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Drug Delivery Workshop

Thursday the 6th and Friday the 7th of August 2015

at

Bangor University, School of Chemistry
The Orton Lecture Theatre
LL57 2UW

Registration opens at 11:30 am

Please email
c.d.gwenin@bangor.ac.uk
to register

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Foreword

Professor David Shepherd
Pro-Vice Chancellor for Research and Enterprise, Bangor University

Dear Participants

I am delighted to welcome you to Bangor University, the host of this Life Sciences Research Network Wales funded Drug Delivery Workshop. This workshop is aimed at highlighting the novel research that is taking place at the multidisciplinary drug delivery interface for therapeutics. Drug delivery is of paramount importance for the effective use of novel therapeutic drugs; as such this meeting will bring together researchers from across Wales both to present their research and to meet global researchers in the field. By bringing together local and international experts in the field it is hoped the event will generate new research collaborations and future funding. The meeting is open to researchers at all career stages and Masters and PhD students are particularly encouraged to attend. The meeting is also supported by an international field of speakers.

I wish you all an exciting and profitable day.

David Shepherd

Acknowledgements

Conference Organising Committee:

Dr. Chris Gwenin, Dr. Jenny Halliwell, Stevie Scanlan, Tracey Roberts and Joanne Hacking. With additional support from the administrative and technical staff and many of our postgraduate students.

The committee would like to thank all the presenters for not only presenting but for their help with the organisation.

Gratefully supported by the Life Sciences Research Network Wales

As well as donations from Penderyn Distillery

And a prize offer from ThermoFisher Scientific for £100 for the best question!

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Welcome to Bangor University

Opening its doors in 1884, the University was founded as the University College of North Wales as a direct result of a campaign in the late nineteenth century for higher education provision in Wales. An important feature of its foundation was the voluntary contributions made by local people, including farmers and quarrymen, from their weekly wages over a period of time. In 1893 the University of Wales, Bangor became one of the three original constituent colleges of the University of Wales.

Today we have over 10,000 students and 2,000 members of staff.

The School of Chemistry at Bangor has a long and distinguished history over 125 years. It was one of the founding schools of the University College of North Wales (now Bangor University) and has a proud tradition of excellent chemists both working in and being trained at the School. The School of Chemistry offers a wide range of undergraduate courses, including its flagship MChem programmes. Research work in the school is of the highest quality and covers traditional areas of organic, inorganic and physical chemistry together with the newer areas of computational, environmental, materials and biological chemistry.

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DRUG DELIVERY WORKSHOP

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Gratefully supported by the Life Sciences Research Network Wales

This workshop will highlight the novel research that is taking place at the interface between biology and chemistry; as well as enhancing the networking possibilities on a regional and international level with regards to drug delivery research. The research area of drug delivery has changed dramatically in the last few decades, with even greater changes being anticipated in the near future. Research into therapeutics has not only contributed substantially to our understanding of the physiological barriers to efficient drug delivery, but has contributed to the development of a number of new modes of drug delivery which have entered clinical practice. Despite the advancements, many medications still have undesirable side effects; as such these side effects limit the applicability of optimal drugs for many diseases such as cancer, neurodegenerative diseases and infectious diseases.

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NRN background

Background

With an increasingly ageing population and a number of major drugs coming off patent, there is a pressing need to develop new drugs and therapeutic agents that address un-met medical needs. The Life Sciences Research Network was established to bring together researchers from across Wales and provide a platform for engaging with companies and research organisations from across the World to develop better science to support new drug discovery.

The Need

Innovations in health sciences have resulted in dramatic changes in our ability to manage human disease and improve the quality of life. Unquestionably, a major element of this is pharmaceutical development. However, despite increasing spend (2010, ca $85Bn on R&D) by the pharmaceutical industry, new drug approvals show a steady downward trend as compared to 15 years ago. The inverse of this, the cost per new drug, shows a steady increase; the Association of the British Pharmaceutical Industry now estimate a cost per new drug (a New Chemical Entity) of £1.15Bn and an average time from target identification to approval of 12-14 years.

The aim of the Network is to bring together academic researchers from across Wales to form a critical mass of research excellence which can more effectively compete for research funding and engage with external organisations. Rather than focus on a particular therapeutic area, the Network will support research excellence in a broad range of scientific disciplines which meet the Network's investment criteria.

