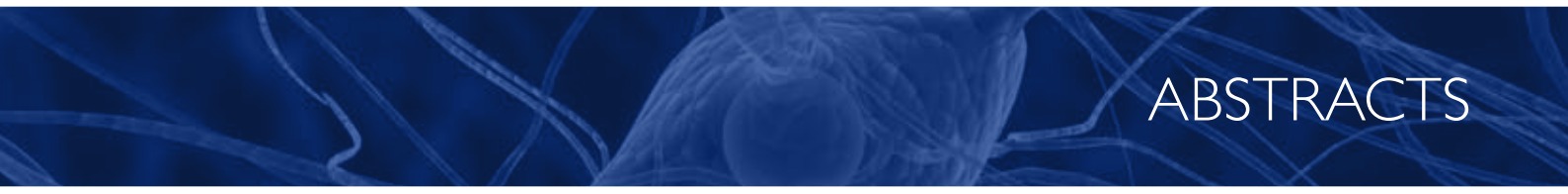
2013 RESEARCH CONFERENCE

The Daphne Jackson Trust



FRIDAY 25TH OCTOBER 2013
10.00am to 4.30pm

At The Royal Society
6-9 Carlton House Terrace
London SW1Y 5AG

Daphne Jackson Trust

As the Chair of the Board of Trustees, I am proud to be leading the Daphne Jackson Trust as it develops as a forward looking organisation.

The Daphne Jackson Trust was established in 1992 and since then has made a real difference to the lives of hundreds of scientists, technologists, engineers and mathematicians wishing to return to research following a career break.

Today, as the landscape in higher education changes there is increasing recognition that more can be done to support and retain a diverse and talented workforce within the sector. The Trust has an increasingly important role to play in supporting returners, and ensuring that women in particular are able to return to research following a break, without facing barriers to career progression.

We hope you will take the opportunity that this conference presents, to speak to Trustees and staff about how the Trust can work with you in new and innovative ways to support STEM professionals wishing to return to research.

Dame Glynis Breakwell,
Vice Chancellor University of Bath and
Daphne Jackson Trust, Chair of Trustees

Welcome to the Daphne Jackson Trust 2013 Research Conference

We are delighted to be hosting the second Daphne Jackson Trust Conference at the Royal Society, the national academy for science in the UK, and we are very grateful to the Royal Commission for the Exhibition of 1851 and the Royal Society for sponsoring the event.

Today's conference showcases much of our current Fellow's original research and includes an exciting programme of oral and poster presentations that reflect the breadth of STEM disciplines to which Daphne Jackson Fellows are returning. The event gives our fellows a platform to present their research and demonstrate just how they are benefiting from the unique opportunity that a Daphne Jackson Fellowship affords. Prizes will be awarded for the best oral and poster presentations and we are very grateful to our judges who have the difficult task of choosing the winners.

We currently have 42 Fellows in post and are pleased that most of them are joining us today. We also welcome several past fellows whose scientific careers have gone from strength to strength since returning to research with a Daphne Jackson Fellowship. Today's conference will be an excellent opportunity for our Fellows, past, present and future, to share and learn from each other's experiences.

With the generous support of our host universities and sponsoring organisations, the Daphne Jackson Trust has, to date, supported over 250 scientists, technologists, engineers and mathematicians wishing to return to their research careers. Overall, seven out of ten Fellows remain active in research for at least two years after successfully completing their fellowship and many go on to secure permanent research-based positions. This high success rate would not be achievable without the support and dedication that the Fellows receive from their Daphne Jackson fellowship advisors as well as their host institutions and supervisors. We are very pleased to welcome representatives from host organisations and supervisors here today, and hope you will take the opportunity to talk to them about the benefits of working with Daphne Jackson fellows.

We are also delighted to welcome representatives from some of our sponsoring organisations including the research councils, universities, charities and learned societies. In the past 18 months alone we have developed new sponsored fellowship agreements with 16 universities. It is an exciting time for the Daphne Jackson Trust and as we look ahead, we continue to develop new partnerships that allow us to extend the reach and increase the impact of flexible working opportunities for STEM researchers. We expect that in the near future, all universities will have hosted, and hopefully sponsored, a Daphne Jackson Fellow.

Today's event will demonstrate beyond doubt that the barriers that a career break can create for those wishing to return to research careers, can be successfully challenged and overcome.

We look forward to sharing an inspiring day.

