



(Bio)pharmaceutical and  
Pharmacological Sciences

## Research Day Tuesday, January 11th 2011

### Dublin City University Nursing Building (HG20 and foyer) Programme

- 8.45 – 9.00**      **Poster set up**
- 9.00 – 9.15**      **Welcome and Opening**  
**Professor Brian MacCraith, President, Dublin City University.**
- 09.15 – 11.15**    PhD/Post-doc talks: Andrew Murphy (DCU), Peadar Rooney (UCD), Arman Rahman (DCU), Rebecca Ring (UCD), Michael P. Carroll (UCD)  
Chairperson: Prof. Anita Maguire
- 11.15 – 12.00**    *Coffee+ Posters*
- 12.00 – 13.00**    **Keynote talk**  
**Professor Stephen Clarke, Head of School of Chemistry, University of Glasgow.**  
***Total synthesis of bioactive marine diterpenes of the Cladiellin family.***  
Chairperson: Prof. Patrick Guiry
- 13.00 – 14.00**    **Lunch (Catered)**
- 14.00 – 16.00**    PhD/Post-doc Talks: Ahmed Al-Sabi (DCU), Elaine. M. Boyle (TCD),  
Charlotte M. Miller (UCC), Anthony Deally (UCD), Marie O’Connell (DCU)  
Chairperson: Prof. Ciaran Regan
- 16.00 – 16.45**    *Coffee + Posters*
- 16.45 – 17.45**    **Keynote talk**  
**Professor Theo Meert, Head of Neuroscience, Johnson and Johnson.**  
***Drug discovery in the novel environment exemplified in the pain field.***  
Chairperson: Prof. Oliver Dolly
- 17.45 – 18.15**    **Addresses by funders;**  
**Dr. Eucharía Meehan, Head of Research and Capital Programmes, HEA.**  
**Science Foundation Ireland representative**  
**Dr. Keith O’Neill, Director of Life Sciences and Food Research Commercialisation,**  
**Enterprise Ireland.**  
**Bill Godwin, Manager-Business Development, Life Sciences, IDA.**  
**Alan Clancy, Finance Director, Allergan Pharmaceuticals, Ireland.**
- 18:15**            ***Wine and Appetizer reception and poster removal.***



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An tÚdarás um Ard-Oideachas





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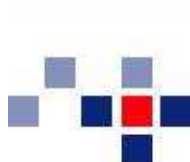
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Wine and Appetizer Reception sponsored by Pall Life Sciences



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## Keynote speaker:

### Professor Stephen Clarke

WestCHEM, School of Chemistry, University of Glasgow, University Avenue, Glasgow G12 8QQ, UK

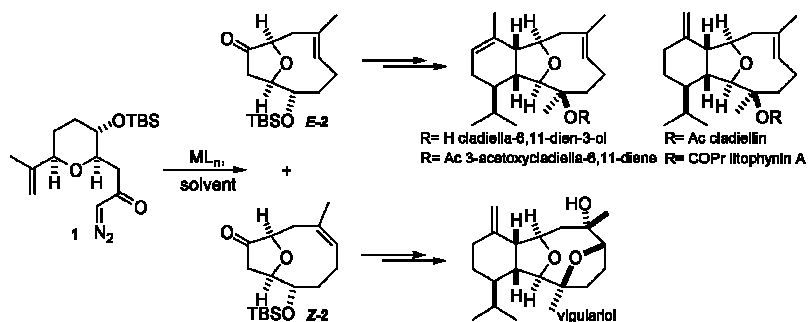
E-mail: [stephen.clark@glasgow.ac.uk](mailto:stephen.clark@glasgow.ac.uk)

Stephen Clark was born and raised in Scotland. He graduated from the University of Edinburgh with a 1<sup>st</sup> Class Honours Degree in Chemistry in 1985 and completed his PhD at the University of Cambridge in 1988, where he worked on the total synthesis of marine natural products under the supervision of Professor A B Holmes FRS. He then joined the research group of Professor David Evans at Harvard University as an SERC-NATO Postdoctoral Research Fellow and performed research on the use of stereoselective aldol reactions to construct polypropionate systems. He commenced his independent academic career at the University of Nottingham in 1990 and was promoted to Professor in 2000. In 2006, he moved to the University of Glasgow as Head of Organic Chemistry and in April 2010 was appointed Head of School. His research interests include the development of new strategies and methodology for the synthesis of complex polycyclic systems and the application of this work to the total synthesis of bioactive natural products of high structural complexity.

Stephen Clark was elected Fellow of the Royal Society of Edinburgh in 2009 and is Vice-President of the Organic Division of the Royal Society of Chemistry. He has been the recipient of several awards and prizes including the prestigious Novartis European Young Investigator Award in 2004.