Sêr Cymru

The Welsh Government has committed up to £50 million to enhance and build upon the research capability in Wales, to attract world-leading scientists and their teams to Wales and to support the establishment of a collaborative National Research Network in each of the three "Grand Challenge" research areas identified in the "Science for Wales" strategy:

- Advanced engineering and materials
- Life sciences and health
- Low carbon, energy and environment

NRN background

Prof. Mark Baird, Professor of Organic Chemistry and NRN management board member

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Mark Baird spent some 40 years as an academic in Newcastle and Bangor Universities. The core of his research was in molecules containing small rings of carbon atoms. In recent years, his group has published the first syntheses of a range of types of mycolic acid, and of their trehalose esters. These molecules are key components of the cell envelope of mycobacteria and a number of related species. They have unique effects on the immune system, which are being examined through a number of collaborations, and are very effective in serodiagnostic assays for tuberculosis. With Chris Gwenin, Mark set up Diagnostig to ensure these highly bioactive molecules are fully exploited. Mark has published over 200 research papers and is an inventor on a number of patents. As an academic, he collaborated widely with companies and other academics in five continents.

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Programme - Day 1

6th of August 2015

Registration:

11:30 Registration & Networking & Early Lunch

Welcome:

12:30 **Dr. Chris Gwenin** Bangor University
School of Chemistry
Welcome and overview

12:40 **Prof. David Shepherd**
Bangor University
Pro Vice Chancellor
(Research & Enterprise)
A Bangor welcome

12:50 **Prof. Mark Baird** Life Sciences Research Network Wales
Life Sciences Research Network Wales overview

Companies:

13:00 **Prof. Alex Mullen** Bio-Images Drug Delivery Ltd
OrlogiK: New advances in chronotheraputics

13:30 **Prof. Randy Mrsny** Applied Molecular Transport
Bacterial virulence factors for the oral delivery of protein and peptide biopharmaceuticals

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6th of August 2015

Companies:

14:00 **Dr. Kirsty Gapp** — 3M Drug Delivery Systems

Microneedle Drug Delivery: A Novel Delivery Platform for Small Molecules and Macromolecules

14:30 Coffee & Cake & Networking

Clinical perspective:

15:00 **Rebecca Burns** — Health Research Wales

The role of Health Research Wales

15:30 **Prof. Dyfrig Hughes** — Centre for Health Economics & Medicines

Patient preferences for the subcutaneous route of medication administration: Findings from a systematic review

Universities:

16:00 **Dr. Jenny Halliwell** — Bangor University School of Chemistry

Magnetic particles for drug delivery; fact or fiction?

16:30 Wine & Networking

19:00 Dinner

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Programme - Day 2

7th of August 2015

09:20 **Dr. Chris Gwenin**

Universities:

09:30 **Associate Prof. Deyarina Gonzalez**
Swansea University

Antibody Drug Conjugates for gynaecological cancers.

10:00 **Dr. Sion Coulman** Cardiff University

Micro- and macro- needles in drug delivery

10:30 **Dr. Martin Greenall** Aberystwyth University

Modelling of micelles and vesicles for drug delivery

11:00 Coffee & Networking

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7th of August 2015

Universities:

11:30 **Dr. Peter Searle** — University of Birmingham

Trials and tribulations: Prodrug activation gene therapy using E. coli nitroreductase and CB1954

Funding:

12:00 **Dr. Louise Jones** — Medical Research Council

Opportunities to deliver translational research through partnership

12:30 **Sam Williams** — Development Manager Welsh Government

The Innovation Triangle

13:00 Lunch & Networking

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Speakers

Prof. Alex Mullen
Chief Scientific Officer,
Bio-Images Drug Delivery Ltd

Contact details
Telephone +44 (0)141 552 8791
Email enquiries@bddpharma.com

Professor Alex Mullen is a Professor at the University of Strathclyde and a registered pharmacist with commercial R&D experience, specialising in oral dosage formulation development.

Professor Mullen has an extensive research portfolio, encompassing oral and vesicular drug delivery technologies, controlled release, drug eluting stents, liposomes and vaginal drug delivery. Professor Mullen provides scientific direction as Chief Scientist for drug delivery and formulation. He is one of the inventors of OralogiK™.