Dr Katie Perry,
Chief Executive, Daphne Jackson Trust

PROGRAMME

10.00-10.30
REGISTRATION AND COFFEE

10.30
SESSION ONE
Chaired by Dr Katie Perry,
Chief Executive, Daphne Jackson Trust

10.30
Welcome by Dr Julie Maxton,
Executive Secretary of the Royal Society

10.35
Introduction by Professor Dame Glynis Breakwell, Chair of Trustees

10.40
Predicting plant adaptation in the face of climate change
Dr Sarah M Buckland,
Department of Animal and Plant Sciences,
University of Sheffield

11.00
Modelling maintenance strategies for long life water industry assets
Dr Helen Cornwell,
Department of Mechanical Engineering,
University of Bath

11.20
Atom economical pharmaceutical scaffolds through palladium catalysed multi-component reactions
Dr Joanna Geden,
Department of Chemistry,
University of Warwick

11.40
Mapping changes in the chromatin landscape of the human genome
Janet Harwood,
Department of Biosciences,
Cardiff University

12.00-14.00
LUNCH, NETWORKING AND POSTER SESSION

14.00
SESSION TWO
Chaired by Dr Pia Ostergaard,
St Georges, London

14.05
Understanding nucleation and ice growth in collagen slurry
Dr Anke Husmann,
Dept of Materials Science & Metallurgy,
University of Cambridge

14.25
Reducing anxiety in young people with autism spectrum disorders through an immersive virtual reality environment
Dr Morag Maskey,
Institute of Neuroscience,
Newcastle University

14.45
Is black the new green? The potential of pyrolysis products in fuel and agricultural applications
Dr Josephine Mmojieje,
School of Engineering & Applied Science,
European Bioenergy Research Institute,
Aston University

15.05
Habitat characteristics and the incidence of bovine tuberculosis in cattle
Dr Betina Winkler,
College of Life and Environmental Sciences,
University of Exeter

15.25
The Daphne Jackson Trust - Looking forward
Dr Katie Perry,
Chief Executive, Daphne Jackson Trust

15.40
Prize giving

16.00-16.30
NETWORKING RECEPTION, TEA AND COFFEE

DR SARAH M BUCKLAND

Department of Animal and Plant Sciences, University of Sheffield.

Sponsored by the Natural Environment Research Council (July 2011 - December 2013)

Predicting plant adaptation in the face of climate change

SM Buckland, TA Burke, JP Grime, K Evans

This presentation will report on results obtained from one of the longest running field experiments (20 years of continuous climate manipulations) through which to study the mechanisms of species persistence, in species-rich calcareous grassland, in the face of climate forcing. Genetic diversity is an important feature of these grasslands and is thought to be a critical property that maintains species richness and provides the genetic variation to allow adaptation to anticipated global environmental change. Two species, *Briza media* and *Carex flacca*, widespread across the UK, have responded differently to the experimental treatments. Soil heterogeneity (variation in soil depth and pH) gives rise to a variety of microsites and has already been found to be crucial for allowing some species, at a community scale, resistance to climate change.

I will present evidence for the role that phenotypic plasticity and contemporary evolution might play in these two clonal species. Genotypes have been identified using molecular markers (developed from microsatellite analyses) and special pots (a deep and vegetated section adjacent to a shallow and bare section) have been designed to examine the influence of soil heterogeneity on their response to summer drought. Through mapping shoot growth in the pots for each species, results will be presented on their contrasted spatial and temporal growth.

Furthermore, flowering phenology (i.e. timing and period of flowering) was recorded over the summer across the whole plant community present in the field experiment. Last year preliminary measurements were taken to assess the maximum abundance of flowering shoots in relation to estimates of vegetative cover and soil depth (Table 1). Data will be presented that reveal the effect on the potential changes developing in the seed input arising from the different climate treatments and therefore may indicate potential shifts in plant community dynamics of these important conservation pastures.

