Strathclyde Institute for Pharmacy and Biomedical Sciences

MRes and MSci Research Project Descriptor

Project Title: Identification of protein kinase substrates

Primary Supervisor: Dr Martin Wiese
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Secondary Supervisor: Prof Craig Roberts
Email: c.w.roberts@strath.ac.uk

MRes Research Area, select one or two of the following:
Biochemistry / Molecular Biology / Parasitology

MSci Research Area, select ONE of the following:
Not suitable

Project Description:

Protein kinases are important regulators of all cells and play a role in vital processes like differentiation, proliferation, adaptation and motility. The human parasite *Leishmania mexicana* like other eukaryotes relies on signal transduction via reversible phosphorylation. As such parasite protein kinases are potential drug targets to be used to treat leishmaniasis which dependent on the parasite species and the immunological background of the host can be a fatal disease. In fact, protein kinases are part of signal transduction networks. Here, we want to identify substrates of protein kinases. This will allow setting up an enzymatic assay which can be used to identify specific inhibitors for parasite protein kinases. The main parts of the project are protein expression using a bacterial expression system followed by purification and enzyme assays.

Techniques to be used:
Molecular biology, protein purification using different affinity purification media, enzyme assays

References:

1. *Erdmann, M., Scholz, M., Melzer, I.M., Schmetz, C., and* ***M. Wiese***. Interacting protein kinases involved in the regulation of flagellar length. Mol Biol Cell. 17, 2035-2045 (2006)
2. ***Wiese, M.*** *Leishmania* MAP kinases – familiar proteins in an unusual context. Internat. J. Parasitol. 37(10), 1053-62 (2007)
3. ***Wiese, M.***. A mitogen-activated (MAP) protein kinase homologue of *Leishmania mexicana* is essential for parasite survival in the infected host. EMBO J., 17, 2619-2628 (1998)

Strathclyde Institute for Pharmacy and Biomedical Sciences

MRes and MSci Research Project Descriptor

Project Title: Protein kinases from *Leishmania*

Primary Supervisor: Dr Martin Wiese
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Secondary Supervisor: Prof Craig Roberts
Email: c.w.roberts@strath.ac.uk

MRes Research Area, select one or two of the following:
Biochemistry / Molecular Biology / Parasitology

MSci Research Area, select ONE of the following:
Not suitable

Project Description:

Protein kinases are important regulators of all cells and play a role in vital processes like differentiation, proliferation, adaptation and motility. The human parasite *Leishmania mexicana* like other eukaryotes relies on signal transduction via reversible phosphorylation. As such parasite protein kinases are potential drug targets to be used to treat leishmaniasis which dependent on the parasite species and the immunological background of the host can be a fatal disease. Protein kinases are part of signal transduction networks. Here, we want to analyse the interaction of *Leishmania* protein kinases and test their potential to activate each other. Activated protein kinases will be used to identify the natural substrate(s).

Techniques to be used:
protein purification and analysis, molecular biology, enzymatic assays, cell culture

References:

1. *Erdmann, M., Scholz, M., Melzer, I.M., Schmetz, C., and* ***M. Wiese***. Interacting protein kinases involved in the regulation of flagellar length. Mol Biol Cell. 17, 2035-2045 (2006)
2. ***Wiese, M.*** *Leishmania* MAP kinases – familiar proteins in an unusual context. Internat. J. Parasitol. 37(10), 1053-62 (2007)
3. ***Wiese, M.***. A mitogen-activated (MAP) protein kinase homologue of *Leishmania mexicana* is essential for parasite survival in the infected host. EMBO J., 17, 2619-2628 (1998)

Strathclyde Institute for Pharmacy and Biomedical Sciences

MRes and MSci Research Project Descriptor

Project Title: Polymorphism of (±)-mephedrone hydrochloride

Primary Supervisor: Dr Oliver Sutcliffe
Email: oliver.sutcliffe@strath.ac.uk

Secondary Supervisor: Dr Iain Oswald
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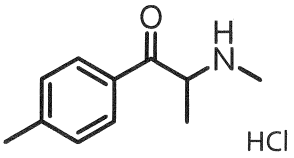
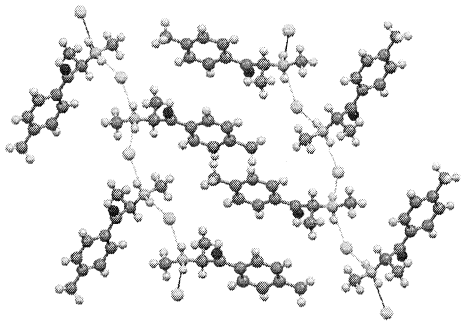
MRes Research Area: (select one or two of the following)
Drug Delivery; Pharmaceutical Materials and Formulation
MSci Research Area, select ONE of the following:
Not Applicable

Project Description:

(±)-Mephedrone hydrochloride [1] is a synthetic β-ketoamphetamine that has been used as a *"legal high"* replacement for controlled psychostimulants including amphetamines such as methamphetamine and MDMA (*"Ecstasy"*). Previous research in our team has successfully identified a number of polymorphs (*i.e.* different physical forms [2]) of this substance and we believe that these polymorphs may have the different chemical/physical properties which may affect its bioavailability in humans.





Our interests lie in the investigation of the solid-state properties of mephedrone and how these properties may relate to its bioavailability and hence the potential risks associated with the use of this illicit drug. The project will utilise a number of techniques including: (i) polymorph screening; (ii) Raman and Infra-red spectroscopy; (iii) X-ray (single crystal and powder) diffraction under a range of temperatures and pressures – which have been successfully applied in the solid-state characterisation of other pharmaceutically relevant materials [3].

Techniques to be used:

(i) Polymorph screening;
(ii) Raman and Infra-red spectroscopy;
(iii) X-ray (single crystal and powder) diffraction under a range of temperatures and pressures

References:

[1] Sutcliffe et al, *J. Pharm. Biomed. Analysis*, **2011**, *56 (2)*, 246-255
[2] Bernstein, in *Polymorphism in Molecular Crystals*, IUCr Mongraphs on Crystallography; Clarendon Press: Oxford, **2002**.
[3] (a) Fabbiani et al, *Crystal Growth & Design*, **2007**, *7 (6)*, 1115-1124; (b) Oswald et al, *CrystEngComm*, **2010**, *12*, 2533-2540.

Strathclyde Institute for Pharmacy and Biomedical Sciences

MRes and MSci Research Project Descriptor

Project Title: Analysis of a medicinal plant for anti-diabetic/anti-obesity compounds

Primary Supervisor: Prof Alexander I. Gray
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Secondary Supervisor: Prof Roger D. Waigh
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MRes Research Area, select one or two of the following:
Biochemistry / Pharmacology (Drug Discovery from natural products)
MSci Research Area, select ONE of the following:
Biochemistry / Pharmacology / Immunology / Microbiology

Project Description:

The project will involve the analysis (both phytochemical and pharmacological screening) of a known herbal remedy used for the treatment of diabetes and from which we have isolated one active compound that has been fully characterised.

In the past some samples of the plant material were found to be devoid of activity leading us to believe that there may be seasonal variation in the chemical composition of the plant. Samples of the plant collected at intervals and/or from different sources will be extracted using selected solvents, components separated by chromatographic methods and analysed by NMR, MS, LC-MS techniques for the presence of target components.

The initial objectives will be to establish reliable *in vitro* methods for screening plant extracts or fractions or purified compounds for possible anti-diabetic activity; e.g. effects on insulin release and action plus other hypo-glycaemic signalling pathways; using biochemical assays such as PTP1B, DDP-IV, α-glucosidase inhibition (relevant to absorption of sugars from GI tract?), in cell assays such as HepG2 liver-derived cells used to monitor glucose uptake. Some assays may be developed by the student in collaboration with colleagues in SIPBS (Ms Louise Young, Carol Clements, Prof Alan Harvey).

Techniques to be used: Extraction using hot or cold solvent extraction, chromatographic analysis and bioassay-guided fractionation for purification of active substances. NMR and MS analysis for qualitative and quantitative examination of separated substances.

References:

1. Palit, P, Furman, BL & Gray, AI (1999) Novel weight-reducing activity of *Galega officinalis* in mice. *J Pharm Pharmacol*, **51**, 1313-1319.
2. Harvey, AL (2010) Plant Natural Products in Anti-diabetic Drug Discovery. *Current Organic Chemistry*, **14**, xxxx.

Strathclyde Institute for Pharmacy and Biomedical Sciences

MRes and MSci Research Project Descriptor

Project Title: Screen a flavonoid library: insights into the mechanisms of anti-MRSA and modulation of *Shigella*-host cell interaction

Primary Supervisor: Jun Yu
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Secondary Supervisor: Veronique Seidel
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MRes Research Area, select one or two of the following:
~~Biochemistry / Immunology /~~ Microbiology / Molecular Biology ~~/ Parasitology / Pharmacology Drug Delivery /~~ Pharmaceutical Materials ~~and Formulation~~
MSci Research Area, select ONE of the following:
~~Biochemistry / Pharmacology~~ / ~~Immunology~~ / Microbiology

Project Description: (suitable for both MRes and Msci)

Staphylococcus aureus and the pathogenic lineages of *Escherichia coli* known as *Shigella* are important bacterial pathogens. The former is a leading cause of bacterial infection with a wide spectrum of diseases. The latter have been prevalent agents that cause bacillary dysentery (shigellosis) worldwide particularly in developing countries. Treatment of infections by both microorganisms have been compromised due to the wide spread of multi-drug resistant strains, of which methicillin resistant *S. aureus* (MRSA) is a notorious super-bug. Therefore, it is urgent to search for new druggable targets in the bacteria and new strategies that offer low risk of antibiotic resistance.

A natural compound, propolin D, has been reported to exhibit anti-MRSA activity in vitro (1). Furthermore, propolin D has been found to modulate *Shigella*-host cell interaction, able to prevent *Shigella* intracellular growth to negligible level (2). Hence, propolin D holds great potential in treatment of infections by both pathogens. Moreover, propolin D belongs to the flavonoid family, bearing complete different structure compared to current used antibiotics; it most likely targets novel target(s) in staphylococcal, which could overcome current resistant mechanisms that the microbes have acquired. Additionally, propolin D most likely enhances a cellular mechanism that in turn controls *Shigella* growth in the cell. This holds a very low risk for the microbe to develop resistance as bacterial genes are not under direct selection.

Some important questions remain: **a**, are there other products of the flavonoid family exhibit greater activity than propolin D; and **b**, what is the structural basis for the observed functions. This project is designed precisely for answers to these questions. Dr D Tasdemir at London School of Pharmacy has kindly supplied a flavonoid library (3). You will perform agar dilution assay to determine the minimal inhibition concentration (MIC) on MRSA for each of the products. You will perform gentamicin-killing assay to assess the reduction of *Shigella* growth in the cell for each of the products. Finally, you will deduce structure-function relationship, which shall form the basis for further studies in rational design of the molecules to maximise the activity.

You will benefit from this interdisciplinary study by gaining new knowledge in medicinal chemistry and molecular and cellular pathogenesis, and mastering a set of lab techniques below.

Techniques to be used:
1, Culture bacteria and determine MIC
2, Culture human epithelial cell-lines and perform gentamicin-killing assay.
3, Structural comparison using various online programs.

References:
1. Raghukumar R, Vali L, Watson D, Fearnley J, Seidel V. 2010. Phytother Res. 24, 1181-117.
2. Xu D, Saeed A, Wang Y, Seidel V, Sandstroum MG, Yu J. 2011. J Med Microbiol. [Epub ahead of print].
3. Tasdemir D, Lack G, Brun R, Rüedi P, Scapozza L, Perozzo R. J Med Chem. 2006.