### Total synthesis of bioactive marine diterpenes of the Cladiellin family

In recent years, a multitude of highly bioactive oxygen-bridged cembranoids has been isolated from marine sources.<sup>1</sup> This family of compounds can be divided into four distinct structural classes – the cladiellins (eunicellins), briarellins, asbestinins and sarcodictyins – of which the cladiellin group is the largest, comprising over 40 members. The cladiellins possess a wide range of biological activities and some of them display significant cytotoxic activity against tumor cell lines. The structural complexity of these ether-bridged marine natural products coupled with their biological activities makes them attractive synthetic targets.<sup>1,2</sup>



We have recently developed an entirely general strategy for the synthesis of the core structure of the cladiellins that should be applicable to the synthesis of this entire family of marine natural products.<sup>3</sup> The key step in the assembly of the tricyclic core of the cladiellins involves reaction of the diazo ketone **1** with a copper or rhodium catalyst to give a highly reactive oxonium ylide or metal-bound ylide equivalent which then rearranges to give the isomeric bridged bicyclic ethers **Z-2** and **E-2** in excellent yield. Intriguingly, we have found that it is possible to tune the stereochemical outcome of the reaction simply by altering the metal, ligand and solvent. Thus, under optimized conditions it is possible to get a 7:1 preference for either the *Z* or *E* isomer. We have already reported the elaboration of ketone **Z-2** to give the natural product vigulariol,<sup>3</sup> and the lecture will focus on the construction of relatively inaccessible cladiellins that contain a highly strained *E*-alkene embedded in the medium ring (e.g. cladiellin and litophynin A).

#### References

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## Keynote speaker:

### Prof. Theo Meert

Head of Neuroscience, Johnson and Johnson

Prof. Theo F Meert is a Senior Director External Innovation in the Neurosciences group of Janssen Pharmaceuticals of J&J responsible for EU and AP. During his career at J&J, started in 1981, he is also appointed to multiple international global functions. He was born in 1958 in Oostham, and obtained a Ph.D. on psychopharmacology in Experimental Psychology at the university of Brussels (1986) and a Ph.D. in Medicine/Anesthesiology at the University of Antwerp (1994).

Within his various functions obtained within J&J up to senior Research Fellow, he guided different multidisciplinary research teams within the field of CNS (Psychiatry- Pain –Neurology/ Alzheimer). The activities of these groups covered the complete drug discovery process from early TI/TV over drug candidate selection to POC and further human testing. Dr Meert also supports some Full Development products and is involved in the scientific support of novel and marketed products.

He was a key driver for several advanced projects in the CNS area leading to marketed drugs and has constructed an extensive network within J&J and external scientific and clinical organizations. His scientific expertise is reflected in multiple patents (>15), publications (> 200), congress communications(> 200) and invited lectures (>100).

He is professor and scientific advisor/researcher at different universities (Leuven (Dept Biological psychology), Antwerp (Dept Pharmac Biomed Vet Sciences), Brussels (VUB, Dept Biolog Psychology) and Hasselt (Dept Med Biomed sciences)), (co)promoter of various mainly (bio)medical PhD students and editorial board member of several scientific journals.

## Drug discovery in the novel environment exemplified in the pain field

Despite various classes of analgesics and a range of non-pharmacological treatment options available today, still a majority of patients suffers from (chronic) pain urging the development of new treatment options. Ultimate goal is not only effective pain relief but also disease modification and prevention of chronic pain.

During the last decades, there is a growing knowledge of the pain pathways, the adaptive changes of these systems during the development of chronic pain and different forms of peripheral, spinal and central sensitization. Also the impact of genetic, psychological and environmental factors on different pain states becomes further elaborated.

Based on this knowledge, and combined with improved research tools in the fields of genetics and biomarkers as well as quantification of pain, a whole new series of drug targets have been identified. The selection and validation of these targets and their unique differentiating features to existing treatment options is extremely important, especially also in the light of the enormous expenses and failure rates often observed in the development of a new (analgesic) drug.

In the process of target validation and proof of concept testing in translational models and selected patient populations, there is a unique possibility of collaborations between industry and academia.

## PhD/Post-doc presentations (morning):

[Andrew Murphy](#)<sup>1,2</sup>, Mishan Britto<sup>3</sup>, Brian McDonnell<sup>3</sup>, Paul Fitzpatrick<sup>3</sup>, Philip Cummins<sup>1,2</sup>, Ronan Murphy<sup>2,3</sup>

<sup>1</sup>School of Biotechnology, Dublin City University

<sup>2</sup>Targeted Therapeutics & Theranostics T3 Programme, DCU

<sup>3</sup>School of Health & Human Performance, DCU

### The role of miRNA in strain-induced endothelial inflammation

**Background:** Endothelial inflammation (dysfunction) is a primary committal step in the progression and pathology of atherosclerosis. We hypothesized that miRNA have a central role in this process. **Methods:** *In vitro* alterations of physical haemodynamic forces, including cyclic strain, has been demonstrated to both initiate and mimic the inflammatory state displayed by endothelial cells *in vivo*. Primary-derived human aortic endothelial cells were subjected to equibiaxial cyclic strain of varying magnitudes (0, 5 and 10 %) and durations (0, 1, 3, 6, 12, and 24 hours). The inflammatory state of the cells was assessed using an NF- $\kappa$ B luciferase reporter assay and qRT-PCR analysis of various endothelial inflammatory markers (e.g. VE-CAM and E-Selectin) and miRNA targets. **Results:** Endothelial cells exhibited a robust dose-dependent inflammatory response to cyclic strain, with NF- $\kappa$ B activity peaking at an early time point (3 hours) and inflammatory gene expression peaking after 24 hours. In order to investigate the role of miRNA in this process, the differential expression of 667 individual miRNAs were analysed across the various time points and magnitudes of cyclic strain, using novel TaqMan Low Density Arrays (TLDA). We succeeded in identifying a panel of the strain-regulated miRNAs potentially involved in strain-mediated inflammation and gene expression. **Conclusion:** Functional analysis using both pri-Mir and anti-Mir technology is being carried out on specific miRNA targets with a view to identifying their role(s) in mediating strain-dependent endothelial processes (including inflammation).