FIGURE 1.
Experimental plots at the Buxton Climate Change Impacts Laboratory Field Site

DR HELEN CORNWELL

Department of Mechanical Engineering, University of Bath

Sponsored by University of Bath and the Royal Academy of Engineering (April 2012 - April 2014)

Modelling maintenance strategies for long life water industry assets

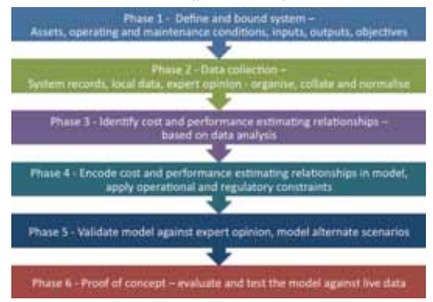
H Cornwell, L Newnes

Water is a major global industry, with a world market of €250 billion in 2008, and investments of more than €33 billion per annum. Water is a key input to the economy, environment, industry, and to the health and well-being of society. However, factors such as increasing population and urbanisation, combined with climate change put water resources under increasing pressure. An efficient and economic asset management system is necessary to deliver a resilient, secure and affordable water industry, and to support management decision making on investment and day to day activities.

Effective management of assets requires an optimised maintenance regime in order to reduce in-service costs, which can be up to 75% of the through-life cost of an asset. Whilst through-life cost estimating research within the water industry is relatively immature, this paper proposes that mature techniques from industries sharing similar asset characteristics can guide a methodology for modelling in-service costs. These techniques can be combined with existing principles from maintenance theory to create a robust model for management of an asset system.

This paper describes an industrial pilot study as part of research into modelling and optimisation of an asset system. The model will encode cost and performance estimating relationships, encompassing maintenance and operational costs, reliability, availability, and contractual and regulatory obligations. The model will allow evaluation of alternative maintenance scenarios, and trade-off analysis between cost and performance (benefits). The pilot study has been used to validate the methodological approach, the data available, the definition of cost estimating relationships, and the modelling and evaluation of alternative scenarios. The next stage of the study is to extend the work into other asset groups, and encode further cost and performance estimating relationships. Testing and validation will then be undertaken with industry to confirm the effectiveness of the model and methodology.

FIGURE 1. Phased methodology for modelling in-service



DR JOANNA GEDEN

Department of Chemistry, University of Warwick

Sponsored by the Engineering and Physical Sciences Research Council and University of Warwick (Feb 2012 - Jan 2013)

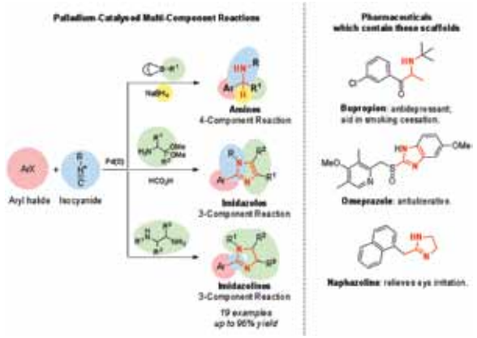
Atom economical synthesis of pharmaceutical scaffolds through palladium catalysed multi-component reactions

JV Geden, AK Pancholi, M Shipman

Multi-component reactions (MCRs) are powerful chemical transformations. They combine several bond-forming events in one pot, and result in the generation of complex and diverse molecules from simple reagents in a single operation. Fewer reactions are needed to produce a target molecule, and the majority of atoms in the reactants become incorporated into the product. The consumption of resources is reduced, waste is minimised, and compounds are prepared in a time and cost efficient manner. Multi-component reactions have found widespread application in drug discovery, materials science, and natural product synthesis.

The aim of the research was to develop novel, palladium catalysed, MCRs to prepare classes of compounds which have potential applications as medicines; namely amines, imidazoles, and imidazolines (Figure 1). The amine scaffold is found in drugs such as bupropion. Amines have been prepared by the one pot, four-component reaction between an aryl halide, an isocyanide, an organoborane, and a borohydride in yields up to 55%. The imidazole motif, found in omeprazole, has been assembled by the three-component reaction between an aryl halide, an isocyanide and an amine in up to 46% yield. The imidazoline ring, which is a feature of the drug naphazoline, has been prepared in excellent yield by the three-component reaction between an aryl halide, an isocyanide, and a diamine. All three methods involve fewer chemical steps than traditional multi-step methods used to prepare these compounds, and enable the introduction of up to three points of structural diversity in one pot. These novel reactions will enable the efficient preparation of libraries of compounds for biological screening in the pharmaceutical industry.