About Bio-Images Drug Delivery Ltd

BDD aims to be the number one integrated pharmaceutical development centre. Because we recognise that one size does not fit all we specialise in providing responsive, flexible and innovative solutions to our customers.

Our success is built upon solid scientific ability, strengthened by shared values across the Company. Our commitment to our customers is at the forefront of everything we do; we always keep our promise and deliver when we say we will. We are a company of integrity and value and we take pride in everything that we do.

Presentation title:

OrlogiK: New advances in chronotheraputics

Abstract:

The development of controlled release formulations has brought many clinical and economic benefits. BDD has developed oral drug delivery preparations that provide a range of drug release profiles that can be developed for single or multiple drug delivery. The profiles can combine separate 'pulse' releases or an initial release combined with delayed sustained release. Their behaviour in man has been demonstrated by the use of the nuclear imaging technique: gamma scintigraphy. Potential applications in sleep maintenance, pain management and cardiovascular disease have been demonstrated in this way, although the formulations are not limited to these therapeutic areas; indeed, they could be applied to a broad range of drugs and disease groups.

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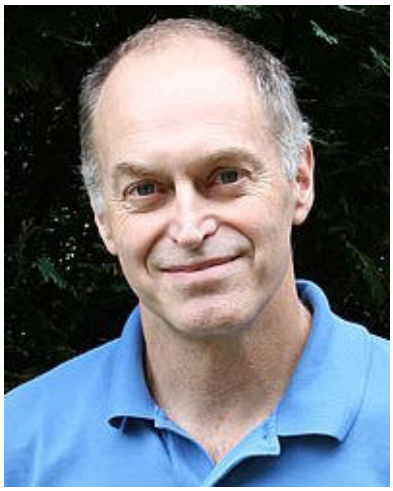

Prof. Randy Mrsny
Professor, Department of Pharmacy and Pharmacology, University of Bath

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Randall Mrsny obtained a BS degree in Biochemistry and Biophysics and a PhD degree in Anatomy and Cell Biology from the University of California at Davis undergraduate and medical school campuses, respectively. As an NIH post-doctoral fellowship he studies membrane lipid-protein interactions at the Institute of Molecular Biology located in the University of Oregon Eugene campus. Prior to taking Professors' post in Cardiff University and now the University of Bath, Randy led research groups in two companies: ALZA and Genentech. He has been involved in starting two new biotech companies through the acquisition of venture capital funding. Randy has been elected president of an international society and organized international meeting. He currently serves as a reviewer or advisor for multiple international agencies and companies and is the Chief Scientific officer of the start-up Applied Molecular Transport.

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Research Interests

The current research interest of the Mrsny Laboratory focuses on a variety of aspects of epithelial cell structure/function in health and disease. This work is supported through grants from governmental agencies and private foundations as well as through collaborative partnership with pharmaceutical companies.
Identification of molecules secreted by intestinal and airway epithelial cells which can control neutrophil and eosinophil transmigration. Identification of molecules that allow epithelial cells regulation to lymphocyte activation. Examine the role played by tight junction elements in controlling epithelial cells oncogenesis. Examine endogenous mechanisms that dynamically control tight junction opening and closing for drug delivery. Examine epithelial transcytosis mechanisms used by bacterial toxins for the delivery of biotherapeutics such as proteins, peptides, and siRNA through activities performed at the US company Applied Molecular Transport.

Presentation title:

Bacterial virulence factors for the oral delivery of protein and peptide biopharmaceuticals.

Abstract:

Oral delivery of protein and peptide therapeutics has been a long-sought goal of the pharmaceutical industry. While this route of delivery should increase the compliance of patients who must receive these biopharmaceuticals by subcutaneous injection, we have focused on the delivery of biopharmaceuticals that could specifically benefit from directly accessing the intestinal submucosa and/or the hepatic portal system. In order to achieve this goal we have identified endogenous transcytosis pathways used by specific bacterial virulence factors. Our studies have focused on the preparation and testing of chimeric materials composed of biopharmaceuticals connected to a minimal and non-toxic element of the bacterial virulence factor that can be used to co-opt the transcytosis pathway. Data that illuminates this pathway and proof of concept studies in vivo will be presented.

