a targeting ligand that binds specifically to the sigma receptor that is over-expressed on prostate cancer cells.

**Methods:** Gold nanoparticles were synthesized with a 60 nm core diameter. The targeted nanoparticle was prepared by grafting cationic PEI onto the gold surface followed by conjugation of anisamide onto the PEI. The ability of the NP to complex siRNA was assessed by gel retardation and size and charge was measured using dynamic light scattering. Competitive uptake was investigated by Haloperidol pre-incubation. The toxicity and ability to silence the target RelA gene was quantified at 24 hours post-transfection in both serum-containing and serum-free media.

**Results:** The resulting nanoparticles were a suitable size for gene delivery (untargeted and targeted NP diameter ~60-70 nm). The untargeted nanoparticle fully complexed siRNA at mass ratio gold:siRNA of 1. In contrast the targeted nanoparticle did not fully complex siRNA until mass ratio 7.5. The targeted gold nanoparticle showed high cell uptake which was reduced with Haloperidol pre-treatment. In contrast the untargeted nanoparticle had low cellular uptake. The gold nanoparticles were non-toxic up to a 200 nM siRNA concentration and the targeted nanoparticle mediated high levels of gene knockdown in serum-free conditions (~70% gene knockdown).

**Conclusion:** Anisamide-targeted gold nanoparticles were successfully synthesized to mediate receptor-mediated uptake and gene knockdown in prostate cancer cells. Future work will focus on enhancing the stability of the gold nanoparticles via the incorporation of polyethylene glycol (PEG) into the formulation whilst retaining the receptor-mediated uptake function of the anisamide-targeting moiety.

Acknowledgement: This project is supported by the Irish Cancer Society Project Grant PCI11ODR

*Anirudh Jaisimha, Department of Pharmacology & Therapeutics, University College Cork*

## *"Use of GPN-mediated lysosomal rupture to identify a unique pool of amyloid precursor protein (APP) metabolites in cultured cortical neurons."*

Anirudh Vinay Jaisimha and Dr Barry Boland

## Abstract:

**Introduction:** Altered catabolism of amyloid precursor protein (APP) and its metabolites is widely implicated in the pathogenesis of Alzheimer's disease (AD). Lysosomal flux refers to the catabolic clearance of autophagic and endocytic cargo by lysosomes and this anti-amyloidogenic mechanism has been shown to be impaired in AD [1]. We have previously shown that specific lysosomal enzymes regulate the turnover of APP C-Terminal fragments (CTFs) within cultured neurons and that their pharmacological inhibition causes a preferential accumulation of truncated APP-CTFs, referred to as CTF-6 and CTF-7 [2].

**Methods:** In this study, we investigated the role of lysosomes in the catabolism of APP-CTFs by using Glycyl-L-phenylalanine 2-naphthylamide (GPN), a substrate of cathepsin C that causes rapid intralysosomal storage and subsequent lysosomal rupture [3]. Cultured rat primary cortical neurons were labeled with Lysotracker Red (50nM, 10 min), to identify acidic organelles of autophagic-lysosomal compartments. Neurons were subsequently treated with GPN (200□M). The effect of GPN was also tested on neuron cultures which were treated with specific lysosomal protease inhibitors (cathepsin L inhibitor III (10□M, 48hr), cathepsin B inhibitor (CA074-Me, 10□M, 48hr).

**Results:** Treatment of neurons with GPN caused a rapid loss in Lysotracker fluorescence (< 5 mins), representative of lysosomal compartment rupturing. Neuron cultures treated with specific lysosomal protease inhibitors caused an accumulation of APP-CTFs, with a preferential increase in low molecular weight truncated CTFs (CTF-6 and CTF-7). GPN-mediated lysosomal rupture caused a selective loss of CTF-6 and -7 in cultures treated with inhibitors of cathepsin L and B, in a subcellular fraction that also contained full-length APP and full-length APP dimers.

**Conclusion:** Our observations highlight a key step in APP catabolism, involving the lysosomal degradation of truncated APP-CTFs, which may be used as novel biomarkers of impaired lysosomal flux in AD.

## *Dr Mortimer O'Connor, Mercy University Hospital*

## *"Vaccine status of a group of elite international rugby players in Ireland"*

Mortimer B. O'Connor[1,2], Mary Horgan[1,3], Colm J. Bergin[4,5], Niall P. Conlon[4,6,], Rod McLoughlin[7], Michael G. Molloy[1,8], Éanna C. Falvey[1,7]

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8. Department of Rheumatology, Cork University Hospital, Cork, Ireland.

## Abstract:

**Introduction:** The positive benefits of exercise are well documented. Despite this, there is also a theory that high intensity exercise, such as that undertaken by professional sports persons, may have a negative impact on their immune system. This may leave them exposed to infections. To prevent this, vaccination against certain infections may be beneficial. In this study we examine what a group of elite international rugby players self-report to be vaccinated against and cross correlate this with their serology and GP records.

**Methods:** A cross sectional self-completed questionnaire, on vaccines and travel, was administered to all 2014 - 2015 Irish National Senior Men's Rugby team players in October 2014. Phlebotomy for serological titres for MMR, VZV and Hepatitis B were carried out on all players. GPs of players with equivocal serological results were contacted to trace records of MMR, VZV and/or Hepatitis B vaccinations. Players with non-immunity to MMR, VZV and/or Hepatitis B were offered vaccinations during the off season.

**Results:** There was a 100% participation rate (n = 39). The mean age of the cohort was 27.1 years. There were equal numbers of back and forward position players. A statistically significant number of players were unable to confirm their vaccine history, which includes travel vaccines and recent vaccinations. Serological results showed that 30 out of 39 players require vaccination against at least one of measles, mumps, rubella, varicella or hepatitis B based on non-immunity. GP records for vaccinations are poor.

