



Institute of Technology

Ciência sem Fronteiras / Science Without Borders

Postgraduate Project Template

Institution:	Dundalk Institute of Technology
Title of Postgraduate Opportunity: (include level of study)	PhD Project entitled: Novel BK channel openers for treating erectile dysfunction.
PI Name & Contact Details:	Dr Keith D Thornbury Principal Investigator Smooth Muscle Research Centre Dundalk, Co. Louth Keith.thornbury@dkit.ie
Department/School:	Nursing and Science
Research Centre /Group:	Smooth Muscle Research Centre
Research Centre/Group website:	www.smoothmusclegroup.org www.icbc.ie
Brief Summary of PI research / research group /centre activity <p>The multidisciplinary Smooth Muscle Research Centre is a centre of excellence in pure & applied research capable of exploiting opportunities in life sciences. The commercialisation arm of our Centre (the Ion Channel Biotechnology Centre) uses a combination of physiology, pharmacology, molecular biology, electrophysiology and synthetic organic chemistry to focus on commercializing the results of our academic research in the Smooth Muscle Research Centre into a number of disease states including urinary incontinence, erectile dysfunction, lymphoedema, and asthma. The research involves the use of a large number of techniques which are commonly used in R&D departments of the pharmaceutical industry and include single cell and single channel patch clamping, in vitro intracellular recording from whole tissue with sharp microelectrodes, ultra high speed live cell confocal Ca²⁺ imaging, molecular biology, synthetic chemistry, ion channel cloning and mutagenesis, tissue culture and tension recording. Our state of the art laboratories are equipped with dedicated facilities to permit the study of biological processes from the molecular level through to the whole tissue. The SMRC staff were recruited from the Physiology Department, Queens University of Belfast and comprise 4 PIs (Prof Noel McHale, Dr Keith Thornbury, Dr Gerard Sergeant and Dr Mark Hollywood), 5 postdoctoral fellows and 6 PhD students. The PI's bring considerable expertise as evidenced by their publications (100 peer-reviewed papers 1998-2008) and grant income (€7.5 million 2005-2012) from NIH, Wellcome Trust, Science Foundation Ireland, Health Research Board and Enterprise Ireland. We are the only Centre in Ireland to have received NIH funding independently of US investigator involvement. The team also consists of 5 postdoctoral fellows and 6 PhD students.</p>	
Brief Description of PhD Project <p>Research Aim: The aim of this proposal is to investigate the molecular mechanisms underlying the action of a novel class of compounds on large conductance Ca²⁺ activated (BK) channels.</p>	

Our group has now developed a novel series of openers of large conductance Ca^{2+} -activated potassium channels (BK channels) designated, GoSlo-SR (patent application: IPN WO2012/035122 A11). Several of these GoSlo-SR compounds activate BK channels at negative membrane potentials and therefore are likely to have potent effects on cells under physiological conditions. The principle that potassium channel openers are an effective tool for modulating erectile activity has been demonstrated by us in preliminary experiments. Our objectives are now to examine the effect of these GoSlo-SR compounds on electrical activity, Ca^{2+} signalling and contractile activity in the corpus cavernosum muscle of the penis. In collaboration with RCSI, we will also examine the molecular site on BK channels where these compounds act with a view to developing even more effective compounds in future.

We now wish to examine the effect of these molecules on cells isolated from erectile smooth muscle and examine if these drugs relax the tissue. Secondly, we wish, in collaboration with RCSI, to examine the site of action of these molecules on BK channels. In this proposal our objective is to use the combined strengths of electrophysiology, molecular biology, mathematical modelling and synthetic chemistry to help answer the questions detailed in the following work packages.