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Speakers

Dr. Kirsty Gapp
3M TDD EMEA Business Manager

Contact details
Telephone +44 (0) 15 09 613 660
Email kvgapp@mmm.com

Kirsty Gapp has a background in Molecular Biology and gained her PhD from the University of Warwick. She is currently the Global Business Team Leader for 3M's Microneedle Platform and Business Manager for 3Ms Transdermal Drug Delivery Platform (Europe). Over the last 15 years Kirsty has held various technical and commercial roles within 3M Health Care with a focus on medical devices. She now works in 3M's Drug Delivery Systems Division in the areas of transdermal and intradermal technology platforms.

About 3M

3M Drug Delivery Systems (DDS) partners with global pharmaceutical and biotech companies to develop and manufacture pharmaceuticals using 3M's inhalation or transdermal drug delivery technology including microneedles, to help get their product to market. With over 50 years experience 3M DDS offers both traditional & innovative technologies suitable for the biopharmaceutical & pharmaceutical sectors: solid & hollow Microneedle Systems, Pressurised Metered Dose Inhalers, Drug-in-Adhesive and Transdermal Patches.

Presentation title:

Microneedle Drug Delivery: A Novel Delivery Platform for Small Molecules and Macromolecules

Speakers

Rebecca Burns
Industry Manager at Health Research Wales

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Telephone +44 (0) 29 20 230 457
Email Rebecca.Burns@wales.nhs.uk

Experienced Health Care Professional with in depth knowledge of how to set up and run clinical trials in the NHS. With experience and working knowledge of the regulatory and research environment both at the local and national level. Having worked as a Clinical Nurse, Research Nurse and Industry Manager I have an understanding of the needs and drivers of clinical teams and patients as well as those of SMEs and the pharmaceutical industry within the life science sector.

I am passionate about supporting and enabling stakeholders to collaborate through research for the betterment of future treatments/ interventions and care.

Presentation title:

The role of Health Research Wales

Abstract:

The National Institute for Social Care and Health Research (NISCHR), Welsh Government commissions and funds an infrastructure to support excellence and capacity building in health and social care R&D across Wales.

Health Research Wales was set up in March 2013 to facilitate an increase in commercial research being undertaken in health and social care in Wales.

Working closely with national and international stakeholders from industry, academia and the health and social care sector, the Health Research Wales Industry Team provides a range of services to deliver this aim. These services and the commercial research landscape in Wales will be described.

Speakers

Prof. Dyfrig Hughes
Centre for Health Economics & Medicines

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Dyfrig is Professor of Pharmacoeconomics (personal chair, 2010) and co-director of the Centre for Health Economics and Medicines Evaluation at Bangor University. He is also academic lead for Pharmacy and Medicines Management at the Betsi Cadwaladr University Health Board. Having registered as a pharmacist and researched in pharmacology, he was subsequently awarded an NHS fellowship in health economics. His main research activities, which have led to over 90 publications, concern pharmaceutical economics and policy, health technology assessment and medication adherence. Dyfrig was a member of NICE's technology appraisal committee (2006-9), deputy health economist for the All Wales Medicines Strategy Group (2003-9) and founding president of the European Society for Patient Adherence, Compliance and Persistence. He is currently a member of the Health Technology Assessment Clinical Evaluation and Trials Board and is an editorial board member of the journals PharmacoEconomics, and Pharmacoepidemiology & Drug Safety. Dyfrig was elected fellow of: The Learned Society of Wales (2013), The British Pharmacological Society (2013), and the Faculty of the Royal Pharmaceutical Society (2014).

Presentation title:

Patient preferences for the subcutaneous route of medication administration: Findings from a systematic review.

Co-authors are: Colin H. Ridyard PhD, Dalia M. M. Dawoud PhD and Lorna Tuersley PhD MRPharmS

Speakers

Dr. Jenny Halliwell
ARCH Laboratory Manager
School of Chemistry
Bangor University

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Jen came to Bangor in 2007 to study for a BSc in Chemistry. She joined ARCH in 2009 (then the Electrochemistry and Biosensors Research Group) to complete her third year dissertation which was entitled 'The Use of Esterases for the Detection of Narcotics'. In 2010 she started her PhD studying 'Novel Methods of Detecting Botulinum Neurotoxins' where she developed a colourimetric method of detecting the toxin using gold nanoparticles and an electrochemical impedance spectroscopy method. After her PhD she moved onto the role of Research Officer within ARCH which allowed her to carry on her research into Botulinum Neurotoxin detection along with the detection of Tuberculosis and Magnetic Nanoparticle Directed Enzyme Prodrug Therapy (MNDEPT). Today she is continuing with these research topics and has taken an active role as lab manager for ARCH.