**Conclusions:** The level of non-immune individuals in this cohort is higher than would be expected. A substantial number need vaccinations to reduce the risk of preventable infections for which vaccines are available. The authors would support the introduction of a vaccine passport as part of professional rugby player's contract and that repeat serological testing for appropriate vaccine should be carried out on the signing of each new contact.

## *Dr Mortimer O'Connor, Mercy University Hospital*

## *"Fracture risk assessment of patients with inflammatory joint disease receiving biological agents attending a rheumatology service in a university affiliated teaching hospital"*

Órla McDonnell[1], Mortimer B. O'Connor[2,3], Ursula Bond[2], Mark J. Phelan[2]

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2. Department of Rheumatology, South Infirmary Victoria University Hospital, Cork, Ireland
3. The Dr John Walsh Research Foundation, South Infirmary Victoria University Hospital, Cork, Ireland

## Abstract:

**Objectives:** Osteoporosis, characterised by deteriorating bone microarchitecture with a concomitant increase in bone fragility, represents a growing public health concern. From an inflammatory arthropathy perspective, especially RA, it is a well-known extra-articular characteristic of concern. Fracture risk can be examined using the World Health Organization Fracture Risk Assessment Tool (FRAX®) which has been formulated to estimate a 10-year absolute risk of fracture using validated clinical risk factors. The aims of our study were to determine the fracture risk in patients receiving biologic therapies using the FRAX® tool and to determine if a care-gap exists in this cohort.

**Materials & Methods:** A cross-sectional telephone based questionnaire study, employing the FRAX® tool, was conducted on Inflammatory arthropathy patients (RA, PsA, SNA, AS), receiving biological therapies, attending our Rheumatology service. Patients received a letter informing them of the study and pending telephone call one week in advance. Those not contactable within two attempted telephone calls were excluded from the study. Patients were randomly selected from the Departments Biologics database. Following FRAX® assessment, patients were classified as low, intermediate or high fracture risk using The National Osteoporosis Guideline Group (NOGG) analysis.

**Results:** 182 patients were telephoned with 123 patients being contactable within two attempts. 101 patients partook in the study. 8 (8%) had a prior osteoporosis diagnosis. 93 (92%) were eligible for FRAX® assessment with a mean age was 55.5 years (range: 40-75) and 53% male. Of the untreated group 77% had RA, 14% PsA and 8% AS. FRAX® assessment gave a median 10-year hip osteoporotic fracture probability of 2.1% (mean = 3.5%) and major osteoporotic fracture probability of 11% (mean = 12.4%). NOGG analysis would advise offering treatment to 25%, DXA imaging to 56% and osteoporosis/fracture risk lifestyle advice to 19% of patients. Thus a potential 81% of untreated patients may require osteoporosis/risk fracture prevention measures.

**Conclusion:** A large care-gap was identified among this patient group. Results highlight the need to identify and modify fracture risk in patients with inflammatory arthropathies receiving biologic therapies.

*Dr Adel Ali Shelfah, Trinity College Dublin*

## *"Consultant geriatricians' attitude and their usage of new oral anticoagulants in patients with non-valvular atrial fibrillation"*


## Abstract:

**Background:** Atrial fibrillation is the most common cardiac arrhythmia, and a major cause of ischemic stroke. Despite being effective, warfarin was found underused due to its well-known limitations as well as compliance with guidelines is influenced by variables at physician, patient, and hospital level. As a result, NOACs developed to overcome some of perceived shortcomings with warfarin. This study looked at a specific group of physicians (geriatricians) to understand their perception of safety and efficacy of NOACs and their preferences for OACs.

**Methods:** A cross-sectional online survey of Irish geriatricians who registered under ISPGM. 110 geriatricians were examined. The response rate was 28% (i.e.28 completed the survey). The questionnaire was distributed electronically using the survey monkey website. Survey questions asked about the number of AF-patients and their management in clinical practice, NOACs and perception of efficacy and safety, and the influential reasons for choosing NOACs over warfarin and vice versa.

**Results:** The majority of geriatricians managed about ≥ 20 patients with non-valvular AF per month. For their management, the majority chose NOACs, particularly rivaroxaban and apixaban. In terms of efficacy and safety, NOACs were perceived safe and effective if they were prescribed properly and avoided in those with impaired renal function. With regard to the importance of barriers to prescribing NOACs, bleeding risk was seen as a "significantly important" barrier, while the age group (≥ 85) years old were considered to be a "moderately important" barrier to NOACs prescription. There are some concerns that were expressed with NOACs, such as non-availability of antidotes and lack of ability to monitor anticoagulant effect, especially in certain circumstances, such as bleeding, thrombolysis in patients with ischemic stroke, and monitoring for adherence. Geriatricians also stated that those on NOACs were better to be followed up in order to educate and to raise awareness of NOACs among them.

Variables such as "no need for INR monitoring", and "no period of subtherapeutic INR" were the major cause of choosing NOACs over warfarin, whereas "presence of reversal agent", "familiarity and experience", and "cost" were seen as the main influential reasons for preferring warfarin to NOACs.

**Conclusion:** NOACs were welcomed by geriatricians, particularly rivaroxaban and apixaban for the management of non-valvular AF. INR-related obstacles including the frequent requirement for INR monitoring was considered to be the most influential reason for preferring NOACs to warfarin, in the meantime geriatricians ask for regular follow-up for patients who were prescribed NOACs in order to educate, and to raise awareness of NAOCs among them.