FIGURE 1.
Preparation of pharmaceutical scaffolds using palladium-catalysed multi-component reactions



JANET HARWOOD

School of Biosciences, Cardiff University

Sponsored by the Biotechnology and Biological Sciences Research Council (August 2011 - July 2013)

Mapping changes in the chromatin landscape of the human genome

J Harwood, NA Kent

The human genome comprises 3.2 billion base pairs of DNA that is packaged into a relatively small nucleus of a cell in a highly complex and organised way. This is achieved by coiling approximately 150bp of DNA around a core complex of histone proteins, forming nucleosomes that are further packaged into complex 3D structures, known as chromatin. This protein super-structure packages, protects and manages accessibility to DNA and the regulated alteration of its structure, 'chromatin remodelling', is important for controlling gene activity. Malfunctions in this process affect human mental health, childhood development and can cause cancer.

We are interested in the role of chromatin structure in the regulation of the human genome during neural cell development. We have generated maps of nucleosomes, which are represented by the nuclease-resistant chromatin species that footprint 150bp of DNA.

Using the locations of human regulatory sequences generated by the ENCODE (Encyclopedia of DNA Elements) project, such as REST (RE1-Silencing Transcription Factor) binding sites, we have identified changes in the patterns of nuclease-resistant chromatin particles that occur during neural cell differentiation. The REST complex has chromatin-remodelling activity, binds to specific sites throughout the genome and it is thought to repress the expression of neuronal genes in pluripotent cells. Our chromatin particle maps reveal the presence of positioned nucleosomes surrounding human REST binding sites in both pluripotent cells and neural progenitor cells, but the nucleosome positioned over the REST binding site in pluripotent cells is remodelled during the progression to neural progenitor cells (Figure 1). This suggests a role for these particles in genome regulation during neural cell development.

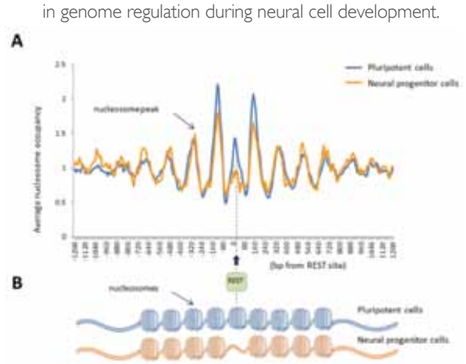


FIGURE 1. Detection of chromatin remodelling in the human genome.
A. Mapping of nucleosomes around REST binding sites in human pluripotent cells (blue) and neural progenitor cells (orange). The nucleosome positioned over the REST binding site is re-modelled in the progression to neural progenitor cells.
B. Cartoon of the nucleosome maps inferred from A.

DR ANKE HUSMANN

Department of Materials Science and Metallurgy, University of Cambridge

Sponsored by University of Cambridge (Oct 2012 - Sep 2014)

Understanding nucleation and ice growth in collagen slurry

A Husmann, KM Pawelec, RE Cameron

Understanding nucleation of ice crystals and their subsequent growth, within a slurry of biological macromolecules such as collagen, is important in the context of fabricating scaffolds via freeze drying for medical applications. Figure 1 shows an example of such a scaffold. In these applications, control over pore size and pore alignment is often fundamental to the success of growing cells, but it is expensive to experimentally explore a wide range of possible growth conditions.

Current work has focused on understanding thermal profiles prior to nucleation within the moulds that are used for fabrication. We have implemented a numerical simulation in Matlab that calculates heat conduction within the setup of the freeze dryer. Experimental results have shown that, within seconds after nucleation at the base, a skeleton of ice crystals will grow where the temperature of the slurry is below the melting temperature, T=0°C, and this skeleton sets a template for further growth. Since no skeleton will form when T>0°C, optimising the location of the surface where T=0°C inside the slurry is critical. Our semi-heuristic simulation calculates the surface where T=0°C within the slurry for different mould designs, and in turn this allows us to manipulate the pore architecture.

Time and results permitting, we will also discuss our phase field theory simulation in progress which addresses the freezing step. Phase field theories are a powerful tool to capture the relevant physics during solidification. The movement of the phase front is driven by the speed by which latent heat generated at the front is removed and by the cost in surface energy as well as the presence of macromolecules.