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About ARCH

The ARCH research team have several collaborations with industry and universities worldwide. Our main research themes are the detection of TB, cancer therapy, the detection of Botulinum toxin and we are a very active member of the WISE network. Our research focus is centred on multidisciplinary translational research in the area of health.

Presentation title:

Magnetic particles for drug delivery; fact or fiction?

Abstract:

Over recent years the number of medicinal uses of nanoparticles has increased greatly. From sensing toxins and diseases to the use of magnetic nanoparticles in MRI yielding a wide range of applications.

We have expanded on the idea of using nanoparticles for drug delivery in our cancer therapy 'Magnetic Nanoparticle Directed Enzyme Prodrug Therapy' (MNDEPT). MNDEPT utilises gold coated magnetic nanoparticles (AuMNPs) to deliver prodrug activating enzymes to tumour sites, holding them in place through an external magnetic field ensuring the cytotoxins are only produced at the tumour and as such targeting the diseased area. The enzymes are genetically modified to include cysteine rich areas which allow them to form strong sulfur-gold bonds onto the AuMNPs allowing the particles to move through the body without the enzyme being desorbed from the surface.

We have made great progress modifying a selection of promising enzymes to include the cysteine tags and screening them to ensure they remain active on the particles through kinetics and cell viability assays. The next stage for this research area will be mouse and then clinical trials hence strategically aligned partners are being actively sought.

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Speakers

Associate Prof. Deyarina Gonzalez
Swansea University

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Deya's research focuses on gene expression and function in the uterus and its relationship to fertility and cancer. Her clinical interests are Polycystic Ovary Syndrome (PCOS), endometriosis, unexplained infertility and gynaecological cancers (endometrial, ovarian and cervical cancer). She has strategic collaborations with clinicians at Abertawe Bro Morgannwg University NHS health board, developing cellular and molecular approaches to determine mechanisms underlying gynaecological pathologies, to identify biomarkers. Her projects on endometrial implantation and differentiation, relate to L-selectin ligands (MUC1), hormone nuclear receptors and WT1 pathway. Her research in gynaecological cancer includes the regulation of tamoxifen target genes in endometrium and new methods to identify biomarkers for pre-disposition of infertile women to develop gynaecological cancers. Her aim is to translate basic research into clinically relevant observations for patient benefit. Her projects involve collaboration with the private sector to expedite validation of clinical diagnostic biomarkers and the development of new drug leads for targeted cancer therapy. She also has multidisciplinary collaborations in the area of nanosensors and improved performance medications in the field of human reproductive biology and hormone therapy. She has received research grants valuing over £1m in the recent years.

Deya has published more than 20 articles during her career on human, animal, plant and yeast research. She is a member of the Endocrine Society and acts as an expert reviewer for Journal of Clinical Endocrinology and Metabolism, Human Reproduction and others. She teaches within the Genetics & Biochemistry (College of Medicine) and Biomedical Engineering (College of Engineering) undergraduate programmes.

About my research group

Reproductive biology and gynaecological oncology research in Swansea covers basic and translational research into uterine pathologies including endometrial cancer, poly-cystic ovary syndrome, endometriosis and unexplained infertility linked to endometrial (the lining of the womb) dysfunction. More recently new research has been established in the areas of ovarian cancer, ovarian reserve and overactive bladder syndrome. Our research involves the study of cell signalling, nanobiology, transcription and epigenetics, the development of clinically relevant biomarkers, and the development of therapeutic interventions. Our group works closely with clinicians in the Departments of Obstetrics and Gynaecology, and Pathology, in the Abertawe Bro Morgannwg University Health Board in Singleton Hospital, Swansea, and The Princess of Wales Hospital in Bridgend.

Presentation title:

Antibody Drug Conjugates for gynaecological cancers.

Abstract:

Antibody drug conjugates (ADCs) combine the specificity of antibodies with the potency of small molecule cytotoxic drugs. This presentation will give an overview about the current state of ADC development. A novel ADC developed by Swansea University as a potential therapeutic for the treatment of gynaecological cancers will be discussed in more detail and latest results will be presented. The evaluation of ADCs activity using screening platforms will be discussed.