**Acknowledgment:** This work was funded by a PRTL 4 grant from the Irish Higher Education Authority for the Neuroscience sections of 'Target-driven therapeutics and theranostics'.

[Peader Rooney](#), Connolly M, Gao W, Veale DJ and Fearon U.

Translational Research Group, Dublin Academic Medical Centre, St. Vincent's University Hospital, Dublin, Ireland

### Acute Serum Amyloid A the NOTCH signaling pathway and cytoskeletal dynamics in Rheumatoid arthritis

**Background:** Acute Serum Amyloid A (A-SAA) is strongly expressed in rheumatoid arthritis (RA) synovial tissue (ST) and is critically involved in regulating cell migration and angiogenesis. Cell migration and EC morphology is dependent on complex signalling interactions which link cytoskeletal rearrangement to extracellular matrix. These processes are also dependent on NOTCH signalling pathways which regulate cell survival and cell shape.

**Methods:** NOTCH1IC and downstream signaling components HRT1, HRT2 were quantified in synovial tissue/cells by immunohistology and Realtime PCR. RAST explants and human microvascular endothelial cells (HDEC) were stimulated with A-SAA (10 and 50 $\mu$ g/ml) or TNF $\alpha$  (10ng/ml) for (3-24 hours), NOTCH1C, its ligand DLL-4 and downstream signaling components HRT1, HRT2 were quantified by Real-time PCR. NOTCH-1IC, and growth factors (VEGF, Angiopoietin-2) were assessed by western blot and ELISA. A-SAA modulation of filamentous actin (F-actin) and focal adhesions (vinculin) was examined by dual immunofluorescence. A-SAA induced angiogenesis and migration were assessed by Matrigel tube formation assays and scratch assays. To examine if A-SAA induced angiogenesis, altered cell shape and migration were mediated by NOTCH signaling, functional assays were performed with A-SAA in the presence of siRNA against NOTCH 1IC.

**Results:** NOTCH 1IC, HRT1, 2 were expressed in the lining layer and perivascular regions of RA synovial tissue. A-SAA (10 $\mu$ g/ml) increased NOTCH1IC and VEGF mRNA and protein expression. A-SAA induced HRT-1mRNA with no effect on HRT2mRNA. A-SAA inhibited DLL-4 mRNA, which is consistent with a negative feedback loop that controls the interactions between NOTCH1IC and DLL-4 in the regulation of EC tip vs stalk cells. No effect was observed for angiopoietin 2. A-SAA induced disassembly of EC F-actin cytoskeleton and loss of focal adhesions as demonstrated by a reduction in vinculin staining. Alterations in cytoskeletal dynamics in response to A-SAA was observed as early as 15 mins with maximal effect at 24 hrs, where dramatic formation of filopodia protrusions were demonstrated. Finally, A-SAA induced angiogenesis and cell migration were inhibited when cells were transfected with NOTCH1IC siRNA.

**Conclusion:** A-SAA induces the NOTCH signalling pathway, VEGF and cytoskeletal rearrangement which allows temporal and spatial reorganization of cells during cell migratory events and EC morphology. Together these results suggest a critical role for A-SAA in driving cell shape, migration and invasion in the inflamed joint.

## PhD/Post-doc presentations (morning):

[Arman Rahman](#) , Christine Loscher, Sandra O'Neill and Dermott Walls  
*T<sup>3</sup> Immunology Stream, Dublin City University, Glasnevin, Dublin 9, Ireland.*

### The role of SNARE proteins in immunomodulation

Soluble NSF Attachment Protein Receptor (SNARE)-mediated docking and fusion of vesicular carriers has been shown to be critical for secretion of immune mediators by immune cells. The aim of the T<sup>3</sup> Immunology Stream is to identify the SNARE proteins that are involved in the secretion of cytokines known to be associated with inflammatory disease. The programme of research examines a variety of immune cells involved in such disease, including dendritic cells, macrophages, B cells and T helper cells. We have demonstrated that activation of immune cells induces increased expression of specific SNARE proteins. The expression of these SNARE proteins is associated with the profile of immune mediators it is secreting when activated. Furthermore, we have demonstrated that knockdown of specific SNARE proteins can block the secretion of such mediators. Our research to date supports our hypothesis that SNARE proteins represent novel targets in diseases such as inflammatory bowel disease and rheumatoid arthritis.

[Rebecca Ring](#), Gannon, S., Pickering, M., Coyle, A., Conboy, L., O'Boyle, N., Scully, D & Regan, C.  
*UCD*, This work was supported by Enterprise Ireland and the HEA PRTL cycle 4.