Strathclyde Institute for Pharmacy and Biomedical Sciences

MRes Biomedical Sciences / MRes Drug Delivery Systems

Research Project Descriptor

Project Title: The role of MAP kinase phosphatase-2 in intestinal helminth infection

Primary Supervisor: Dr Catherine Lawrence
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Secondary Supervisor: Prof Robin Plevin
Email: r.plevin@strath.ac.uk

MRes Research Area, select one or two of the following:
Immunology / Pharmacology
MSci Research Area, select ONE of the following:
Pharmacology / Immunology

Project Description:

The MAP kinase phosphatases (MKPs) are a family dual specific phosphatases (DUSPs) which regulate the activity of the MAP kinase pathway by dephosphorylation. Mitogen-activated protein (MAP) kinase cascades are crucial signal transduction pathways in the regulation of the host inflammatory response to infection. MAP kinase phosphatase (MKP)-1, an archetypal member of the MKP family, plays a pivotal role in the deactivation of p38 and JNK. Studies using MKP-1 knockout mice have defined the critical importance of MKP-1 in the regulation of pro-inflammatory cytokine synthesis in vivo during the host response to bacterial cell wall components. These studies demonstrated that MKP-1 is an essential feedback regulator of the innate immune response, and that it plays a critical role in preventing septic shock and multi-organ dysfunction during pathogenic infection. A number of additional DUSPs including MKP-5 and PAC-1 have also been implicated in the control of immune responses. More recently work done in SIPBS has shown MKP-2 to also play a role in regulating immune function. Deletion of MKP-2 results in a reduced resistance to leishmania infection due to abrogated Th1 responses. However, the effect of MKP-2 deletion upon Th2 responses remain unclear. Expulsion of gastrointestinal helminth parasites from the host requires the induction a profound Th2 response resulting in a profound mastocytosis and intestinal pathology.

The aim of this project is to determine the role of MKP-2 in the induction of Th2 responses, mastocytosis and enteropathy in intestinal helminth infection.

Techniques to be used:
Parasitology, cell culture, histology, ELISA, flow cytometry

References:

1. Lang R, Hammer M, Mages J. (2006) DUSP meet immunology: dual specificity MAPK phosphatases in control of the inflammatory response. J. Immunology 177, 7497-504
2. Li L, Chen SF, Liu Y .(2009) MAP kinase phosphatase-1, a critical negative regulator of the innate immune response. Int J Clin Exp Med. 2:48-67
3. Anthony RM, Rutitzky LI, Urban JF Jr, Stadecker MJ, Gause WC. (2007) Protective immune mechanisms in helminth infection. Nat Rev Immunol. 7:975-87

Strathclyde Institute for Pharmacy and Biomedical Sciences

MRes Biomedical Sciences / MRes Drug Delivery Systems

Research Project Descriptor

Project Title: Role of mast cells in the development of obesity

Primary Supervisor: Dr Catherine Lawrence
Email: catherine.lawrence@strath.ac.uk

Secondary Supervisor: Professor Brian Furman
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MRes Research Area, select one or two of the following:
Immunology / Pharmacology

MSci Research Area, select ONE of the following:
Pharmacology / Immunology

Project Description:

Obesity is a major health problem, being linked especially to the development of type 2 diabetes but also to cardiovascular disease and certain cancers. Current treatments are only moderately effective and a better understanding of the underlying pathophysiology of obesity is required. Cytokines, especially TNFα and IL-1, have been strongly implicated in the insulin resistance associated with obesity[1]. Recently, an important role for mast cells, a major source of these cytokines, was suggested by the reduced weight gain, reduced fat accumulation and improved glucose tolerance in mice lacking mast cells ($Kit^{W\text{-}sh/W\text{-}sh}$) placed on a western diet, which produced marked obesity in wild-type (WT) animals[2]. A similar reduction in the development of obesity was produced by the mast-cell stabilising drugs disodium cromoglycate or ketotifen in WT mice fed a western diet. To further test the hypothesis that mast cells contribute to the development of obesity, the present study will examine the effect of mast cell stabilisation using disodium cromoglycate or mast cell depletion using compound 48/80 on the development of obesity in genetically obese mice (ob/ob).

Ob/ob mice (6 weeks old) will be allocated randomly to one of three treatment groups; the control group will receive 0.9% sodium chloride (1ml/kg daily i.p.) while the other groups will receive daily injections of disodium cromoglycate (8mg/kg i.p.) or 48/80 (0.75 mg/kg i.p.). Body weight and food intake will be measured daily for 12 weeks. At the end of 12 weeks the animals will be killed and a blood sample obtained for determination of blood glucose (Glucometer) and plasma insulin (ELISA). The visceral adipose tissue will be dissected and weighed and samples of adipose tissue prepared for histology and for determination of TNFα and IL-1β (ELISA). Tissue samples will be stained for mast cells and the diameters of adipocytes will be measured.

Techniques to be used:
Histology, ELISA, tissue culture, in vivo biology

References:

1. Tilg H, Moschen, AR (2008) Mol Med. 14:222-31.
2. Liu J, Divoux A, Sun J, Zhang J, Clément K, Glickman JN, Sukhova GK, Wolters PJ, Du J, Gorgun CZ, Doria A, Libby P, Blumberg RS, Kahn BB, Hotamisligil GS, Shi GP. (2009) Nat Med. 158:940-5

Strathclyde Institute for Pharmacy and Biomedical Sciences

MRes and MSci Research Project Descriptor

Project Title: Use of the green fluorescent protein (GFP) to tag *Leishmania* protein kinases and their substrates for *in vivo* and *in vitro* analyses

Primary Supervisor: Dr Martin Wiese
Email: martin.wiese@strath.ac.uk

Secondary Supervisor: Prof Craig Roberts
Email: c.w.roberts@strath.ac.uk

MRes Research Area, select one or two of the following:
Biochemistry / Molecular Biology / Parasitology

MSci Research Area, select ONE of the following:
Biochemistry

Project Description:

Protein kinases are important regulators of all cells and play a role in vital processes like differentiation, proliferation, adaptation and motility. The human parasite *Leishmania mexicana* like other eukaryotes relies on signal transduction via reversible phosphorylation. As such parasite protein kinases are potential drug targets to be used to treat leishmaniasis which dependent on the parasite species and the immunological background of the host can be a fatal disease. In this project protein kinases and/or their substrates fused to the green fluorescent protein will be expressed in *Leishmania* parasites and visualised by fluorescence microscopy. This will provide us with valuable information about their cellular localisation. Moreover, the tagged proteins will be enriched from cell lysates and their activity and phosphorylation state assessed. The information gained will help to understand the role of the kinase and its suitability as a drug target.

Techniques to be used:
Cell culture, electroporation, protein purification, gene cloning, microscopy, kinase assay, immunoblot analysis.

References:

1. ***Wiese, M.*** *Leishmania* MAP kinases – familiar proteins in an unusual context. Internat. J. Parasitol. 37(10), 1053-62 (2007)
2. ***Wiese, M.*** A mitogen-activated (MAP) protein kinase homologue of *Leishmania mexicana* is essential for parasite survival in the infected host. EMBO J., 17, 2619-2628 (1998)

Strathclyde Institute for Pharmacy and Biomedical Sciences
MRes Biomedical Sciences / MRes Drug Delivery Systems
Research Project Descriptor

Project Title: Genetic characterisation of Farmer's Lung causing strains of thermophillic actinobacteria

Primary Supervisor: Dr Paul Herron
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Secondary Supervisor: Dr Paul Hoskisson
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MRes Research Area, select one or two of the following:
Immunology / Microbiology / Molecular Biology
MSci Research Area, select ONE of the following:
Immunology / Microbiology

Project Description:
Composting is a natural biological process of decomposition. In the right environmental conditions, the microorganisms naturally present in vegetation multiply and metabolise organic matter, turning it into a stabilised product with a high nutrient content capable of being used as a soil conditioner. Bacteria that are associated with composting include thermophillic actinobacteria bacteria from the genera *Saccharomonospora*, *Saccharopolyspora* and *Thermoactinomyces* (1). In order to explore their growth and develop genetic tools, systems used in the related genus *Streptomyces* will be applied to type strains of these thermophillic actinobacteria. These strains are associated with Farmer's Lung disease and the main aim of this project is to identify the gene encoding the antigen responsible for causing hypersesensitivity pneumonitis associated with Farmers Lung by genome sequencing of *Thermocatinomyces vulgaris* and *Saccharopolyspora rectivirgula*.

Techniques to be used: Microbiology, molecular biology, immunology

References:

1. **Pati A., J. Sikorski, M. Nolan, A. Lapidus, A. Copeland, T. Glavina Del Rio, S. Lucas, F. Chen, H. Tice, S. Pitluck, J. Cheng, O. Chertkov, T. Brettin, C. Han, J. C. Detter, C. Kuske, D. Bruce, L. Goodwin, P. Chain, P. D'haeseleer, A. Chen, K. Palaniappan, N. Ivanova, K. Mavromatis, N. Mikhailova, M. Rohde, B. J. Tindall, M. Göker, J. Bristow, J. a. Eisen, V. Markowitz, P. Hugenholtz, N. C. Kyrpides, and H. Klenk**. 2009. Complete genome sequence of Saccharomonospora viridis type strain (P101T). U.S. Patent 2. Standards in Genomic Sciences **1**:141-149.

Strathclyde Institute for Pharmacy and Biomedical Sciences

MRes and MSci Research Project Descriptor

Project Title: **New routes to transportation fuels via microalgal cultivation.**

Primary Supervisor: Brian McNeil
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Secondary Supervisor: Linda Harvey
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MRes Research Area, select one or two of the following:
Biochemistry / Microbiology /
MSci Research Area, select ONE of the following:
Microbiology

Project Description:

Petrochemical stocks are diminishing very quickly, and estimates of when they run out vary but generally we can't count on many more years of access to these relatively energy rich and easily obtained sources of transportation fuels. This is unfortunate as over 90% of transportation fuels are derived from fossil fuel sources, which hby definition are not sustainable in the long term. Replacing these pterochemically derived fuels with sustainably derived fuels from biological sources will be difficult, and will lead to changes in our society. So far, there have been numerous attempts to produce biofuels ranging from petrol additives os substitutes, such as bioethanol, to biodiesel, and biohydroegn. One of the most promising routes to biofuels potentially involves the mass cultivation of lipid accumulating microalgae, either photo-heterotrophically or autotrophically. Such microalgal cultivation is not without its challenges but real progress is being made. This project will commence with a detailed analysis of the literature, before moving on to the cultivation of selected species of microalgae in various reactor types. Effective process monitoring techniques will be developed including, if possible, near real time process monitoring of culture state and composition

Techniques to be used: Microalgal cultivation : compositional analysis ; bioprocess monitoring

References:

J.C. Csavina, and B.J.Stuart et al.Optimisation of algae for biodiesel production J.Appl. Microbiol. 111, 312-318. (2011)
C.J.Hulatt, and D.N.Thomas 1Energy efficiency of outdoor microalgal photobioreactor sited at temperate latitudes Biores. Technol 102, 6687-6695. (2011)

Strathclyde Institute for Pharmacy and Biomedical Sciences

MRes and MSci Research Project Descriptor

Project Title: Sustainable novel routes to polymers via organic acid synthesis by fungi

Primary Supervisor: Brian McNeil
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Secondary Supervisor: Linda Harvey
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MRes Research Area, select one or two of the following:
Biochemistry / Microbiology
MSci Research Area, select ONE of the following:
Microbiology

Project Description:

Most polymers in current use are derived from feedstocks derived almost exclusively from petrochemical sources. Given the rapidly increasing scarcity and cost of such materials, the sustainability of such a route to polymers is questionable in the medium term. If we are to produce synthetic processes which are sustainable and environmentally more acceptable than the petrochemicals route, we increasingly need to focus research upon alternative sources of the monomers(building blocks) of industrial polymers using biological solutions. Petrochemical derived feedstocks are characterised by very high concentrations of suitable feestocks and represent highly concentrated reserves of available energy and monomers. In order to replace these with biologically based materials, the biological routes must produce very high concentrations of monomers (100's of g/L at least) reliably and convert the starting material(usually sugars, or waste materials) at very high efficiencies(75-100%) if possible. There are few fermentation processes which can do this, but perhaps the most obvious are fungal fermentation processes for production of organic acids such as citric acid and itaconic acid. Both these processes are carried out by selected strains of *Aspergillus niger*. In this lab based project we will investigate the production of these organic acids in reactor systems, assessing the impact of morphological form on acid production and seeking to develop effective monitoring techniques to offer near real time insights into the process state.