Speakers

Dr. Sion Coulman
Senior Lecturer, Cardiff University

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Tel: +44 (0) 2920876418

Sion Coulman graduated with an MPharm in 2001 and subsequently qualified as a pharmacist. He then returned to academia to follow a career in research. He completed his PhD in 2005 and is now a Senior Lecturer in Cardiff School of Pharmacy and Pharmaceutical Sciences. In this time his research interests have revolved principally around innovative physical methods to enhance transdermal drug delivery. His focus is on the design and performance of microneedle devices in humans and the ability of these drug delivery systems to facilitate intradermal delivery of biologics such as high molecular weight proteins and nucleic acids. He is also interested in the formulation and performance of hard shell capsules in dry powder inhalers. His research is funded by a diversity of national and international funding bodies and commercial partners from the pharmaceutical industry.

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About my research group

My current research interest centres on the development of the microneedle device as an effective non-invasive method of trans/intra-dermal delivery of novel and existing medicines and the translation of the microneedle technology from a laboratory prototype to a clinically useful device. The microneedle device bridges engineering, pharmaceutics and healthcare disciplines and therefore I am part of a multi-disciplinary team that includes academic and non-academic colleagues from the UK, Europe and the USA. The technology is now approaching clinical usefulness and over the forthcoming years will hopefully facilitate non-invasive delivery of a number of therapeutics and hence offer a range of new therapeutic opportunities.

More recently I have also developed a pedagogic interest in calculations, with particular focus on the education of pharmacy students and pharmacists in this area.

Presentation title:

Micro- and macro- needles in drug delivery

Abstract:

The advent of innovative intradermal delivery devices such as the microneedle device has made minimally invasive delivery of macromolecular drugs and vaccines a realistic ambition. This talk will provide an insight into some potential clinical applications of microneedle devices and the latest developments in the area, including the intradermal delivery of peptides, proteins, nucleic acids and nanoparticles into the skin using a variety of microneedle designs. Some of the technical challenges that have been encountered during development of the technology will be highlighted and there will be specific discussion of studies that have been conducted in Cardiff to evaluate successful translation of microneedles from the laboratory and into the clinical setting.

The talk will segue from micron-sized needles to the millimeter sized needles that are used in DPIs to puncture hard shell capsules, focusing specifically on the development of a methodology at Cardiff that has been used to evaluate capsule puncture performance in a DPI.

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PRIFYSGOL ABERYSTWYTH UNIVERSITY
UNIVERSITY OF BATH

Dr. Martin Greenall
Lecturer, Aberystwyth University and the University of Bath

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My research centres on the modelling of the self-assembly of amphiphilic molecules in solution. I have also worked on other topics, including glass formation and fluids at interfaces.

Selected publications

M. J. Greenall and C. M. Marques. Can adding oil control domain formation in binary amphiphile bilayers? Soft Matter 10 7925 (2014).

M. J. Greenall and C. M. Marques. Can Amphiphile Architecture Directly Control Vesicle Size? Phys. Rev. Lett. 110 088301 (2013).

M. J. Greenall and G. Gompper. Simple and complex micelles in amphiphilic mixtures: a coarse-grained mean-field theory study. Macromolecules 45 525 (2012).

M. J. Greenall, P. Schuetz, S. Furzeland, D. Atkins, D. M. A. Buzza, M. F. Butler and T. C. B. McLeish. Controlling the self-assembly of binary copolymer mixtures in solution through molecular architecture. Macromolecules 44 5510 (2011).

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Presentation title:

Modelling of micelles and vesicles for drug delivery

Abstract:

Micelles and vesicles formed of amphiphilic molecules can be used to encapsulate drugs for targeted delivery. A challenge in this field is to understand how the properties of micelles and vesicles, such as their size and internal structure, depend on the architecture of the molecules from which they are formed. Since the synthesis of new molecules can be costly and time-consuming, there is a clear need for mathematical and computational modelling to guide experimental work. In this talk, I will introduce the powerful technique of self-consistent field theory (SCFT), and present results on its applications to three problems, all of relevance to drug delivery: fixing the size of vesicles, producing micelles with a high content of hydrophobic material and controlling domain formation in amphiphilic bilayers.