Objectives: We have discovered a novel group compounds called the *GoSlo-SR* family. These open BK channels in a concentration dependent manner ($\text{EC}_{50}=1\mu\text{M}$) and shift the voltage required for half maximal activation by ~ -100 mV (at $10\mu\text{M}$). In contrast to the majority of other BK channel openers, the GoSlo-SR molecules can activate BK channels at physiological membrane potentials (-80 to 0mV in smooth muscle) in resting $[\text{Ca}^{2+}]$ (100 nM). The proposed project will examine the molecular mechanisms responsible for their actions on BK channels. In this proposal our objective is to use the combined strengths of electrophysiology, molecular biology and mathematical modelling to help answer the questions detailed in the following work packages.

WP1. *Characterisation of the effect of GoSlo-SR BK channel openers on electrical activity in isolated corpus cavernosum smooth muscle cells*

WP2. *Effect of GoSlo-SR BK channel openers on Ca^{2+} signalling in corpus cavernosum smooth muscle cells.*

WP3. *Effect of GoSlo-SR BK channel openers on Ca^{2+} signalling in corpus cavernosum smooth muscle tissue slices.*

WP4. *Effect of GoSlo-SR BK channel openers on tension in corpus cavernosum smooth muscle tissue strips.*

WP5. *Identification of the BK channel molecular domains necessary for drug action*

WP4. Can the Horrigan-Aldrich allosteric model be used to predict the mechanism of action of the GoSlo-SR family of molecules?

Key Attributes of Project for Brazilian Postgraduate Students

This project will allow the student to work in a dynamic, multidisciplinary environment with a world class team of scientists. Students will be exposed to a range of techniques and receive full training in ion channel cloning and mutagenesis, electrophysiology and Ca^{2+} imaging. The successful applicant will also enrol in our 4 Year Structured PhD programme run in collaboration in RCSI, DCU, NUIM & DkIT (BioAnalysis and Therapeutics Programme funded by PRTL V). This work should appeal to students in wish to gain a thorough understanding of ion channel function in health and how they can be targeted in disease. Secondly, the student will focus elucidating the mechanisms of action of a novel BK channel opener that may prove useful in the treatment of erectile dysfunction. Erectile dysfunction affects around 10% of all adult males, with the incidence rising steeply with age to 57% of 70 year olds. Diabetes and vascular disease lead the way as the major causes. While Viagra revolutionised the treatment of erectile dysfunction, it is ineffective in 30-50% of cases. Consequently, there is an unmet medical need to develop new treatments for this disorder. One reason why Viagra is of limited success in some patients is that in the nitric oxide/cGMP signalling system is impaired. A strategy for developing

alternative treatments would, therefore, be to directly target the downstream mechanisms that are activated by cGMP, thus causing relaxation of the corpus cavernosum smooth muscle cells, while bypassing the NO/cGMP system.

Since this work will be carried out in collaboration with the commercialisation arm of the Smooth Muscle Research Centre, the Ion Channel Biotechnology Centre at DkIT, the student will be exposed to our many interactions with industry. In summary, this project will provide a valuable training opportunity in electrophysiology and mutagenesis for a new PhD student, whose skills are likely to be in high demand in the 'knowledge economy'.

Name and contact details for project queries, if different from PI named above:

Please indicate graduate disciplines which are eligible for application:

B.Sc (Hons, 2:1 or higher) in Physiology, Biochemistry, Biomedical Science, BioPhysics or related disciplines.

Alignment with Science Without Borders Priority Areas:

Please indicate the specific programme priority area under which the proposed postgraduate project fits – choose only one (tick box)

Engineering and other technological areas	
Pure and Natural Sciences (e.g. mathematics, physics, chemistry)	
Health and Biomedical Sciences	X
Information and Communication Technologies (ICTs)	
Aerospace	
Pharmaceuticals	
Oil, Gas and Coal	
Renewable Energy	
Minerals	
Biotechnology	
Nanotechnology and New Materials	
Technology of prevention and remediation of natural disasters	
Biodiversity and Bioprospection	
Marine Sciences	
Creative Industry	
New technologies in constructive engineering	