### Identification of captodiamine as a putative antidepressant

Previously, we have shown that chronic treatment with captodiamine, an anxiolytic formerly used in clinical practice, to significantly reduce time spent immobile in the forced swim test [FST], a behavioral paradigm commonly used to assess antidepressant efficacy. We had also shown captodiamine to have significant affinity for the D3 dopamine receptor, the  $\sigma_1$  receptor and the 5-HT<sub>2c</sub> receptor. The aim of the current study was to determine the agonist/antagonist actions of captodiamine at each of these receptors and to investigate the effect of captodiamine on biomarkers of antidepressant action such as BDNF and CRF.

The action of captodiamine at the  $\sigma_1$  receptor was determined by administration of rimcazole (5mg/kg, i.p.); a sigma 1 receptor antagonist, to C57Bl/6 male mice, with and without captodiamine (5mg/kg, i.p.), and assessing activity in the FST. HEK293T cells over-expressing the 5-HT<sub>2c</sub> receptor were used to determine the influence of captodiamine (100nM-1mM) on serotonin-induced (10 $\mu$ M) increases in intracellular calcium concentration as measured using a fluorescence-based confocal microscopy assay. HEK293T cells over-expressing the D3 receptor were used to determine the ability of dopamine, a known D3 receptor agonist, and captodiamine to induce ERK phosphorylation. Downstream biomarkers of antidepressant action such as BDNF and CRF were measured using ELISA techniques in animals treated with 5mg/kg captodiamine and vehicle treated controls.

Using the above procedures, we observed administration of rimcazole to reverse the decreased immobility induced by captodiamine in the FST (vehicle vs rimcazole/captodiamine-treated;  $p=0.76$ ; Student-t-test). It was found that dopamine significantly elevated pERK1/2 levels, in HEK293T-D3R cells, at a concentration of 1 $\mu$ M ( $p=0.0007$ ; Students t-test  $n=3$ ). Similarly captodiamine significantly elevated pERK1/2 levels in these cells at a dose of 100 $\mu$ M ( $p=0.0353$ ; Students t-test  $n=3$ ). Captodiamine, at doses of 1 $\mu$ M, 10 $\mu$ M and 1mM, was found to significantly inhibit 5-HT-induced Ca<sup>2+</sup> release in HEK 293T cells over-expressing the 5-HT<sub>2c</sub> receptor (10 $\mu$ M 5-HT [control] vs 10 $\mu$ M 5-HT + captodiamine;  $P=0.0131$ ; One-way Anova,  $n=3$ ). It was also found that captodiamine (5mg/kg) induces a significant up-regulation of BDNF in the mouse hypothalamus ( $p=0.0033$ ; Students t-test  $n=8$ ) and a significant decrease in CRF in the same brain region compared to vehicle treated control animals ( $p=0.0445$ ; Students t-test  $n=4$ ).

Collectively, these findings indicate captodiamine to exert agonist action at the  $\sigma_1$  receptor and an antagonist action at the 5-HT<sub>2c</sub> receptor. As both 5HT<sub>2c</sub> receptor antagonism and  $\sigma_1$  receptor agonism have separately been demonstrated to decrease immobility time in the FST, the findings reported here support captodiamine to be a potential antidepressant. Further captodiamine induces an up-regulation of a known molecular marker of antidepressant action - BDNF in the mouse hypothalamus and induces a significant down-regulation of CRF in the same brain region, supporting the antidepressant potential of this drug.

This work was supported by Enterprise Ireland and the HEA PRTL cycle 4.

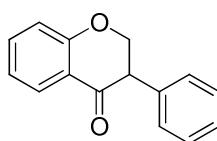
## PhD/Post-doc presentations (morning):

**Michael P. Carroll** and Patrick J. Guiry

UCD Conway Institute of Biomolecular and Biomedical Research, Centre for Synthesis and Chemical Biology, School of Chemistry and Chemical Biology, University College Dublin, Belfield, Dublin 4, Ireland

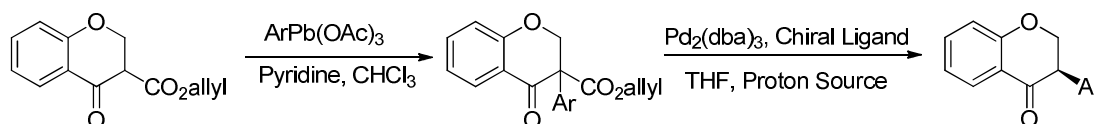
### Development of an Asymmetric Synthesis of Isoflavanones

Isoflavanones (Fig.1) are a class of naturally occurring plant secondary metabolites which display a range of medicinal properties, including anti-cancer activity.<sup>1</sup> Despite their potential as therapeutic agents and the many reported syntheses of isoflavanones,<sup>2</sup> only one stereoselective synthesis has been developed.<sup>3</sup> This synthesis employed the use of chiral auxiliaries. A more efficient approach could be envisioned using asymmetric catalysis.



**Fig1.** General structure of isoflavanones

The focus of this research project is the development of an expedient asymmetric synthesis of isoflavanones, using a lead mediated arylation,<sup>4</sup> followed by a novel palladium-catalysed transformation which can generate the required stereocenter (Scheme 1). This talk will highlight our recent progress in this area.