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Speakers

Dr. Peter Searle
Senior Lecturer, School of Cancer Sciences,
University of Birmingham

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Dr. Searle established the Gene Therapy Research Group in the School of Cancer Sciences, leading the development of prodrug activation gene therapy using the enzyme nitroreductase (*E. coli* NfsB) in combination with the prodrug CB1954. The group developed both retroviral and adenoviral vectors for delivery of nitroreductase, using cell cultures and mouse models to evaluate the system. Through collaboration with ML Laboratories plc, these studies led to a series of clinical trials of CB1954 alone, the CTL102 adenovirus alone, and finally both in combination. The trials established the safety and tolerability of the treatment, and provided encouraging evidence of anti-tumour activity in some patients.

Stimulation of tumour-specific immune responses could allow a localised gene therapy to have systemic benefit. In one approach, we have investigated the ability of viruses expressing co-stimulatory proteins (including CD80 and 4-1BBL) to enhance immune responses. The cytokine GM-CSF has been widely investigated in immune-stimulatory gene therapies, and we found that combining GM-CSF expression with nitroreductase-mediated CB1954 activation increased the anti-tumour efficacy in mouse models. The combination of Ad-NRGM (a replication-defective adenovirus co-expressing nitroreductase and human GM-CSF) with CB1954 is currently being investigated in a phase I clinical trial in men with locally relapsed prostate cancer.

The maximum achievable concentration of CB1954 in patients is far below the KM of the NfsB nitroreductase, thus limiting the rate of CB1954 activation in vivo. Potentially greater clinical efficacy could be achieved

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through enzyme engineering for improved catalytic properties. In collaboration with Drs Eva Hyde and Scott White in the School of Biosciences at Birmingham, we have undertaken site-directed mutagenesis of active site residues of nitroreductase, developing a series of single, double, and — with the help of a direct positive selection for enzymes with improved CB1954 activation — triple mutants showing significantly improved efficiency of CB1954 activation (up to ~100-fold greater k-cat/KM). These could be candidates for use in future clinical trials.

Some of the most exciting developments in cancer gene therapy involve tumour-selective, conditionally replicating (oncolytic) viruses. The group demonstrated that expressing nitroreductase from an oncolytic adenovirus modelled on the ONXY015 (dl1520) adenovirus showed much increased nitroreductase expression and improved antitumour activity in mice; however there was less apparent benefit from combining prodrug activation with more less attenuated oncolytic viruses. The current focus of research, in collaboration with Dr Simon Afford (School of Immunology & Infection, Birmingham) and Oncos Therapeutics, has turned towards the use of oncolytic adenoviruses expressing immune-stimulatory proteins in the context of liver cancer.

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Continued……

Prof. Peter Searle - Continued

Presentation title:

Trials and tribulations: Prodrug activation gene therapy using *E. coli* nitroreductase and CB1954

Abstract:

Expression of prodrug-activating enzymes in cancer cells enables them to be killed by concentrations of prodrug that are harmless to cells that lack the enzyme. This provides a new, experimental approach to cancer treatment, using viral vectors administered to the patient to express the enzyme in their cancer cells.

The prodrug CB1954 (5-[aziridin-1-yl]-2,4-dinitrobenzamide) is a weak, mono-functional alkylating agent that can be converted to a much more reactive, bi-functional DNA-crosslinking agent which is highly cytotoxic, by the NAD(P)H-dependent activity of bacterial nitroreductase enzymes. We have developed replication-defective adenovirus vectors that express the NfsB nitroreductase of E. coli, and tested these in early phase, prodrug activation gene therapy clinical trials, focusing on men with localised prostate cancer.