Techniques to be used:

Fungal culture ; bioreactor operation ; bioprocess monitoring

References:

C.P. Kubicek, P. Punt, and J. Visser Production of organic acids by filamentous fungi in Industrial Applications 2nd Edn.The Mycota M.Hofrichter (Ed)Springer, Heidelberg (2010)
T. Wilke, and K-D. Vorlop, Biotechnological production of itaconic acid Appl. Microbiol. Biotechnol. 56, 289-295 (2001)

Strathclyde Institute for Pharmacy and Biomedical Sciences

MRes and MSci Research Project Descriptor

Project Title: Drug delivery across the barriers

Primary Supervisor: M N V Ravi Kumar
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Secondary Supervisor: Chris van der Walle
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MRes Research Area, select one or two of the following: Pharmacology Drug Delivery, Pharmaceutical Materials and Formulations
MSci Research Area, select ONE of the following: Pharmacology

Project Description:

From the site of administration, drugs have to overcome a series of biological barriers before they can elicit therapeutic response. Solubility of the compounds (water insoluble) adds to the complexity posing difficulties in the development of dosage forms that can facilitate the permeability across the barriers. Traditionally a variety of approaches such as salt formation, permeability enhancers have been used to overcome the problems. However, there are many existing compounds as well as the new chemical entities emerging out of drug discovery program that are least benefited by the conventional approaches. The project is aimed at developing sub-micron particulates that are capable of transporting the poorly soluble compounds across the intestine, which is the first barrier for *peroral* route of administration. These carriers will further be modified to facilitate the brain uptake of the compounds which otherwise is not possible. We will pick up three compounds of varied physicochemical properties and investigate the ability of the sub-micron carriers on the oral bioavailability and brain uptake.

Techniques to be used:

Emulsion techniques will be used to prepare the dosage forms and the developed forms will be thoroughly characterised by the state of the art techniques such as Zeta sizer, HPLC, DSC etc. *In vitro* and *in vivo* evaluation of the dosage forms will be performed.

References:

1. G. Mittal, et al. Journal of Controlled Release 150 (2011) 220–228.
2. J. Shaikh, et al. European Journal of Pharmaceutical Sciences 37 (2009) 223-230.
3. J. L. Italia, et al. Pharmaceutical Research 26 (2009) 1324-1331.

Strathclyde Institute for Pharmacy and Biomedical Sciences

MRes and MSci Research Project Descriptor

Project Title: Biochemical analysis of the *Leishmania* thiol-dependent reductase (TDR1) and glutaredoxins to investigate their role in redox regulation

Primary Supervisor: Prof. Graham H Coombs
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Secondary Supervisor: Dr. Gareth D. Westrop
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MRes Research Area, select one or two of the following:
Biochemistry / Immunology / Microbiology / Molecular Biology / Parasitology / Pharmacology
Drug Delivery / Pharmaceutical Materials and Formulation
MSci Research Area, select ONE of the following:
Biochemistry / Pharmacology / Immunology / Microbiology

Project Description: S-glutathionylation is a reversible modification of protein cysteine residues involving the addition of a glutathione molecule to form a mixed disulfide. This is thought to protect essential cysteine residues from irreversible oxidation under oxidative or nitrosative stress and may also regulate the activity of enzymes and cell-signalling proteins in unstressed cells (1). Glutaredoxin, a small thioredoxin like protein has been implicated in both S-glutathionylation and de-glutathionylation with its activity depending on the balance of oxidizing and reducing (redox) conditions in the cell.

Thiol-dependent reductase (TDR1) is a very unusual two domain protein with an N-terminal glutaredoxin domain and a C-terminal domain resembling an omega class glutathione S-transferase. The protein is found in the protozoan parasite *Leishmania,* the causative agent of Leishmaniasis, a group of human diseases common in tropical and subtropical regions. TDR1 is found in other trypanosomatid parasites but there are no homologs in other organisms. TDR1 has a glutaredoxin-like thiol transferase activity *in-vitro* and it can also reduce dehydroascorbate (2). A recent metabolomic analysis of a TDR1 knockout strain of *Leishmania* conducted in our laboratory indicates that TDR1 has a role in the regulation of central energy metabolism. This leads us to the hypothesis that TDR1 functions in redox regulation by S-glutathionylation. TDR1 could act directly through its N-terminal glutaredoxin domain to catalyse the S-glutathionylation or de-glutathionylation of a target enzyme or could be involved indirectly through the activation of a regulatory protein. In addition to TDR1, *Leishmania* encodes two types of glutaredoxins, Grx1 and Grx2 (3), that could also be important for S-glutathionylation.

The aim of the project is to compare the activity of recombinant TDR1, Grx1 and Grx2 in enzymic assays for S-glutathionylation and de-glutathionylation to determine whether *Leishmania* has the enzymic capacity for redox-regulation by S-glutathionylation. Recombinant *E.coli* strains expressing TDR1 and Grx1 are available and a strain expressing Grx2 will be constructed using recombinant DNA techniques. Modified proteins in which putative key residues have been changed could also be generated to confirm their importance.

Techniques to be used: Measurement of enzymic activity using established spectrophotometer-based assays. Development of new enzyme assays. Determination of the kinetic parameters K_m, V_{max} and k_{cat} to compare the catalytic efficiencies (k_{cat}/K_m) of different proteins. Homology based searching of genome databases. Preparation of *Leishmania* genomic DNA. Cloning of *Leishmania* genes by PCR. Site-directed mutagenesis. Expression of recombinant proteins in *E. coli.* Protein purification. SDS-PAGE. Protein quantification.

References:

1. Dalle-Donne, I *et al.* 2008. Trends in Biochemical Sciences, 34, 85-96
2. Denton, H. *et al.* 2004. Biochem. J. 381, 405-42
3. Krauth-Siegal, R.L and Comini, M.A. 2008. Biochemica et Biophysica Acta, 1780, 1236-1248

Strathclyde Institute for Pharmacy and Biomedical Sciences

MRes Biomedical Sciences / MRes Drug Delivery Systems

Research Project Descriptor

Project Title: A systematic approach for modelling interactions between biomolecules and surfaces

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Research Area: (select one or two of the following)
Biochemistry/Immunology/Microbiology/Molecular Biology/Parasitology/Pharmacology
Drug Delivery/Pharmaceutical Materials and Formulation
MSci Research Area, select ONE of the following:
Biochemistry / Pharmacology / Immunology / Microbiology

Project Description:

Protein arrays are tools which are used in medicine, biotechnology and basic research. At their simplest, arrays involve adsorbing protein to surfaces. Proteins 'stuck' to a surface in this manner can then act as supports for mammalian cells (with application to tissue engineering) or as capture agents binding antibodies (with application to medical diagnostics). In both cases the protein must remain functional, which generally means it must retain is 3-dimensional structure. There are several analytical techniques to assess structure/function but none are as powerful as neutron reflectivity which has the ability to 'see through' multiple protein layers, that would otherwise remain hidden. However, the drawback of this technique is that interpretation of data can be complex and ambiguous, particularly for complex protein arrays. Complete interpretation of the data, such as an understanding of the key steps involved in, and governing, the protein adsorption process, will require a molecular modelling approach. The modelling approach must be able to propose solutions which describe the orientation, shape and density of the adsorbed proteins. A successful modelling approach may be able to make predictions for related proteins through some fundamental insight. More immediately, should the approach be successful, we shall be able to fully characterise the model arrays for which we already have neutron reflectivity data, and thereby move forward in the rational design of cell adhesive and diagnostic surfaces.

Techniques to be used: Computational, theoretical methods will be employed. These will include classical molecular dynamics (MD) simulations of a number of proteins and surface types and a detailed analysis of the resulting trajectories.

References:

1. Kreiner M, Chillakuri CR, Pereira P, Fairhead M, Li Z, Mardon HJ, Holt SA, van der Walle CF (2009) Orientation and surface coverage of adsorbed fibronectin cell binding domains and bound integrin α5β1 receptors. Soft Matter, 5, 3954-62.
2. Le Brun AP, Holt SA, Shah DS, Majkrzak CF, Lakey JH, (2008) Monitoring the assembly of antibody-binding membrane protein arrays using polarised neutron reflection. Eur. Biophys. J., 37, 639-45.

Strathclyde Institute for Pharmacy and Biomedical Sciences

MRes and MSci Research Project Descriptor

Project Title: G protein-coupled receptor dimerisation

Primary Supervisor: Dr. Charles Kennedy
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MRes Research Area, select one or two of the following:
Pharmacology

MSci Research Area, select ONE of the following:
Pharmacology

Project Description:

Overview: In recent years an increasing number of G protein-coupled receptors (GPCR) have been shown to interact with each other to form dimers and it is now recognised that this is common and perhaps even crucial for their trafficking, membrane expression and functional activity. Furthermore, such dimers often have novel pharmacological and signalling properties (Milligan, 2004). For example, P2Y receptors are a family of GPCR that are activated by nucleotides, such as adenosine 5'-triphosphate (ATP) (Abbracchio *et al.,* 2006) and in a previous MRes project we showed that the $P2Y_1$ and $P2Y_{12}$ subtypes form functional heterodimers with pharmacological properties that are different from the individual receptors (Shakya Shrestha *et al.,* 2010). Since these receptors are coexpressed in some tissues this may have important implications for their biological activity.

Aim: The aim of this project is to extend our previous studies and characterise in more detail how the $P2Y_1$ and $P2Y_{12}$ receptors functionally interact. The student will use a number of cutting edge techniques to study GPCR dimerisation, including confocal microscopy, FRET imaging analysis, Western blotting and co-immunoprecipitation. They will also learn tissue-culture and will use receptor subtype-selective antibodies and immunohistochemical techniques to study native protein expression. Together, these experiments will help advance the search for new, effective analgesics.

Techniques to be used:

Confocal microscopy, FRET imaging analysis, Western blotting, co-immunoprecipitation, tissue-culture, immunohistochemistry

References:

1. Abbracchio MP, Burnstock G, Boeynaems JM, Barnard EA, Boyer JL, Kennedy C, Fumagalli M, Gachet C, Jacobson, KA and Weisman GA (2006) International Union of Pharmacology. Update of the P2Y G protein-coupled nucleotide receptors: from molecular mechanisms and pathophysiology to therapy. Pharmacol. Rev., **58**, 281-341.
2. Milligan G (2004) G protein-coupled receptor dimerization: function and ligand pharmacology. *Mol. Pharmacol.,* **66**, 1-7.
3. Shakya Shrestha, S., Parmar, M., Kennedy, C. and Bushell, T. (2010). Two-pore potassium ion channels are inhibited by both $G_{q/11}$- and G_i-coupled P2Y receptors. *Mol. Cell. Neurosci.,* **43**, 363-369

Strathclyde Institute for Pharmacy and Biomedical Sciences

MSci Research Project Descriptor

Project Title: Using novel small molecule kinase inhibitors of the inhibitory kappaB kinases (IKKs) to target the activation of the non-canonical NF-kappaB (NFkappaB) cascade in prostate cancer.

Primary Supervisor: Dr. Andrew Paul
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MRes Research Area, select one or two of the following:
Biochemistry / Pharmacology
MSci Research Area, select ONE of the following:
Biochemistry / Pharmacology

Project Description:

The signalling of the NFkappaB transcription cascade and its regulation of cellular gene transcription is well recognised to influence the development of a number of pathological conditions including bacterial and viral infection and cardiovascular diseases (see 1 & 2). More recently, this cascade has been recognised to provide an inflammatory basis for the development of various cancers, including that of the prostate. Therefore this pathway may be a viable target for drug intervention.