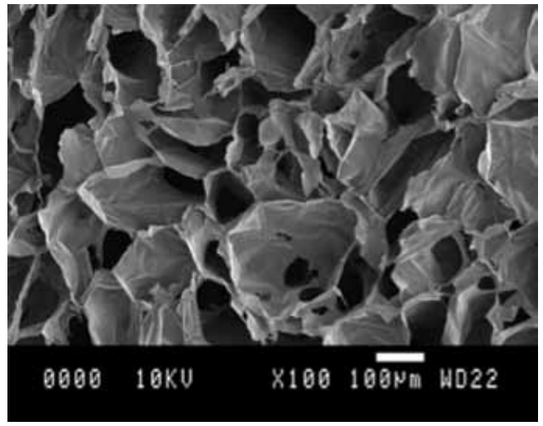


FIGURE 1.
A micrograph of a collagen scaffold with isotropic pore structure at 100x magnification.

7 out of 10 Fellows stay in research for at least 2 years after completing their Daphne Jackson Fellowship

FIGURE 1. Scenes from a virtual reality room used to reduce anxiety in young people with autism

DR MORAG MASKEY

Institute of Neuroscience, Newcastle University,

Sponsored by Newcastle University (Nov 2011 - Oct 2013)

Reducing anxiety in young people with autism spectrum disorder through an immersive virtual reality environment

M Maskey, J Lowry, J Rodgers, H McConachie, J Parr

Autism spectrum disorders (ASDs) are common, affecting at least 1 in 88 children.

Young people with ASDs are prone to anxiety, including specific phobia/fears. Studies indicate around 50% of those with ASD meet criteria for at least one anxiety disorder. Parents have reported that the impact of anxiety is more substantial than the impact of ASD itself.

Graduated exposure and cognitive behavioural therapy (CBT) are evidence-based treatments for anxieties and phobias but may require adaption for individuals with autism. One adaption is use of virtual reality environments (VREs) to reproduce situations that cause specific phobia/fear.

In this development study, we: 1. explored the use of VRE as a therapeutic tool for young people with ASD with situation specific anxiety; 2. tested the feasibility and acceptability of the methodology, and investigated the most appropriate outcome measures.

Nine, verbally fluent volunteer young people (8-14 years old) with ASD were recruited. In partnership with the company Third Eye, young people attended a VRE known as the Blue Room. An individualised VRE scene was designed for their specific phobia/fear (e.g. crowded buses, supermarkets). In the VRE (during four 30 minute sessions) each participant received coaching from a psychologist in relaxation techniques and coping self-statements.

All children found the VRE acceptable and attended for all sessions. Of the nine children who have taken part, eight children's phobia/fear was more manageable; for five children, the problem disappeared completely. Data will be presented on these nine children.

This development study is the first study to show that VRE is an effective treatment for specific phobia/fear in young people with ASD. Data are being used to support funding applications for a larger NHS-based study.

250 women and men returned to research between 1992 and 2012, thanks to a Daphne Jackson Fellowship

DR JOSEPHINE MMOJIEJE

European Bioenergy Research Institute (EBRI), Aston University

Sponsored by Aston University (Nov 2012 - Nov 2014)

Is black the new green? The potential of pyrolysis products in fuel and agricultural applications

J Mmojieje, A Hornung

With the increasing interest in the development of more sustainable practices, the use of pyrolysis products, formed from the decomposition of biomass material, in fuel and agricultural applications has received increasing attention (see Figure 1). However, the potential of these products, i.e. bio-oil (liquid) and biochar (solid), to play a leading role in the development of a renewable energy infrastructure will be strongly dependent, amongst other things, on the development of a quality assurance regime which is able to secure consumer confidence. For example, the reported thermal instability associated with bio-oil is a problem which has the potential to have a detrimental effect on storage and operational issues, particularly when the oil is in an atomised form, hence the importance in developing a quality assurance protocol to quantify the effect.

The findings of preliminary studies on bio-oil produced from pyrolysis of wood show a marked increase in the viscosity of the oil when subjected to elevated temperatures of the order of 80°C, which coincides with changes to the highly reactive carbonyl functional group at 1700cm^{-1} in infra-red spectroscopy. However, the findings do not substantiate previous studies which suggest the formation of water is a direct indication of the effects of "thermal ageing".

The implications of such findings suggest that previous studies which have employed the Karl Fischer titration method to determine the change in water content, as a means of quantifying the effect of thermal ageing, should also employ additional complementary analytical methods, e.g. Fourier Transform Infra-red Spectroscopy (FTIR), with more focus placed on changes to the carbonyl functional group as a means of quantifying the effect of thermal ageing. In doing so, it is hoped that a more accurate and consistent regime can be developed to quantify the effect, thereby ensuring a product which is fit for purpose.