**Scheme 1.** Palladium-catalysed enantioselective transformation to yield enantioenriched isoflavanones.

### Acknowledgement

This work was funded by a grant from the PRTL Cycle 4-(Bio)pharmaceuticals and Pharmacological Sciences National Graduate Enhancement Programme.

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## PhD/Post-doc presentations (afternoon):

[Ahmed Al-Sabi](#) and J. Oliver Dolly

*International Centre for Neurotherapeutics, Dublin City University, Glasnevin, Dublin 9, Ireland.*

### Re-creation and characterizations of heteromeric Kv1 channels as target for neurotherapeutics

Neuronal voltage-gated K<sup>+</sup> channels (Kv1) are membrane protein complexes composed of 4 transmembrane  $\alpha$  subunits and 4 cytoplasmically-associated, auxiliary  $\beta$  constituents. The  $\alpha$  subunits (Kv1.1-1.6 and Kv1.8) can assemble into homo- and hetero-tetramers, leading to a diversity of channel subtypes precisely tailored for tuning electrical signaling. Accordingly, certain neurological conditions associated with changes in Kv1 channel multimers usually alter neuronal excitability. To recreate uniform populations of heteromeric channels as authentic drug targets, a recently-devised gene concatenation was utilized. Hetero-tetrameric Kv1 channels were expressed as single-chain proteins in the plasmalemma of mammalian cells, so their constituents could be arranged in different positions. In one approach, Kv1.1 and 1.2 genes tandem linked with like genes adjacent (Kv1.1-1.1-1.2-1.2 or Kv1.2-1.2-1.1-1.1) yielded voltage-dependent K<sup>+</sup> currents with similar biophysical properties to the products of the diagonally-positioned genes (Kv1.1-1.2-1.1-1.2 or 1.2-1.1-1.2-1.1). Pore-blocking petidergic toxins were unable to distinguish between the adjacent and diagonal concatamers. Unprecedentedly, external application of the pore-blocker tetraethylammonium (TEA) differentially inhibited the adjacent versus diagonal subunit arrangements, with diagonal constructs having enhanced susceptibility. Concatenation did not directly alter the sensitivities of homomeric Kv1.1 or 1.2 channels to TEA or the toxins.

Another approach exploited N-type rapid inactivation of Kv1.4-containing channels, mediated through an N-terminal inactivation ball (NIB); which can be over-ridden by an associated Kv1.6  $\alpha$  subunit, via its N-type inactivation prevention (NIP) domain. Placing Kv1.4 and 1.6 genes together, followed by two copies of Kv1.2 yielded a potassium current devoid of fast inactivation. Mutation of critical glutamates within the NIP endowed rapid inactivation. Moreover, separating Kv1.4 and 1.6 with a copy of Kv1.2 gave a fast-inactivating current with steady-state inactivation shifted to more negative potentials and exhibiting slower recovery. These collective findings indicate that the proposed gene concatenation generates  $\alpha$  subunits in pre-determined positions to create heteromeric Kv1 channels mimicking those exist in neurons; with dictated biophysical profiles and as targets for neurotherapeutics.

**Acknowledgment:** This work was funded by a PRTL1 4 grant from the Irish Higher Education Authority for the Neuroscience sections of 'Target-driven therapeutics and theranostics'.

[Elaine M. Boyle](#), Thomas McCabe and Thorfinnur Gunnlaugsson

*School of Chemistry, Centre for Synthesis and Chemical Biology, Trinity College Dublin, Dublin 2, Ireland.*

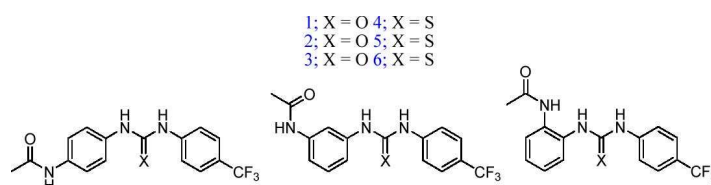
### Synthesis, Photophysical and NMR Evaluations of Thiourea-based Anion Receptors Possessing an Acetamide Moiety

The synthesis and photophysical evaluation of three diaryl thiourea-based anion receptors (**4-6**) for comparison with their urea counterparts (**1-3**) is outlined<sup>1</sup>. These anion receptors possess an acetamide functionality on one of the aryl groups and an electron withdrawing CF<sub>3</sub> group on the other. By varying the position of the acetamide group, in the *o*-, *m*- and *p*-positions of **4-6**, respectively, the anion binding ability was both tuneable and found to be, in some cases, significantly different to that seen for the urea analogues **1-3**<sup>2</sup>.

The binding affinities of the receptors **4-6**, as well as the binding stoichiometries, were evaluated using UV-Vis absorption spectroscopy in MeCN. However, these receptors were not sufficiently emissive to quantify the anion recognition using fluorescence. The results confirmed strong binding of these receptors to anions such as fluoride, acetate, phosphate, pyrophosphate, and chloride.

Nevertheless, the overall results obtained did not conform to the anticipated trends seen for **1-3**, which is most likely due to the enhanced binding affinity of the thiourea analogues **4-6**. The binding interactions were also investigated by using <sup>1</sup>H NMR which confirmed that these receptors interacted with the anions in a stepwise manner, where the primary anion binding interaction occurred at the thiourea side, which lead to an activation of the acetamide moiety towards the second anion binding interaction, an example of an allosteric activation mode.