Central to the regulation of NFkappaB-mediated gene transcription is the activation of the classical inhibitory kappaB kinases (IKKs); IKKα and IKKβ regulate the canonical and non-canonical pathways respectively. Recent evidence (3) implicates both IKKα- and IKKβ-mediated NFkappaB activation in the regulation of the development of prostate cancer. In particular, it has emerged that whilst IKKβ may be important in early stage development, IKKα plays a key in the development of late stage hormone independent cancer (3), for which there are a dearth of viable therapeutics. Therefore inhibition of IKKα, IKKβ or both isoforms may be effective in treating prostate cancer however the availability of selective inhibitors of IKKα is an ongoing challenge in the medicinal chemistry and signalling fields.

In this project novel small molecule inhibitors selective for IKKα, developed as part of a current medicinal chemistry project, will be utilised in parallel to IKKβ inhibitors and validating molecular interventions (e.g. siRNA and adenovirus delivery) to determine the role(s) of the IKKs in regulating the canonical (e.g. p65 RelA-IκBα) vs. non-canonical (e.g. p100/52-RelB) NFkappaB pathways. Furthermore, the impact of inhibition of these kinases at the level of nuclear function (e.g. NFkappaB translocation) and expression of gene products, including adhesion molecules (e.g. ICAM/VCAM), chemokines (e.g. CXCL12) and inflammatory markers (e.g. matrix metalloproteinase-9 (MMP-9)) will be examined.

The student involved will gain experience of working in a multi-disciplined team pursuing modern drug discovery and development linking molecular signalling and cell biology to medicinal chemistry and molecular modelling approaches.

Techniques to be used:
Western Blotting, siRNA trasfection/protein 'run-down', adenovirus infection, nuclear extraction, indirect immunofluorescence.

References:

1. Integrating cell-signalling pathways with NF-kappaB and IKK function. Perkins ND. (2007) Nat Rev Mol Cell Biol. 8(1):49-62.
2. Inhibitory kappa B kinases as targets for pharmacological regulation Carly Gamble, Kathryn McIntosh, Rebecca Scott, Ka Ho Ho, Robin Plevin and Andrew Paul Brit. J. Pharmacol. Accepted manuscript online: 28 JUL 2011 06:13AM EST | DOI: 10.1111/j.1476-5381.2011.01608.x
3. B-cell-derived lymphotoxin promotes castration-resistant prostate cancer. Ammirante M, Luo JL, Grivennikov S, Nedospasov S, Karin M (2010). Nature 464: 302–305.

Strathclyde Institute for Pharmacy and Biomedical Sciences

MRes and MSci Research Project Descriptor

Project Title: Role of autophagy for Methicillin-resistant *Staphylococcus aureus* (MRSA)

Primary Supervisor: Edmond Chan
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MRes Research Area, select one or two of the following:
Biochemistry / Microbiology
MSci Research Area, select ONE of the following:
Biochemistry

Project Description:

Autophagy is a widely conserved degradation pathway that promotes cell health though a number of routes. During autophagy, cell membranes wrap around cytoplasmic proteins and organelles to form vesicles which are then transported to the lysosome. Autophagy plays multiple roles in the cellular immunity defence against pathogens such as bacteria and virus[1]. One mechanism involves the direct recognition and targeting of bacteria for degradation, thereby inhibiting bacterial survival and replication inside of the cell. Recognition and degradation of bacteria are better characterised for *Streptococcus*, *Shigella* and *Salmonella,* as examples. However, other bacteria such as *Brucella* and *Legionella pneumophila* display an alternate mechanism in which autophagy membrane structures are hijacked, modified and used to promote bacterial survival. Thus, appropriate tackling of infections with autophagy requires knowledge of the bacterial strain and mechanisms involved.

Methicillin-resistant *Staphylococcus aureus* (MRSA) cause hospital-acquired infections in a variety of human tissues. Hypervirulent strains in particular present a major health care challenge in the UK and globally. Some evidence shows that *S. aureus* is a type of bacteria that inactivates and manipulates the autophagy defence system for its own advantage[2]. Studies found that the role of autophagy was dependent upon the *agr* group of bacterial virulence factors and the host-cell Atg5 autophagy signalling pathway. More details on the autophagy / Staphylococcus interaction need to be clarified as better understanding in this area could have potential medical applications.

1. The student will compare the autophagy response triggered by *Staphylococcus* strains with varying levels of virulence.
2. The student will study the role of autophagy during *Staphylococcus* replication, in particular the role of the ULK kinase pathway. Our other work has focussed on the essential function of ULK1 signalling for autophagy [3, 4].

Techniques to be used:
Culture of mammalian cells, infection of cells with bacteria, analysis of bacteria and autophagy using western blotting biochemistry, microscopy and microbiology assays.

References.

1. Levine, B., N. Mizushima, and H.W. Virgin, *Autophagy in immunity and inflammation.* Nature, 2011. **469**(7330): p. 323-35.
2. Schnaith, A., et al., *Staphylococcus aureus subvert autophagy for induction of caspase-independent host cell death.* J Biol Chem, 2007. **282**(4): p. 2695-706.
3. Chan, E.Y. and S.A. Tooze, *Evolution of Atg1 function and regulation.* Autophagy, 2009. **5**(6): p. 758-65.
4. Chan, E.Y., et al., *Kinase-inactivated ULK proteins inhibit autophagy via their conserved C-terminal domains using an Atg13-independent mechanism.* Mol Cell Biol, 2009. **29**(1): p. 157-71.

Strathclyde Institute for Pharmacy and Biomedical Sciences

MRes and MSci Research Project Descriptor

Project Title: Role of autophagy for chemotherapy resistance in Chronic Myeloid Leukaemia

Primary Supervisor: Edmond Chan
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MRes Research Area, select one or two of the following:
Biochemistry /Pharmacology
MSci Research Area, select ONE of the following:
Biochemistry

Project Description:

Chronic Myeloid Leukaemia (CML) is a cancer of white blood cells characterised by uncontrolled growth in the bone marrow [1]. CML is caused by translocation between chromosomes 9 and 22, which creates a BCR (breakpoint cluster region) and cABL tyrosine kinase fusion protein. Unregulated kinase signalling stemming from BCR-ABL produces cancer by increasing cell survival, proliferation and resistance to limiting growth factors.

Clinical treatment of CML has been revolutionised by tyrosine kinase inhibitors such as imatinib (Gleevec) which suppress the action of BCR-ABL and initially reduces abnormal cell proliferation in 60% of patients treated. However, initial and acquired resistance to imantib needs to be solved before the disease can be better eradicated in more patients.

Recent work from our groups shows autophagy to play a critical role for CML resistance leading to the concept of autophagy inhibition as combinatorial strategy [2]. Autophagy is a degradation pathway that serves to promote overall cell survival by through multiple beneficial mechanisms [3]. In most mammalian cells, on-going levels of autophagy clear proteins and organelles that become damaged through normal turnover. The importance of pro-survival autophagy is supported by results from a range of different cancers. In CML, autophagy is activated following imatinib treatment. Blocking autophagy simultaneously with imatinib helps kill CML cells, as predicted by the working model.

The aim of this project is to develop methods to target autophagy in CML. Currently, autophagy is targeted in CML using the anti-malarial drug chloroquine which blocks the lysosome, but affects other cell functions. Our other work has studied the essential ULK1 kinase pathway for autophagy, which is another potential route for blocking the process [4].

1. The student will engineer CML cell lines using viral genetic vectors to target the 3 main autophagy signalling pathways.
2. The student will compare the efficiency of each genetic targeting strategy to sensitise CML cells to imatinib and related tyrosine kinase inhibitors

Techniques to be used:
Culture of CML cells, engineering of cells with retrovirus and lentivirus, analysis of autophagy using western blotting biochemistry and microscopy, analysis of cell viability

References.

1. Perrotti, D., et al., *Chronic myeloid leukemia: mechanisms of blastic transformation.* J Clin Invest, 2010. **120**(7): p. 2254-64.
2. Bellodi, C., et al., *Targeting autophagy potentiates tyrosine kinase inhibitor-induced cell death in Philadelphia chromosome-positive cells, including primary CML stem cells.* J Clin Invest, 2009. **119**(5): p. 1109-23.
3. Mizushima, N., et al., *Autophagy fights disease through cellular self-digestion.* Nature, 2008. **451**(7182): p. 1069-75.
4. Chan, E.Y. and S.A. Tooze, *Evolution of Atg1 function and regulation.* Autophagy, 2009. **5**(6): p. 758-65.

Strathclyde Institute for Pharmacy and Biomedical Sciences

MRes and MSci Research Project Descriptor

Project Title: Getting more bang for your buck or how to kill tumours more efficiently

Primary Supervisor: David Flint
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MRes Research Area, select one or two of the following:
Biochemistry / Pharmacology
MSci Research Area, select ONE of the following:
Biochemistry

Project Description:

Radiation remains a major frontline therapy for killing tumours. However, the effects of radiation are greater than would be anticipated form the radiation damage alone. Thus many tumour cells which are not killed by the radiation are effectively "sterilised" in a process known as the bystander effect. Thus, after irradiation, cells secrete into their surroundings, unknown factors which kill neighbouring cells. This project is focussed upon identifying these factors in order to try to develop them for therapeutic use, perhaps without the need to resort to radiotherapy at all.

Perhaps surprisingly, under less drastic circumstances, dying cells can signal to their neighbours to repair and replace the dying cells in order to effect wound healing. Thus there can be both positive and negative signals emanating from injured cells, depending upon the context or severity of injury.

It is also possible that the signals released from cells as they are irradiated are also released by cells undergoing various other stresses such as hypoxia or oxidative stress. Thus this project could utilise a wide variety of stressors which have implications for other important diseases such as cardiovascular disease and cirrhosis of the liver as well as various disease associated with ageing in order to identify factors which could be developed to aid in wound healing processes..

Techniques to be used:
Cell culture, immunocytochemistry, western blotting,

References:

1. Marie Boyd, Susan C. Ross, Jennifer Dorrens, Natasha E. Fullerton, Ker Wei Tan, Michael R. Zalutsky, Robert J. Mairs. Radiation-Induced Biologic Bystander Effect elicited In Vitro by Targeted Radiopharmaceuticals, Labeled with a-, b-, and Auger Electron–Emitting Radionuclides. J Nucl Med 2006; 47:1007–1015

2. Sureshbabu A, Okajima H, Yamanaka D, Shastri S, Tonner E, Rae C, Szymanowska M, Shand JH, Takahashi S, Beattie J, Allan GJ, Flint DJ. IGFBP-5 induces epithelial and fibroblast responses consistent with the fibrotic response. Biochem Soc Trans. 2009 37:882-85.

Strathclyde Institute for Pharmacy and Biomedical Sciences

MRes Biomedical Sciences / MRes Drug Delivery Systems

Research Project Descriptor

Project Title: Cannabidiol: a constituent of cannabis with psychoactive properties?

Primary Supervisor: Profesor Judith Pratt
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Secondary Supervisor: Dr Trevor Bushell
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Research Area: (select one or two of the following)
Pharmacology

Project Description:

Cannabis contains a wide range of cannabinoids, including Δ^9-tetrahydrocannabinol (THC) and cannabidiol (CBD). THC is proposed to be the main psychoactive component of cannabis and recent evidence suggests that cannabis rich in THC is more likely to produce adverse effects such as psychosis than cannabis containing a mix of CBD and THC. Hence it is thought that CBD may modulate the psychoactive effects of THC. Indeed, CBD is currently used at a 1:1 ratio with THC in Sativex® for the treatment of chronic pain in patients suffering from multiple sclerosis and advanced cancer [1,2]. This has led to CBD emerging emerged as an interesting compound due to its potential therapeutic application in a number of neurological and neuropsychiatric disorders [2]. However, we have recently shown that CBD inhibits synaptic transmission in rat hippocampal cultures and slices via multiple receptor pathways [3] which highlights that further investigations into the actions of CBD in the CNS are required in order to fully elucidate the therapeutic potential of CBD.