In collaboration with ML Laboratories plc, the NfsB-expressing adenovirus CTL102 was injected under ultrasound guidance directly into cancer-containing prostates via the transrectal route. Safety of the virus alone (at doses escalating from 1x1010 to 1x1012 virus particles), and expression of nitroreductase, were first demonstrated in men with operable disease, in whom radical prostatectomy was performed a few days after virus injection. Subsequently, men with inoperable, locally recurrent prostate cancer received similar intraprostatic injections of CTL102, followed after 2 days by intravenous CB1954 (24 mg/m2). Patients had rising blood levels of the tumour marker, prostate specific antigen (PSA) at recruitment. Several patients showed marked reductions in their PSA levels following treatment; by 6 months after treatment,

9/19 patients had progressive disease (>10% increase in PSA), 4/19 showed stable disease (PSA within 10% of baseline value), while 6/19 showed >10% reduction in PSA, including 2/19 whose PSA was still >50% below baseline. These reductions in PSA suggest that the treatment successfully killed a proportion of the cancer burden in these patients. Interestingly, the extended duration of the responses suggests the treatment may induce some immune-mediated tumour control, although attempts to measure T-cell responses to tumour antigens were inconclusive.

Another, ongoing phase I clinical trial incorporates two important changes designed to improve both proposed mechanisms of action. Firstly, the virus is being delivered to many more locations throughout the prostates, via template-guided stereotactic injection, aiming to achieve saturation coverage with delivery of virus to all tumour cells. Secondly, the virus AdNRGM has been engineered to co-express the immune-stimulatory cytokine GM-CSF, in addition to nitroreductase. This is expected to recruit antigen-presenting cells, which would then be able to take up debris from tumour cells killed by the activated prodrug, helping to activate stronger immune responses targeting tumour antigens. This trial is currently recruiting patients.

Additional approaches to improve the efficiency of prodrug activation gene therapy include the use of replicating vectors, the development of improved prodrugs, and engineering of the enzyme for more efficient prodrug activation. I will summarise our engineering of the *E. coli* NfsB nitroreductase, which has improved its efficiency of CB1954 activation by ~100-fold.

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Speakers

MRC Medical Research Council

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Louise Jones has been working in translational research for over 15 years. She joined the Medical Research Council (MRC) in January 2014 as Head of Translation. Her current portfolio comprises oversight of MRC's translational funding and industry initiatives, including the MRC/Innovate UK Biomedical Catalyst and the recently launched MRC-Industry Asset Sharing Initiative.

Louise performed her PhD at the Clinical Sciences Centre, Hammersmith Hospital on haemophilia A. Following post-doctoral research at the CR-UK laboratories at St Bart's in leukaemia, she joined the Children's Cancer Group as a non-clinical Lecturer, where she spent 7 years specialising in the molecular aetiology of paediatric leukaemias. Louise then moved into research management and spent 7 years at Cancer Research UK (CR-UK) working in the Clinical and Translational Research Directorate. As Head of Translational Research, a position she held for 4 years, she had responsibility for cancer drug discovery, biomarkers and imaging research. This followed three years working on CR-UK Strategy for tissue resources and biomarkers and running the ECMC Network Secretariat.

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Presentation title:

Opportunities to deliver translational research through partnership

Abstract:

The challenges associated with the discovery of new treatments for disease are well documented. Biology is complex, and much of the low-hanging fruit of drug discovery have already been picked. We need to understand more about the biology of human disease if we are to develop new effective and safe treatments. We also need to understand the complexity of disease, to work out which patients might respond well to particular drugs, and why some do not.

The development path of a new therapeutic is a long, expensive and difficult task, with a low probability of success. However, by bringing together the strengths of academic researchers — who investigate the underlying biology of diseases — with the drug development, testing and production know-how of pharmaceutical companies, we hope to accelerate the discovery of safer, more effective medicines.

The MRC supports a range of activities that increase our understanding of the mechanisms of human disease, how we can identify markers of disease and its progression, and ways to understand and evaluate the effects of treatments, be they pharmaceutical, surgical, or behavioural; the MRC also funds academic researchers to work with industry in a variety of ways at the very beginning in many of our strategic activities.

Speakers

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Part of the Business Innovation team who are working in partnership with manufacturing businesses, that have a Welsh footprint, to maximise technological innovation in new products/ processes from concept through to commercialisation.

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Presentation title:

The Innovation Triangle

Abstract:

This presentation will explore the Innovation triangle of research organisations, business and government, focussing on the Welsh Government's SMART Expertise Operation and the support available for research organisations and industry to form collaborative R&D projects within a demand led R&D environment.

SMART Expertise forms part of a suite of operations within the Welsh Government's Innovation department with an integrated approach towards business and academia, aimed at all elements of the RD&I environment. The presentation will look at what the Welsh Government has done so far within the innovation triangle, where we are going and what we can do to help.

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