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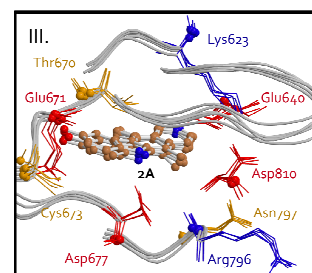
Charlotte M. Miller<sup>a\*</sup>, Damien Thompson<sup>b</sup>, Florence O. McCarthy<sup>a</sup>.

<sup>a</sup> Department of Chemistry, Analytical and Biological Chemistry Research Facility, University College Cork, Western Road, Cork. <sup>b</sup> Tyndall National Institute, Lee Maltings, University College Cork, Ireland. \*c.miller@student.ucc.ie

### Design and synthesis of novel ellipticine c-Kit kinase inhibitors.

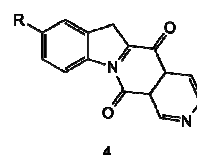
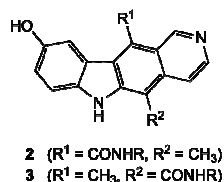
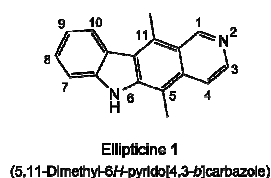
Receptor tyrosine kinase (RTK) enzymes regulate cell-signaling pathways and are an important target for cancer chemotherapy.<sup>1</sup> c-Kit kinase, a key RTK, has no specific inhibitor against the most common mutated variant (Asp816Val), associated with highly malignant cancers.<sup>2-4</sup>

However, recent research has shown the ellipticine pharmacore **1** to inhibit both wild type and mutated c-Kit.<sup>5</sup> The present combined simulation/experimental study probes the binding of ellipticine-based derivatives to c-Kit using high-level simulation tools in conjunction with synthesis of key novel ellipticine derivatives. In our molecular modeling work,<sup>6</sup> we found a large preference for protonation of the ellipticine pyridine moiety when bound to c-Kit, stabilizing the negative protein residues in the active site.



On the basis of these results, two key derivatives **2**, **3** were identified for synthesis.

In the synthetic strategy, an intermediate ketolactam **4** is subjected to sequential regioselective alkylation affording access to a wide variety of substituted ellipticines. This approach will be discussed in detail.



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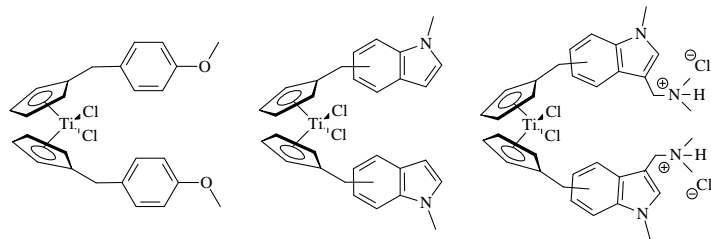
Anthony Deally, M. Tacke

UCD Conway Institute of Biomolecular and Biomedical Research, Centre for Synthesis and Chemical Biology, School of Chemistry and Chemical Biology, University College Dublin, Belfield, Dublin 4, Ireland

### Novel Achiral Indole-Substituted Titanocenes: Synthesis and Preliminary Cytotoxicity Studies

Ever since the discovery of cisplatin for the treatment of a variety of tumours, there has been an increased effort devoted to the identification and clinical development of novel organometallic compounds which overcome cross resistance in patients and have more favourable toxicity profiles[1]. Despite this effort, movement of other transition-metal antitumor agents toward the clinic has been extremely slow. This is perhaps due to the assumption that organometallic chemistry and biology are mutually incompatible with many organometallic compounds being sensitive to water and oxidation. Research over the last decade by Alberto [2] and Jaouen [3] has shown that organometallic pharmaceuticals can in fact be formulated.

More recently, novel methods starting from fulvenes [4] allow direct access to antiproliferative titanocenes via hydridolithiation of fulvenes followed by transmetalation with titanium tetrachloride. Using this approach we have synthesised a series of eight new indole substituted titanocene dichloride derivatives. The compounds were tested for their *in vitro* cytotoxicities against the human kidney cancer cell line CAKI-1 and their results are compared with previously synthesised structural analogues. These complexes were further tested on this cell line using the co-solvent Soluphor P, which has been shown to improve both solubility and cytotoxicity of similar complexes[5].



[1] Y. K. Yan, M. Melchart, A. Habtemariam, P. J. Sadler, *Chem. Commun.*, 2005, 4764.

[2] R. Alberto, R. Schibli, U. Abram, A. P. Schubiger, *Coord. Chem. Rev.*, 1999, 190-192, 901-919.

[3] F. Le Bideau, M. Salmain, S. Top and G. Jaouen, *Chem. Eur. J.*, 7, 2001, 2289-2294.