Thus this project aims to further investigate the actions of CBD on CNS function utilising a variety of animal models utilised to investigate normal rodent behaviour as well as that in models of schizophrenia and anxiety. The student will determine whether CBD is psychoactive per se, whether it antagonises the psychoactive effects of THC and whether it reduces the effects of other agents used in models of psychosis, such as phencyclidine (PCP).

Participation in this project will mean that the student will become part of an experienced laboratory with state-of-the-art equipment performing *in vivo* behavioural experiments.

Techniques to be used:
Behavioural tests including locomotor activity, open field tests, elevated plus maze, sensory motor gating and prepulse inhibition.
Study design and data analysis.

References:

1. Izzo AA et al., (2009). Non-psychotropic plant cannabinoids: new therapeutic opportunities from an ancient herb. *Trends Pharmacol Sci* **30:**515-27.

2. Parolaro D et al., (2010) The endocannabinoid system and psychiatric disorders *Exp Neurol.* **224**:3-14.

3. Ledgerwood CL et al., (2011). CBD inhibits synaptic transmission in rat hippocampal cultures and slices via multiple receptor pathways. *Brit J Pharmacol* **162:**286-94.

Strathclyde Institute for Pharmacy and Biomedical Sciences

MRes and MSci Research Project Descriptor

Project Title: Control of human immune cell responses by new prostaglandins and related Endocannabinoids/ ethanolamide metabolites.

Primary Supervisor: Dr. Dino Rotondo
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Tertiary Supervisor: Dr. Jillian Davidson
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MRes Research Area, select one or two of the following:
Immunology / Pharmacology

MSci Research Area, select ONE of the following:
Immunology

Project Description:

Prostaglandins are well established secondary mediators of inflammation which are derived from arachidonic acid and their synthesis can be inhibited by aspirin-like drugs. However, more recently it has been recognised that prostaglandins, particularly PGE_2 can suppress the production of the primary inflammatory mediators, specifically tumour necrosis factor-alpha (TNF-α) in a negative-feedback regulation. Indeed PGE_2 has been shown to be one of the most potent immunoregulatory mediators so far studied [1, 2], with the ability to completely abolish many immune cell activities such as monocyte TNF-α release, monocyte phagocytic activity and also T-cell proliferation. There are many different series of prostaglandins in addition to PGE_2 such as PGD_2, $PGF_{2\alpha}$ and the more recently discovered PGE_2-ethanolamide (thought to be derived from anandamide which is arachidonyl-ethanolamide [3]). This raises the question of whether other fatty acid acid-derived lipids that can be synthesised during immune responses, can also regulate those responses and if so the nature/ mechanisms by which they do so. This project will study the effects of various PG metabolites especially 15d-PGJ2 the more recently discovered resolvin-1 on TNF-α release from human monocytic cells and the proliferation of human T-cells initially and expand to include other immune cell activities e.g. phagocytosis etc. It is also intended to ascertain the signalling/ receptor systems by which the novel PGs induce their effects. This will be achieved both pharmacologically, using drugs which interfere with the signalling systems, and also by directly measuring the levels of intracellular mediators such as cyclic AMP and cyclic GMP.

Techniques to be used:
Cell isolation from human blood, ELISA, thin layer chromatography, flow cytometry, radiotracer labelling.

References:

1. DAVIDSON, J., KERR, A., GUY, K. and ROTONDO, D. (1998) Prostaglandin and fatty acid modulation of *E. Coli* O157:H7 phagocytosis by human monocytic cells. Immunology, **94**, 228-234.

2. ROTONDO, D., EARL, C.R.A., LAING, K., and KAIMAKAMIS, D. (1994) Inhibiton of cytokine-stimulated thymic lymphocyte proliferation by fatty acids: The role of eicosanoids. Biochim. Biophys. Acta. **1223,** 185-195.

3. Bakker A.M., Davidson J. and ROTONDO D. (1995) Arachidonyl ethanolamide (Anandamide) modulation of cytokine-stimulated thymic lymphocyte proliferation. Br. J. Pharmacol. **116**, 353.

Strathclyde Institute for Pharmacy and Biomedical Sciences

MRes and MSci Research Project Descriptor

Project Title: Control of human inflammatory and cell responses by novel and classical steroids.

Primary Supervisor: Dr. Dino Rotondo
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Tertiary Supervisor: Dr. Jillian Davidson
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MRes Research Area, select one or two of the following:
Immunology / Pharmacology
MSci Research Area, select ONE of the following:
Immunology

Project Description:

TNFα is a major proinflammatory cytokine which is released in response to many pathogenic stimuli especially pathogenic bacteria and their products. This reaction can classically be suppressed by steroids, specifically glucocorticoids and their analogues such as dexamethasone. In addition several new steroids have been described which may have protective properties, especially 7βOH–epiandrosterone (7βOH-EPIA). This steroid can selectively enhance the production of prostaglandins D_2 and 15 deoxy- PGJ_2, however, the mechanism by which this occurs is unclear. The aim of this project is to compare the effects of different steroids such as 7βOH-EPIA and dexamethasone especially those that are used as therapeutic drugs. This will be studied on the production of inflammatory cytokines, particularly TNF-α, IL-1 and IL-12 in human blood and by human monocytes stimulated by different pathogenic pathways such as bacterial and viral routes. It also intended to study the cytoprotective actions of these compounds on their ability to prevent both apoptotic and cytotoxic cell death. The effects of the steroids on the pathways which lead to the production of the different PGs will also be studied using labelled precursors.

Techniques to be used:
Cell isolation from human blood, ELISA, thin layer chromatography, flow cytometry, radiotracer labelling

References:

1. Davidson, J. Milton, A.S. and Rotondo, D. (1990) The Immunostimulatory Actions of Tumour Necrosis Factor are Suppressed by Dexamethasone. Br. J. Pharmacol., **100**, 445P

2. Davidson, J., Wulfert, E. and Rotondo, D. (2008). 7 beta-hydroxy-epiandrosterone modulation of 15-deoxy-Delta(12,14)-prostaglandin J(2), prostaglandin D(2) and prostaglandin E(2) production from human mononuclear cells. J. Steroid Biochem. Mol. Biol. **112**, 220-227.

Strathclyde Institute for Pharmacy and Biomedical Sciences

MRes and MSci Research Project Descriptor

Project Title: Control of human brain tumour cells (glioma) function by Prostanoid Receptor Pathways

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Tertiary Supervisor: Dr. Jillian Davidson
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MRes Research Area, select one or two of the following:
Biochemistry / Pharmacology
MSci Research Area, select ONE of the following:
Biochemistry

Project Description:

Prostaglandins are well established secondary mediators of inflammation which are derived from arachidonic acid and their synthesis can be inhibited by aspirin-like drugs. It is well established that prostaglandins, particularly PGE_2, can control many cellular processes such as cell proliferation or cell death. This is also the case with human brain tumours where it has been shown that PGE_2 can enhance the growth of tumour cells in vitro [1, 2]. In addition, the expression of enzymes involved in the biosynthesis of prostaglandins are also upregulated in glioma cells [1, 2] indicating that glioma cells not only respond to PGE_2 but they can also produce it in an autocrine manner. The disruption of PGE_2-induced proliferation, by either inhibiting PG biosynthesis or blocking PGE_2 receptors, can lead to the death of these cells by apoptosis [1]. Thus, interfering with these pathways is a potential target for tumour therapy. This is supported by a study which has shown that the use of celecoxib (a cyclooxygenase inhibitor of PG production) can prevent the occurrence of colon cancer in patients over a 5 year period [3]. It is not known whether this also occurs for other tumours such as gliomas. In addition, it is unclear which PGs are involved in the control of glioma functions as there are a very wide variety of arachidonic acid-derived metabolites from cyclo-oxygenase. In a recent project it appeared that PGD_2 decreased glioma cell cytotoxicity and that a DP_2 receptor antagonist increased cell death. The aim of the present study is to characterise the effects of different PGs i.e. compare the actions of PGD_2 and its metabolite, 15deoxy-PGJ_2 to PGE_2 on the proliferation and death of glioma cell lines and glioma cells derived directly from human tumour tissue. This will be carried out by using a variety of agonists and antagonists of the specific PG-receptor subtypes and different inhibitors of PG-synthesis will also be used. If time permits the production of PGs from the cells will be evaluated using ELISA and radiolabel tracer techniques.

Techniques to be used:
Cell isolation, ELISA, thin layer chromatography, flow cytometry, radiotracer labelling

References:

[1] Payner, T., Leaver, H. A., Knapp, B., Whittle, I. R., Trifan, O. C., Miller, S. and Rizzo, M. T. (2006). Microsomal prostaglandin E synthase-1 regulates human glioma cell growth via prostaglandin E(2)-dependent activation of type II protein kinase A. Mol Cancer Ther 5: 1817-26.

[2] Baryawno, N., Sveinbjornsson, B., Eksborg, S., Orrego, A., Segerstrom, L., Oqvist, C. O., Holm, S., Gustavsson, B., et al. (2008). Tumor-growth-promoting cyclooxygenase-2 prostaglandin E2 pathway provides medulloblastoma . therapeutic targets. Neuro Oncol 10: 661-74.

[3] Bertagnolli, M. M., Eagle, C. J., Zauber, A. G., Redston, M., Breazna, A., Kim, K., Tang, J., Rosenstein, R. B., et al. (2009). Five-year efficacy and safety analysis of the Adenoma Prevention with Celecoxib Trial. Cancer Prev Res (Phila Pa) 2: 310-21.

Strathclyde Institute for Pharmacy and Biomedical Sciences

MRes and MSci Research Project Descriptor

Project Title: Identification of an amphotericin B formulation for the treatment of leishmaniasis

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MRes Research Area, select one or two of the following:
Microbiology / Parasitology / Pharmacology
Drug Delivery / Pharmaceutical Materials and Formulation
MSci Research Area, select ONE of the following:
/ Pharmacology / Microbiology

Project Description:

Leishmaniasis is a disease caused by infection with the protozoan parasite *Leishmania.* It is endemic in 88 countries and can cause disease symptoms ranging from cutaneous lesions, mucocutaneous lesions or death depending on the infecting species and the immune response of the host (1). The World Health Organisation estimates that 350 million people are considered at risk of contracting leishmaniasis, and some 2 million new cases occur each year (2). Amphotericin B (AMB) is one of the drugs often used to treat antimony resistant leishmanial infections. This drug is highly effective in treating leishmaniasis but its toxicity and the necessity for intravenous dosing means that it is not an ideal drug. We have shown that intravenous treatment with AMB formulated into non-ionic surfactant vesicles (AMB-NIV) increased drug efficacy compared to similar treatment with AMB solution (3). We have shown the feasibility of using an AMB-NIV formulation for treatment by inhalation using animal models of cutaneous and visceral leishmaniasis and a pulmonary model of aspergillosus. We found that using treatment with NIV by inhalation resulted in better delivery to the lungs but could also be used to target entrapped solutions to the liver if a multiple dosing regimen was used. We would now like to improve the formulation so that it is more effective *in vivo* using a murine models of cutaneous and visceral leishmaniasis. This project shall use the IVIS® imaging system to determine the effect of drug treatment on parasite survival over time in the same animals.

Techniques to be used:

Parasitology, tissue culture, drug formulation, HPLC analysis, use of the IVIS imaging systems. This project will involve *in vivo* studies therefore the student will be expected to apply for a Home Office animal licence.

References:

1. Clam A. A current perspective on leishmaniasis. 2010: 2: 124-126

2. WHO, Report of a meeting of the WHO Expert Committee on the Control of Leishmaniases, Geneva, 22–26 March 2010, WHO Technical Report Series 949 WHO Press

3. Mullen AB, Carter KC, Baillie AJ.Comparison of the efficacies of various formulations of amphotericin B against murine visceral leishmaniasis. Antimicrob Agents Chemother. 1997, 10:2089-92.

Strathclyde Institute for Pharmacy and Biomedical Sciences

MRes and MSci Research Project Descriptor

Project Title: Adaption of *Leishmani donovani* for survival in rodents.

Primary Supervisor: Dr K. C. Carter
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Secondary Supervisor:
Email:

MRes Research Area, select one or two of the following:
Microbiology / Parasitology / Pharmacology/ Drug Delivery /
MSci Research Area, select ONE of the following:
Microbiology

Project Description:

Leishmaniasis is a disease caused by infection with the protozoan parasite *Leishmania.* It is endemic in 88 countries and can cause disease symptoms ranging from cutaneous lesions, mucocutaneous lesions or death depending on the infecting species and the immune response of the host (1). The World Health Organisation estimates that 350 million people are considered at risk of contracting leishmaniasis, and some 2 million new cases occur each year (2). Using luciferase-expressing parasites in animals to monitor parasite survival over time would facilitate selection of suitable drug formulations or treatment regimens. Other researchers have already used these types of parasites (3). We have already developed luciferase-expressing *Leishmania donovani* but the parasite is poorly infective to animals. In this project different methods will be tested for their ability to increase the infectivity of the parasites. Once this has been achieved then it will be possible to look at the effect of different drug formulations on parasite survival.

Techniques to be used:
Parasitology, tissue culture, use of the IVIS imaging systems. This project will involve *in vivo* studies therefore the student will be expected to apply for a Home Office animal licence.

References:

1. Clam A. A current perspective on leishmaniasis. 2010: 2: 124-126

2. WHO, Report of a meeting of the WHO Expert Committee on the Control of Leishmaniases, Geneva, 22–26 March 2010, WHO Technical Report Series 949 WHO Press

3. de La Llave E, Lecoeur H, Besse A, Milon G, Prina E, Lang T.A combined luciferase imaging and reverse transcription polymerase chain reaction assay for the study of *Leishmania* amastigote burden and correlated mouse tissue transcript fluctuations. Cell Microbiol. 2011 Jan;13(1):81-91

Strathclyde Institute for Pharmacy and Biomedical Sciences

MRes and MSci Research Project Descriptor

Project Title: Effects of brain states on neural communications

Primary Supervisor: Shuzo Sakata
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Secondary Supervisor:
Email:

MRes Research Area, select one or two of the following:
Pharmacology
MSci Research Area, select ONE of the following:
Pharmacology

Project Description:
Our brain is never at rest. Brain circuits spontaneously generate coordinated activity even in the absence of sensory inputs. Although such spontaneous activity was traditionally ignored as "noise", recent studies have shown that spontaneous activity plays a pivotal role in normal brain functions. Moreover, abnormalities in spontaneous activity are also associated with many brain diseases, such as schizophrenia and Alzheimer's disease.

The form of spontaneous activity is associated with brain/behavioural states. During non-REM sleep, for example, slow and large fluctuation of cortical electroencephalograms (EEG) is observed whereas fast and small fluctuation of EEG is observed during a conscious state. How is such brain state organized by individual neural activity? What is the impact of brain state on information processing, such as sensory perceptions?

In this project, we aim to investigate the neural mechanism of brain-state-dependent auditory information processing *in vivo*. We will study ensembles of neurons because our brain works as a network and because we know little about how diverse neurons work together to process sensory signals. We will test the hypothesis that during an activated state, neurons efficiently communicate each other. To this end, we will combine several *in vivo* experimental techniques (*in vivo* electrophysiological, behavioural, and optogenetic approaches) with advanced statistical analyses.

Techniques to be used:
in vivo electrophysiology, behavioural testing, optogenetics, multivariate statistical analysis

References:
1. **Sakata S**, and Harris KD. (2009). Laminar structure of spontaneous and sensory-evoked population activity in auditory cortex. *Neuron* 64 (3), 404-418.
2. Curto C, **Sakata S**, Marguet S, Itskov V, and Harris KD. (2009). A simple model of cortical dynamics explains variability and state-dependence of sensory responses in urethane-anesthetized auditory cortex. *Journal of Neuroscience* 29 (34), 10600-10612.
3. Harris KD, Bartho P, Chadderton P, Curto C, de la Rocha J, Hollender L, Itskov V, Luczak A, Marguet SL, Renart A, and **Sakata S**. (2011). How do neurons work together? Lessons from auditory cortex. *Hearing Research* 271 (1-2), 37-53.

Strathclyde Institute for Pharmacy and Biomedical Sciences

MRes and MSci Research Project Descriptor

Project Title: New antimicrobials for *Acanthamoeba*

Primary Supervisor: Craig W Roberts
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Secondary Supervisor: Martin Wiesse
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MRes Research Area, select one or two of the following:
Biochemistry / Immunology / Microbiology / Molecular Biology / Parasitology / Pharmacology
Drug Delivery / Pharmaceutical Materials and Formulation
MSci Research Area, select ONE of the following:
Biochemistry / Pharmacology / Immunology / Microbiology

Project Description:

Acanthamoeba (species) are opportunistic parasites of humans where they can cause sight-threatening keratitis or life-threatening encephalitis. Current treatments are inadequate and unreliable. Identification of new antimicrobial targets in *Acanthamoeba* is important for the development of therapeutics and contact lens solutions. The following project will identify new antimicrobial agents and their targets in *Acanthamoba* using molecular biological techniques and tissue culture techniques.

Techniques to be used:
Tissue Culture, PCR, cloning, sequencing and bioinformatics

References:

1. McBride, J., Mullen, A.B., Carter, K.C. & ROBERTS, C.W. (2007). Differential cytotoxicity of phospholipid analogues to pathogenic Acanthamoeba species and mammalian cells. Journal of Antimicrobial Chemotherapy 60, 521-5

2. Henriquez, F.L., Ingram, P.R., Muench, S.P. Rice, D. & ROBERTS, C.W. (2008). A molecular basis for the resistance of Acanthamoeba tubulins to all major classes of anti-tubulin. Antimicrobial Agents and Chemotherapy 52, 1133-5.

3. 16. ROBERTS, C.W. and Henriquez, F.L. (2010). Drug target identification, validation, characterisation and exploitation in Acanthamoeba. Experimental Parasitology 126, Issue 1, 91-96

Strathclyde Institute for Pharmacy and Biomedical Sciences

MRes Biomedical Sciences / MRes Drug Delivery Systems

Research Project Descriptor

Project Title: Preparation of ricenoleic acid derivatives as antituberculosis agents

Primary Supervisor: Professor Alex Mullen
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Secondary Supervisor: Dr Oliver Sutcliffe
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Research Area: (select one or two of the following)
Drug Delivery/Pharmaceutical Materials and Formulation

Project Description:

Tuberculosis continues to represent a major challenge to world health, with around 1.7 million deaths recorded in 2009. The emergence of drug-resistant strains of mycobacteria, and the co-existence of TB in HIV-positive individuals means that new and effective treatments are urgently required.

A major lipid component of mycobacteria is tuberculostearic acid (Figure 1) which is derived from the methylation of oleic acid esterified as a component of a phospholipid, with *S*-adenosylmethionine as the methyl donor. The resulting 10-methylene-octadecanoyl residue is reduced to the 10-methyl compound with NADPH as the cofactor. Making structural analogues of tuberculostearic acid as potential disruptors of lipid metabolism is attractive from a drug targeting perspective as these lipids are unique to certain species of bacteria including mycobacteria.

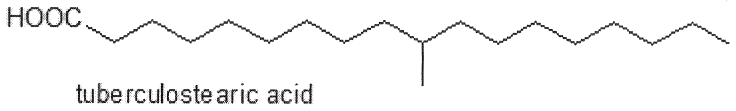
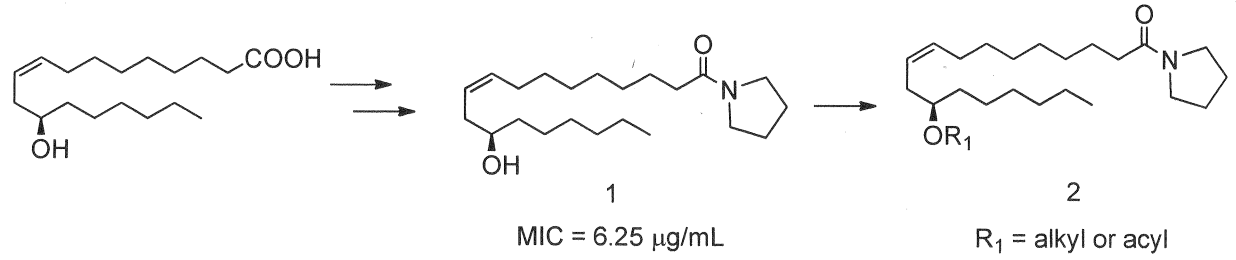


Figure 1. Chemical structure of tuberculostearic acid.

Ricinoleic acid is a constituent found in castor oil which has been show recently to be a potential lead for the development of anti-tuberculosis agents. D'Oca *et al.* have prepared a number of amide derivatives and found that they are active against *Mycobacterium tuberculosis* H37Rv, M. tuberculosis rifampicin resistance (ATCC 35338), and *M. tuberculosis* isoniazid resistance (ATCC 35822). The fatty acid amide derivate (1) was the most potent among a series, with a MIC 6.25 μg/mL for resistance strains. Using this compound as a model we shall prepare a small library of O-alkyl and O-acylated derivatives (2) and evaluate them against *M. tuberculosis* strains in-house.



Scheme 1. Synthesis of ricinoleic acid derivatives.

Techniques to be used:

(i) Synthetic organic chemistry coupled with structural elucidation/chemical analysis;
(ii) Microbial culture and antibiotic testing

References:

[1] MGM D'Oca *et al., Bioorg. & Med. Chem. Lett.*, **2010**, *20*, 5255 – 5257.

Strathclyde Institute for Pharmacy and Biomedical Sciences

MRes and MSci Research Project Descriptor

Project Title: Identification of novel sphingosine kinase 1 and 2 inhibitors with anti-cancer activity.

Primary Supervisor: NJ Pyne
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MRes Research Area, select one or two of the following:
Biochemistry and Pharmacology
MSci Research Area, select ONE of the following:
Biochemistry and Pharmacology

Project Description:

Sphingosine 1-phosphate (S1P) is a biologically active lipid. It is produced by sphingosine kinase (two forms, SK1 and SK2) and removed by S1P phosphatase and S1P lyase (Pyne & Pyne, 2010). S1P stimulates cells to divide and migrate by activating S1P-specific G-protein coupled receptors at the plasma membrane (Pyne & Pyne, 2010). However, it also has intracellular protein targets that affect cell function.

Increasing evidence supports a key role for sphingosine kinases in cancer progression. Cancer cells have a survival and growth advantage over non-cancer cells, which correlates with high levels of SK1. Indeed, we reported that high levels of SK1 in oestrogen receptor positive (ER^+) breast cancer patient tumours correlates with poor patient survival rates and induction of resistance to the first line therapeutic option, tamoxifen (Long et al. 2010; Watson et al., 2010). Therefore, SK inhibitors have the potential to be developed as anti-cancer agents. Despite this, poor SK inhibitor potency has been a major problem in translating these compounds into the clinic.

However, we have recently identified new properties of SK1 that can be exploited in developing anti-cancer therapeutics. For example, we have shown that SK1 (i) is an allosteric enzyme, i.e. it has an additional site that can be targeted by inhibitors and (ii) undergoes inhibitor-induced removal from cancer cells (by proteolytic degradation) (Loveridge et al., 2010; Tonelli et al., 2010; Lim et al., 2011). Also, others have produced inhibitors with high potency.

The aim of this project is to test a number of potential inhibitors for their ability to:

(i) inhibit SK1 and SK2 activity (and identify their manner of inhibition - catalytic or allosteric)
(ii) induce degradation of SK1 in cancer cells
(iii) inhibit cancer cell migration (by visualising their effects on actin rearrangement)
(iv) inhibit DNA synthesis in cancer cells (a measure of cancer cell growth)
(v) induce programmed cell death/apoptosis (measured by DNA fragmentation and cleavage of the DNA repair enzyme polyADP ribose polymerase (PARP)).