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### Novel long-acting anti-nociceptives evaluated in an animal pain model

Pain is a major health problem which affects ~3% of the world population. A majority of sufferers do not respond to currently-available treatments; thus, there is a huge unmet clinical need for new improved therapeutics for long-term alleviation of chronic pain symptoms. Encouragingly, pain relief has been achieved with botulinum neurotoxin (BoNT) type A, which blocks neurotransmitter release, in some of these non-responders (Dodick *et al.* 2010). BoNTs (A-G) bind neurons via the C-terminal half of their heavy chain and undergo internalization by receptor-mediated endocytosis (Black and Dolly, 1986). Following translocation of their light chain endopeptidases to the cytosol, they cleave and inactivate intracellular SNAREs [soluble NSF (N-ethylmaleimide sensitive factor) attachment protein receptors] essential for exocytosis of cell mediators (Dolly *et al.* 2009).

Our research focuses on improving the therapeutic efficacy of this promising anti-nociceptive protein, and validating its effectiveness in pre-clinical models of pain. Thus, a novel therapeutic has been obtained by recombinantly engineering a new generation exhibiting the desired therapeutic profile. A chimera of type E, created by substituting its binding domain with that of BoNT/A, proved to be a superior inhibitor of the release of pain peptides from sensory neurons; moreover, it relived the symptoms of inflammatory pain (Meng *et al.* 2009). This advance led us to discover an even more advantageous form in which the most effective BoNT/E protease is attached to BoNT/A, thereby, greatly prolonging its relief of inflammatory pain responses in a rat model (Wang *et al.* 2010). Recently, a neuropathic pain model was established in rats by ligating the L5 and L6 spinal nerves. Initial data reveal that this promising candidate anti-nociceptive gives a long-lasting attenuation of pain responses; both allodynia and hyperalgesia were suppressed for up to 3 weeks. In conclusion, our findings to date highlight the efficacious and prolonged anti-nociceptive action of this proprietary family of biotherapeutics which can be further refined for clinical application.

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#### References:

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2. Black, J. D. and J. O. Dolly (1986). "Interaction of <sup>125</sup>I-labeled botulinum neurotoxins with nerve terminals. Autoradiographic evidence for its uptake into motor nerves by acceptor-mediated endocytosis." *J Cell Biol* **103**(2): 535-44.
3. Dolly, J. O., G. W. Lawrence *et al.* (2009). "Neuro-exocytosis: botulinum toxins as inhibitory probes and versatile therapeutics." *Curr Opin Pharmacol* **9**(3): 326-35.
4. Meng, J., S. V. Ovsepien *et al.* (2009). "Activation of TRPV1 mediates calcitonin gene-related peptide release, which excites trigeminal sensory neurons and is attenuated by a retargeted botulinum toxin with anti-nociceptive potential." *J Neurosci* **29**(15): 4981-92.
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## POSTER Session

**Researcher:** Paul Adams, DCU

**Supervisor:** Dr. Sandra O'Neill

**Title:** SNARE profiles in alternatively activated macrophages

**Researcher:** Bandita Bagchi, DCU

**Supervisors:** Prof. Oliver Dolly & Dr. Saak Ovsepian

**Title:** Specific targeting of Kv1 channels for neuronal repair in multiple sclerosis

**Researcher:** Michael Carroll, UCD

**Supervisor:** Prof. Pat Guiry

**Title:** New approaches to the asymmetric synthesis of isoflavanones

**Researcher:** Laura Collins, DCU

**Supervisor:** Dr. Christine Loscher

**Title:** RNAi of SNARE Proteins in Bone Marrow Derived Dendritic Cells Suppresses Specific Cytokine Production

**Researcher:** Raihana Edros, UCD

**Supervisor:** Prof. Mohamed Al-Rubeai & Dr. Susan McDonnell

**Title:** Cellular Biomarkers of Productivity in Chinese Hamster Ovary (CHO) Cell Lines

**Researcher:** Kieran Greaney, UCC

**Supervisor:** Dr. Florence McCarthy

**Title:** Synthesis of novel quinoxalines as potential HIV Integrase Inhibitors

**Researcher:** Catriona McKeever, TCD

**Supervisor:** Prof. Isabel Rozas

**Title:** New minor-groove binder and intercalator derivatives as potential anticancer agents

**Researcher:** Maja Kristek, DCU

**Supervisor:** Dr. Christine Loscher

**Title:** A model to examine the role of colonic macrophages in inflammatory disease

**Researcher:** Fiona McEvoy, DCU

**Supervisor:** Prof. Harry Holthoffer and Dr. Christine Loscher

**Title:** Modulation of Pancreatic Beta Cell Function Following TLR ligation

**Researcher:** Marie McGrath, UCC

**Supervisor:** Dr. Abina Crean

**Title:** Formulation of vaccine-loaded microneedles

**Researcher:** Adam Molloy, UCD

**Supervisor:** Prof. Declan Gilheany

**Title:** Novel Synthesis and Reactivity of 1,2-dialkyl-1,2-diphenyldiphosphine

**Researcher:** Marie O'Connell, DCU

**Supervisor:** Prof. Oliver Dolly

**Title:** An animal model of chronic neuropathic pain for evaluation of antinociceptives

**Researcher:** Teodolinda Petrillo, UCD

**Supervisor:** Prof. Jonathan Malthouse

**Title:** Optimising the expression and the isolation of human BACE1



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**Researcher:** Rebecca Ring, UCD