Collectively, this data will provide important leads for the development of new anti-cancer compounds with the potential for development as new therapeutics.

Techniques to be used:

Breast cancer cells (both ER^+ and ER^-) which may express the HER2 (oncogene) will be used. Techniques employed will include sphingosine kinase activity assays, western blotting, immunofluorescence microscopy, cell culture, proliferation assays, gene transfection and protein over-expression.

References:

Pyne, N.J. & Pyne, S (2010) Sphingosine 1-phosphate and cancer. Nature Rev. Cancer 10, 489-503.

Long, J.S., Edwards, J., Watson, C., Tovey, S., Mair, K., Schiff, R., Natarajan, V., Pyne, N.J., & Pyne, S. (2010) Sphingosine kinase 1 induces tolerance to human epidermal growth factor receptor 2 and prevents formation of a migratory phenotype in response to sphingosine 1-phosphate in estrogen receptor positive breast cancer cells. Mol. Cell. Biol. 30, 3827-3841.

Watson, C., Long, J.S., Orange, C., Tannahill, C.L., Mallon, E., McGlynn, L.M., Pyne, S., Pyne, N.J. & Edwards, J. (2010) High expression of sphingosine 1-phosphate receptors, $S1P_1$ and $S1P_3$, sphingosine kinase 1, and extracellular signal-regulated kinase-1/2 is associated with development of Tamoxifen resistance in estrogen receptor-positive breast cancer patients. Am. J. Pathology 177, 2205-2215.

Tonelli, F., Lim, K., Loveridge, C., Long, S., Pitson, S.M., Tigyi, G., Bittman, R., Pyne S. & Pyne, N.J. (2010) FTY720 and FTY720 S-ene phosphonate are novel sphingosine kinase inhibitors and induce proteasomal degradation of sphingosine kinase 1 in mammalian cells *Cell. Signalling.* **22**, 1536-1542.

Loveridge, C., Tonelli, T., Leclercq, T., Lim, KG., Long, S., Berdyshev, E., Tate, R.J., Natarajan, V., Pitson, S., Pyne, N.J. & Pyne, S. (2010) The sphingosine kinase 1 inhibitor 2-(p-hydroxyanilino)-4-(p-chlorophenyl)thiazole induces proteasomal degradation of sphingosine kinase 1 in mammalian cells. *J. Biol. Chem.* **285**, 38841-38852.

Lim, K.G., Tonelli, F., Li, Z., Lu, X., Bittman, R., Pyne, S. & Pyne, N.J. (2011) FTY720 analogues as sphingosine kinase 1 inhibitors: Enzyme inhibition kinetics, allosterism, proteasomal degradation and actin rearrangement in MCF-7 breast cancer cells. J. Biol. Chem. 286, 18633-18640.

Strathclyde Institute for Pharmacy and Biomedical Sciences

MRes and MSci Research Project Descriptor

Project Title: Cancer Chemoprevention: Transcriptional Regulation of AKR7A1 by dietary chemoprotectors

Primary Supervisor: Dr Elizabeth Ellis
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Secondary Supervisor: Prof John Hayes
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MRes Research Area, select one or two of the following:
Biochemistry, Molecular Biology, Pharmacology
MSci Research Area, select ONE of the following:
Biochemistry, Pharmacology

Project Description:
Chemoprevention is the process by which compounds naturally present in the diet can prevent or reduce the development of cancer. One mechanism of chemoprevention is through the induction of protective enzymes, mediated by the transcription factor Nrf2 binding to the Antioxidant Response Element or ARE that is in the promoter of induced genes. Our previous work has investigated the up-regulation of an aldo-keto reductase AKR7A1 that can protect liver cells against aflatoxin B1-induced cancer. We have cloned and analysed a 720 bp promoter region and have identified putative regulatory sequences in this promoter. We have also shown that this promoter can drive expression of a reporter construct in cell lines.
More recently we have obtained BAC clones that contain a further 4kb of upstream sequence. We have subcloned regions of this promoter into reporter vectors and have shown that it is functional in cell lines. The aim of this project is to:
1. Confirm the sequence of this promoter region
2. Create defined mutations in putative ARE sequences in the promoter in order to demonstrate the role of Nrf2/ARE in regulation of AKR7A1
This work will increase our knowledge of chemoprevention and its potential as an anticancer strategy.

Techniques to be used:
Bioinformatics, DNA sequencing, PCR, reporter genes, cell culture

References:
1. Ellis EM, Judah DJ, Neal GE, Hayes JD. (1993) An ethoxyquin-inducible aldehyde reductase from rat liver that metabolizes aflatoxin B1 defines a subfamily of aldo-keto reductases. Proc Natl Acad Sci U S A. 90:10350-4
2. Hayes JD, Ellis EM, Neal GE, Harrison DJ, Manson MM (1999). Cellular response to cancer chemopreventive agents: contribution of the antioxidant responsive element to the adaptive response to oxidative and chemical stress Biochem Soc Symp. 64:141-68.
3. Ellis EM, Slattery CM, Hayes JD. (2003) Characterization of the rat aflatoxin B1 aldehyde reductase gene, AKR7A1. Structure and chromosomal localization of AKR7A1 as well as identification of antioxidant response elements in the gene promoter. Carcinogenesis. 24(4):727-37

Strathclyde Institute for Pharmacy and Biomedical Sciences

MRes and MSci Research Project Descriptor

Project Title: Neuroprotection against oxidative and carbonyl stress

Primary Supervisor: Dr Elizabeth Ellis
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Secondary Supervisor: Dr Ben Pickard
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MRes Research Area, select one or two of the following:
Biochemistry, Molecular Biology, Pharmacology
MSci Research Area, select ONE of the following:
Biochemistry, Pharmacology

Project Description:
Oxidative stress has been implicated in a range of neurodegenerative diseases, as well as ischaemia-reperfusion type injury such as stroke. Neuronal cells have limited intrinsic ability to protect themselves against oxidants, and this may lead to cellular damage to lipids, proteins and DNA. Oxidation of lipids leads to the production of lipid peroxidation products, many of which are highly toxic aldehydes (1).

Previously we have shown that the human neuroblastoma cell line SH-SY5Y cell line is extremely sensitive to carbonyl stress (2). We have also shown that treatment of cells with certain phytochemicals can lead to the induction of protective enzymes and that this is sufficient to cause increased protection against reactive aldehydes and oxidants (2).

The SH-SY5Y cell line is neuronal-like and can be induced to differentiate (3,4). What is not known is to what extent differentiated cells have increased levels of protective enzymes and whether or not this can protect them against reactive carbonyls.

In this study, SH-SY5Y cells will be differentiated, and the effect on protective enzyme expression measured using Western blots and RT-PCR. The effect on cell survival will be monitored using MTT assays.

Techniques to be used:
Mammalian cell culture
Cytotoxicity assays
Gene Expression studies

References:
1. Ellis, E.M. 2007 Pharmacol Ther. 115:13-24.
2. Biedler et al., 1978. Cancer Res. 38:3751-7.
3. Monaghan T et al (2008) J. Neurochem. 104, 74-88

Strathclyde Institute for Pharmacy and Biomedical Sciences

MRes and MSci Research Project Descriptor

Project Title: Molecular basis of selective toxicity of antimicrobial minor groove binders

Primary Supervisor: Dr Elizabeth Ellis
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Secondary Supervisor: Prof Iain Hunter
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MRes Research Area, select one or two of the following:
Biochemistry, Molecular Biology, Microbiology, Drug Delivery
MSci Research Area, select ONE of the following:
Biochemistry, Microbiology

Project Description:
Minor Groove Binders (MGB) are a class of compounds that bind to the minor groove of DNA. By doing so, they can disrupt normal cell processes. Although some MGBs are toxic to mammalian cells and can be used as anticancer drugs, we have identified a class of MGBs that can effectively kill microbial cells, yet which do not display significant toxicity to mammalian cells (1). This makes them ideal for use as antimicrobial agents. However the mechanism of action and the basis for the observed selective toxicity is not known.

The aim of this project is to find out why these compounds can kill bacterial or fungal cells, but cause little damage to mammalian cells. Lines of investigation will include measuring the ability of the compounds to enter cells; to prevent key DNA-dependent processes such as DNA replication and transcription in bacterial and mammalian cells (2); to inhibit topoisomerase activity and supercoiling (3), and perturbation of membrane transport systems.

Techniques to be used:
Fluorescent microscopy
Mammalian and microbial cell culture
Cytotoxicity assays
Toposiomerase, DNA cleavage and supercoiling assays

References:
1. Anthony NG, Breen D, Clarke J, Donoghue G, Drummond AJ, Ellis EM, Gemmell CG, Helesbeux JJ, Hunter IS, Khalaf AI, Mackay SP, Parkinson JA, Suckling CJ, Waigh RD. 2007. Antimicrobial lexitropsins containing amide, amidine, and alkene linking groups. J Med Chem.50:6116-25.
2. Simon H, Kittler L, Baird E, Dervan P, Zimmer C. (2000) Selective inhibition of DNA gyrase in vitro by a GC specific eight-ring hairpin polyamide at nanomolar concentration. FEBS Lett. 2000 Apr 14;471(2-3):173-6.
3. McHugh MM, Woynarowski JM, Sigmund RD, Beerman TA. (1989). Effect of minor groove binding drugs on mammalian topoisomerase I activity. Biochem Pharmacol. 38:2323-8.

Strathclyde Institute for Pharmacy and Biomedical Sciences

MRes and MSci Research Project Descriptor

Project Title: Investigation into the potential therapeutic properties of marine organisms

Primary Supervisor: Dr Val Ferro
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Secondary Supervisor: Prof David Flint
Email:

MRes Research Area, select one or two of the following:
Immunology / Microbiology
MSci Research Area, select ONE of the following:
Immunology

Project Description:

GlycoMar (an Oban-based company) is dedicated to the isolation and characterisation of novel glycobiology products from marine organisms (microalgae and invertebrates). They have several products that have pharmaceutical, cosmeceutical and nutraceutical applications. They have been chemically characterised, but require further investigation into their therapeutic potential. This project will develop cell-based assays for investigating wound healing and wound hydration properties. These products could then be developed into topical cosmeceutical, wound healing or smart bandage applications. In addition, the immunomodulatory properties of these products will be investigated in a monocyte cell stimulation assay that will assess their pro- and anti-inflammatory potential for further drug discovery.

We are looking for a student that is adaptable, able to develop suitable bioassays and problem-solve, can bring their own ideas to the project.

Techniques to be used:
The student will gain experience in a wide range of techniques, such as cell culture, bioassays and immunoassays.

References:

1. Bavington CD, Lever R, Mulloy B, Grundy MM, Page CP, Richardson NV, McKenzie JD. Anti-adhesive glycoproteins in echinoderm mucus secretions. Comp Biochem Physiol B Biochem Mol Biol. 2004 Dec;139(4):607-17.

2. Habeeb F, Stables G, Bradbury F, Nong S, Cameron P, Plevin R, Ferro VA.The inner gel component of Aloe vera suppresses bacterial-induced pro-inflammatory cytokines from human immune cells. Methods. 2007 Aug;42(4):388-93.

3. Gutiérrez T, Mulloy B, Bavington C, Black K, Green DH. Partial purification and chemical characterization of a glycoprotein (putative hydrocolloid) emulsifier produced by a marine bacterium Antarctobacter.Appl Microbiol Biotechnol. 2007 Oct;76(5):1017-26. Epub 2007 Jul 20.

Strathclyde Institute for Pharmacy and Biomedical Sciences

MRes and MSci Research Project Descriptor

Project Title: Development of a Mucosal Anti-fertility Device Based on Copper Nanoparticles

Primary Supervisor: Dr Valerie Ferro
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Secondary Supervisor:
Email:

MRes Research Area, select one or two of the following:
Pharmacology / Drug Delivery /
MSci Research Area, select ONE of the following:
Pharmacology

Project Description:

Control of fertility, is a desirable goal for humans and companion animals, not only for population control, but also for treatment of hormone-dependent diseases (cancer, endometriosis). The main methods of controlling fertility can be categorised under barrier (condoms), devices (coil), pills (oral contraceptive), creams (spermicides) and injectables (depot).

Over the last few decades, another promising approach has been to vaccinate against fertility; known as immunocontraception. Several vaccines are currently being explored that target reproductive hormones (eg GnRH) and components (sperm/ova). All have shown efficacy, safety and reversibility in animal models and first-generation products have appeared on the market (GonaCon, SpayVac to control fertility in companion animals). However, they lack the characteristics of convenience, complete safety, robustness and duration. Additionally, the immune responses have been too short-lived for effective contraceptive use.

Vaccines are generally delivered by subcutaneous or intramuscular injection. The delivery of vaccines through the mucosal routes (eg oral, nasal, vaginal, rectal) is practical, non-invasive and targets the genital tract effectively. These are currently still at experimental stage and unavailable commercially. This is mainly because some routes of mucosal delivery are problematic (for example stomach acid degrades vaccines via the oral route) and genital responses are varied. Therefore, in this project we will examine mucosal routes that are more appropriate for delivery to the reproductive tract (eg uterine, vaginal), combined with release from barrier, devices and creams. We have developed a copper nanoparticle system, which we will examine for release properties of protein and suitability for use in reproductive tract targets. The nanoparticles will be formulated in a gel suspension. Measurements of release properties of proteins, and how their integrity is altered in simulated reproductive tract secretions will be examined. Histological analysis will examine interaction of the nanoparticles with cells in the reproductive tract, while ex vivo studies will assess the uterine contraction impact.

This is a highly multi-disciplinary project and requires a student who wishes to have a broad range of expertise, is flexible and willing to have an in-put into the project.

Techniques to be used:

Chemistry, microbiology, tissue culture, microscopy, analytical techniques.

References:

1. Khan MA, Ogita K, Ferro VA, Kumasawa K, Tsutsui T, Kimura T. Immunisation with a plasmid DNA vaccine encoding gonadotrophin releasing hormone (GnRH-I) and T-helper epitopes in saline suppresses rodent fertility. Vaccine. 2008 Mar 4;26(10):1365-74. Epub 2008 Jan 22.

2. Chengji Cui a,1, Vernon C. Stevens b, Steven P. Schwendemana. Injectable polymer microspheres enhance immunogenicity of a contraceptive peptide vaccine. Vaccine. 2007. 25, 500–509.

3. Sun L, Huang XB, Suo JP, Fan BL, Chen ZL, Yang WX, Li J. Biological evaluation of a novel copper-containing composite for contraception. Fertil Steril. 2011 Mar 15;95(4):1416-20. Epub 2010 Jun 8.

Strathclyde Institute for Pharmacy and Biomedical Sciences

MRes and MSci Research Project Descriptor

Project Title: Imaging changes in mitochondrial architecture and mobility in vascular disease

Primary Supervisor: Prof John McCarron
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Secondary Supervisor: Prof Sue Pyne
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MRes Research Area, select one or two of the following:
Biochemistry / Immunology / Microbiology / Molecular Biology / Parasitology / Pharmacology
Drug Delivery / Pharmaceutical Materials and Formulation
MSci Research Area, select ONE of the following:
Biochemistry / Pharmacology / Immunology / Microbiology

Project Description:
Vascular disease such atherosclerosis and hypertension are characterised by increased proliferation of vascular smooth muscle (VSM) cells. It is the increased proliferation that causes the vascular problems. In this project new methods to prevent the VSM proliferation that occurs in vascular disease will be examined. The project will target mitochondria as a way of preventing proliferation from occurring. Our preliminary results show dramatic, previously unrecognised re-organisation of mitochondria as VSM enters the proliferative state. In non-proliferative VSM, mitochondria are individual, ovoid, immobile structures. In proliferative VSM cells mitochondria are small spheres, rod-shapes, filamentous threads and networks, undergoing continuous changes in shape and position in the form of both long distance and complex local movements. Significantly, when mitochondrial mobility is reduced pharmacologically smooth muscle proliferation decreases. The objective of this project is to determine how mitochondrial mobility alters cell proliferative status and performance. The major hypothesis is that mitochondrial mobility is required for proliferation to occur and acts by altering Ca^{2+} signalling. To carry out this project new methodologies to study and analyze mitochondrial movements have been developed and will be combined with sophisticated molecular techniques to manipulate mitochondrial dynamics. The outcome of these studies will determine if mitochondrial dynamics contribute to the abnormal performance in vascular disease.

Techniques to be used:

1. **Cell imaging and fluorescence microscopy.**
2. **Transfection procedures and shRNA.**
3. **Particle tracking**

References:

1. Saotome M, Safiulina D, Szabadkai G, Das S, Fransson A, Aspenstrom P, Rizzuto R, Hajnoczky G. (2008) Bidirectional Ca^{2+}-dependent control of mitochondrial dynamics by the Miro GTPase. Proc Natl Acad Sci U S A, 105, 20728-33.
2. Chalmers S, McCarron JG. (2008) The mitochondrial membrane potential and Ca^{2+} oscillations in smooth muscle. J Cell Sci, 121, 75-85.
3. Weintraub WS. (2007) The pathophysiology and burden of restenosis. Am J Cardiol, 100, 3K-9K.

Strathclyde Institute for Pharmacy and Biomedical Sciences

MRes and MSci Research Project Descriptor

Project Title: Expression of Mkp2/Dusp4 in the mouse brain

Primary Supervisor: Dr. Ben Pickard
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Secondary Supervisor: Dr Trevor Bushell
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MRes Research Area, select one or two of the following:
Biochemistry / Molecular Biology

MSci Research Area, select ONE of the following:
Biochemistry

Project Description:

A multitude of cellular signalling pathways convert external stimuli, such as receptor-ligand binding, into a cellular response/adaptation directed by the nucleus. A well-studied pathway, the mitogen-activated protein kinase (MAPK) pathway, involves a cascade of kinase activation that culminates in the activation of a set of response genes [REF 1]. However, phosphatase enzymes are also required in this process to regulate signalling and permit the cell to return to a baseline state. Dual-specific phosphatases of the Mkp (MAP kinase phosphatase)/Dusp (dual specificity phosphatase) family are one such class of enzymes that can carry out this function. Our interests lie in determining the role of these proteins in the brain.

Mkp1 has recently been shown to have a potentially important role in depression. We wish to discover if the closely related Mkp2/Dusp4 gene has a similar role in brain function. To date there is some evidence that Mkp2 displays altered levels of brain expression in schizophrenia and depression but the majority of work on this gene has concentrated on its roles in proliferation/survival [REF 2] and in mediating the cellular responses to infection and oxidative stress. Preliminary work in the lab has shown that neurons and glia taken from mice lacking the gene show altered growth properties. These mice also show evidence for altered electrophysiological and behavioural responses.

To determine whether these altered growth properties contribute to the altered electrophysiological and behavioural responses, the aim of the project is to characterise the developmental expression pattern of Mkp2/Dusp4 within the brain and elsewhere in the body. To this end, we will utilise a novel transgenic mouse strain [REF 3] which expresses the beta-galactosidase (β-gal) marker gene under the control of the natural Mkp2/Dusp4 promoter; i.e., wherever Mkp2 is normally expressed, β-gal activity will be found.

This project, utilising techniques well established in our laboratories and building on our preliminary data, will identify Mkp2 expression and localisation within the brain, define specific Mkp2 expressing cell types and determine the stimulus activation properties of the Mkp2 gene and its protein, thus providing a framework for understanding the role of this gene in knockout phenotypes and its potential contribution to human disease.

Techniques to be used:

- Cryosectioning of brain and other tissues
- Beta-galactosidase staining
- Immunofluorescence

References:

1. Mitogen-activated protein (MAP) kinase/MAP kinase phosphatase regulation: roles in cell growth, death, and cancer. (2008) Boutros T, Chevet E, Metrakos P. Pharmacol Rev. 60(3):261-310. Review.

2. Deletion of the dual specific phosphatase-4 (DUSP-4) gene reveals an essential non-redundant role for MAP kinase phosphatase-2 (MKP-2) in proliferation and cell survival. (2011) Lawan A, Al-Harthi S, Cadalbert L, McCluskey AG, Shweash M, Grassia G, Grant A, Boyd M, Currie S, Plevin R. J Biol Chem. 286(15):12933-43.

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Strathclyde Institute for Pharmacy and Biomedical Sciences

MRes and MSci Research Project Descriptor

Project Title: The influence of metabolic inhibitors on peripheral nerve conduction properties

Primary Supervisor: Edward Rowan
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Secondary Supervisor: Robert M. Drummond
Email: robert.drummond@strath.ac.uk

MRes Research Area, select one or two of the following:
Biochemistry / ~~Immunology~~ / ~~Microbiology~~ / Molecular Biology / ~~Parasitology~~ / Pharmacology
Drug ~~Delivery~~ / ~~Pharmaceutical Materials and Formulation~~
MSci Research Area, select ONE of the following:
Biochemistry / **Pharmacology** / Immunology / Microbiology

Project Description:

While it is well established that neurones of the central nervous system have an obligate requirement for glucose, the importance of this energy source for function of peripheral neurones has been less extensively studied. Therefore, the aim of this study will be to examine what effect various procedures, which affect either cellular metabolism or metabolic substrate availability, have on the electrical properties of peripheral nerve fibres. Using the vaseline gap technique, compound action potentials will be recorded upon electrical stimulation of the sciatic nerve *in vitro*. Thereafter, the influence of metabolic inhibitors such as cyanide, azide, and FCCP on the properties of the compound action potential will be determined. In addition, the ability of non-glucose energy sources to support nerve activity will be examined by substituting glucose in the extracellular medium with either pyruvate or lactate.

Techniques to be used:
Electrophysiology , pharmacology.

References:
1. Strachan, M.W., Deary, I.J., Ewing, F.M., Ferguson, S.S., Young, M.J., Frier, B.M. (2001). Acute hypoglycemia impairs the functioning of the central but not peripheral nervous system. *Physiol. Behav.* **72**: 83-92.
2.
3.

Strathclyde Institute for Pharmacy and Biomedical Sciences

MRes and MSci Research Project Descriptor

Project Title: The effect of nitric oxide on peripheral nerve conduction properties

Primary Supervisor: Edward Rowan
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Secondary Supervisor: Robert M. Drummond
Email: robert.drummond@strath.ac.uk

MRes Research Area, select one or two of the following:
Biochemistry / ~~Immunology / Microbiology / Molecular Biology / Parasitology~~ / Pharmacology
~~Drug Delivery / Pharmaceutical Materials and Formulation~~
MSci Research Area, select ONE of the following:
~~Biochemistry~~ / **Pharmacology** / ~~Immunology / Microbiology~~

Project Description:

Following neurotrauma there is an increase in the concentration of nitric oxide (NO) within the central nervous system and this has been implicated in the pathogenesis of the associated neurological deficits. However, the mechanism by which NO produces it's effect on neural tissue is unknown. The aim of this study is to examine the effect of a range of NO donor drugs on the electrical properties of a peripheral nerve and to determine the underlying mechanism involved. Using the vaseline gap technique, compound action potentials will be recorded upon electrical stimulation of the rat sciatic nerve *in vitro*, and the effect of a range of NO donor drugs examined. Thereafter, drugs which act at specific sites along the NO signalling pathway will be used in order to determine the mechanisms involved.

Techniques to be used:
Electrophysiology , pharmacology.

References:
1. Shrager, P., Custer, A.W., Kazarinova, K., Rasband, M.N. and Mattson, D. (1998). Nerve conduction block by nitric oxide that is mediated by the axonal environment. *J Neurophysiol.* **79**: 529-36.

2. Docherty, R.J., Charlesworth, G., Farrag, K., Bhattacharjee, A. and Costa, S. (2005). The use of the rat isolated vagus nerve for functional measurements of the effect of drugs in vitro. *J. Pharmacol. Toxicol. Methods*. 51: 235-242.

3. PubMed nitric oxide compound action potential
2.