**Supervisor:** Prof. Ciaran Regan

**Title:** Identification of captodiamine as a putative antidepressant

**Researcher:** Aoife Ring, UCC

**Supervisor:** Prof. A. Maguire

**Title:** Enantioselective Copper Catalysis in the Intramolecular Buchner Reaction

**Researcher:** Keith Robertson, UCD

**Supervisor:** Dr. Francesca Paradisi

**Title:** A novel synthesis of 4-methylenecyclohex-2-enone

**Researcher:** Honorata Ropiak, UCC

**Supervisor:** Prof. Dmitri Papkovsky

**Title:** Phosphorescence-based oxygen sensing for the analysis of cellular function

**Researcher:** Krisztina Vukman, DCU

**Supervisor:** Dr. Sandra O'Neill

**Title:** SNARE Profiles in Proinflammatory Mast Cells

**Researcher:** Ali Yasir, UCD

**Supervisor:** Dr. Michael Casey

**Title:** Synthesis of Antimicrobial Compounds

**Researcher:** Roya Hakimjavadi, DCU

**Supervisor:** Dr. Dermot Walls

**Title:** Investigation of a role for Bik in B lymphocytes and its regulation by Epstein-Barr virus

**Researcher:** Niamh McGoldrick, TCD

**Supervisor:** Prof. Sylvia Draper

**Title:** From Cyclopentadienone to Polyaromatic Frameworks: A Fascinating Detour on Route

**Researcher:** Keith Rochfort, DCU

**Supervisor:** Dr. Phil Cummins

**Title:** Cytokine-induced blood-brain barrier dysfunction: A microvascular endothelial model involving TNF $\alpha$ -induced IL-6 release

**Researcher:** Fiona Martin, DCU

**Supervisor:** Dr. Phil Cummins

**Title:** Cyclic strain-induced thrombomodulin release: Putative role in macrovascular endothelial injury

**Researcher:** Dr. Christina Despotopoulou, UCD

**Supervisor:** Prof. Pat Guiry

**Title:** Application of Oxazoline Containing Ligands in Asymmetric Synthesis

**Researcher:** Dr. Liam O'Hara, and Ms. Catherine Hagedorn, DCU

**Supervisor:** Prof. Oliver Dolly

**Title:** Selective targeting of a Botulinum Toxin-based core therapeutic using an anti-synaptotagmin recombinant antibody

**Researcher:** Barbara Korzeniowska, DCU

**Supervisors:** Prof. Colette McDonagh & Prof. Brian MacCraith

**Title:** Nanoparticle-based intracellular diagnostics



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**Researcher:** Pavle Mocilac, DCU

**Supervisor:** Dr. John Gallagher

**Title:** Synthesis, structural and conformational analysis of a 3×3 isomer grid based on nine Methyl-*N*-(pyridyl)benzamides

**Researcher:** Pavle Mocilac, DCU

**Supervisor:** Dr. John Gallagher

**Title:** Structures and conformational analysis of a 3 × 3 isomer grid of nine *N*-(fluorophenyl)pyridinecarboxamides

**Researcher:** Joseph DeCoursey, DCU

**Supervisor:** Dr. Christine Loscher

**Title:** SNARE proteins involved in cytokine secretion from specific T<sub>H</sub> cell subsets are potential targets for the treatment of inflammatory disease

**Researcher:** Inga Antyborzec, DCU

**Supervisors:** Prof. Oliver Dolly & Dr. Saak Ovsepian

**Title:** Basal forebrain neurons as a target for novel gene therapy in Alzheimer's disease

**Researcher:** Ciaran McGinn, DCU

**Supervisor:** Dr. Ronan Murphy

**Title:** Characterisation of the Palladin protein in Human Aortic Endothelial Cells

**Researcher:** Chun Xu Shan, DCU

**Supervisor:** Dr. Ronan Murphy

**Title:** The role of merlin protein in the haemodynamic regulation in the human aortic endothelial cell

**Researcher:** Hui Ma, DCU

**Supervisors:** Prof. Richard O'Kennedy & Dr. Sue Townsend

**Title:** Targeted Neurotherapeutics for Persistent Inflammatory Pain

**Researcher:** Anthony Deally, UCD

**Supervisor:** Dr. Matthias Tacke

**Title:** Novel Achiral Indole-Substituted Titanocenes: Synthesis and Preliminary Cytotoxicity Studies

**Researcher:** Peadar Rooney, UCD

**Supervisor:** Dr. Douglas Veale

**Title:** Acute Serum Amyloid A regulates the NOTCH signaling pathway and cytoskeletal dynamics in Rheumatoid arthritis

**Researcher:** Emilia Szwej, UCD

**Supervisors:** Dr. Kevin O'Connor, Prof. Liam Gallagher & Dr. Marc Devocelle

**Title:** Investigating the anti-cancer activity of a modified peptide

**Researcher:** Elaine Boyle, TCD

**Supervisor:** Prof. Thorfinnur Gunnlaugsson

**Title:** Synthesis, Photophysical and NMR Evaluations of Thiourea-based Anion Receptors Possessing an Acetamide Moiety



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