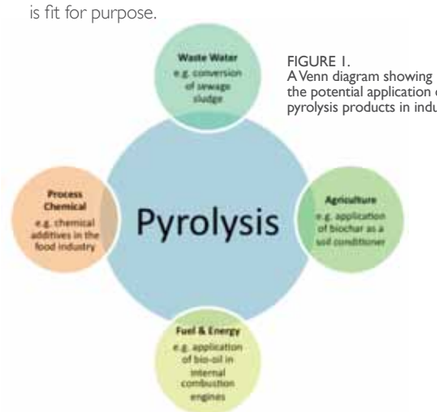


FIGURE 1. A Venn diagram showing the potential application of pyrolysis products in industry

DR BETINA WINKLER

College of Life and Environmental Sciences, University of Exeter

Sponsored by University of Exeter and the Biotechnology and Biological Sciences Research Council (July 2012 - June 2014)

Habitat characteristics and the incidence of bovine tuberculosis in cattle

B Winkler, F Mathews

The incidence of bovine tuberculosis (bTB) in the South West of England, Wales and the Midlands remains very high in spite of a rigorous cattle testing programme and movement restrictions. Cattle are believed to acquire infection from badgers primarily through direct contact with contaminated pasture. In order to reduce the rate of contact between the host communities and the rate of disease transmission there is a need for complimentary control measures, such as mapping risk areas.

FIGURE 1. Different types of field boundaries found on cattle farms

The project aims to test the hypothesis that the contact rate of cattle with contaminated sites is reduced in areas with certain habitat characteristics, such as hedgerow 'rich' farms. We analyse data from the Randomised Badger Culling Trial and other publicly accessible databases. The habitat characteristics of selected farms are analysed through aerial photography and Geographic Information System (GIS). Habitat composition at a landscape scale (including the following variables: size, width and connectivity of hedgerows, size of fields, presence of deciduous woodlands and ungrazed buffer strips) is compared with the bTB status of badgers and cattle. Preliminary results showed that farms with permanent pastures and greater percentage of hedges as internal boundaries have lower risk of bTB outbreak and farms with greater areas of maize planted have a higher risk. The aim of the study is to measure and spatially correlate habitat characteristics on breakdown and control farms and generate guidelines on habitat management and management of cattle that will reduce the spread and persistence of bTB on farms.

DR MARY BOARD

Nuffield Dept of Clinical Lab Sciences, University of Oxford

Sponsored by Make my Day Better (April 2013 -April 2015)

Energy generation in human mesenchymal stem cells

M Board, C Carr

Human mesenchymal stem cells (hMSCs), isolated from bone marrow, have a capacity for very rapid proliferation along with the potential to differentiate into a number of mature cell-types. In order to exploit the potential for repair of damaged and diseased tissues during stem cell therapy, hMSCs must be cultured in vitro prior to transplant into the recipient. However, large-scale culture has proved problematic, producing variable yields of cells. Traditional cell culture techniques result in cultured cells having access only to glucose and glutamine as energy-yielding substrates, whereas, in vivo, cells would be exposed to a wider range of substrates. The availability of more diverse substrates may have consequences for the cells' energy metabolism. The present study aims to elucidate aspects of energy metabolism in hMSCs with a view to optimising the cell culture medium in order to ensure supply of the large amounts of energy that proliferating cells require for synthesis of proteins and other macromolecules. Rates of oxidation of a number of key substrates have been measured and preliminary data suggest that rates of acetoacetate- and pyruvate-oxidation are significantly higher than that of glucose. Calculation of corresponding ATP-yields indicates that cultured hMSCs are likely to generate significantly more ATP if they are cultured in the presence of 10mM acetoacetate than in the presence of 5.5mM glucose alone. Experiments are underway to determine whether longer-term culture of the cells in the presence of acetoacetate alters their energy metabolism and rates of proliferation without changing the mesenchymal phenotype of the cells. It is suggested that growth medium for large-scale culture of hMSCs might be appropriately supplemented with acetoacetate and/or pyruvate.

DR HARRIET DAVIES

School of Biosciences, University of Birmingham

Sponsored by the Biotechnology and Biological Sciences Research Council, the Medical Research Council and the University of Birmingham (Oct 2012 - Oct 2014)

Multiple faces of GATA3 binding in tumour cells

H Davies, A Kanhere

Transcription factors (TF) are families of proteins that bind to specific DNA sequences to regulate gene expression. Traditionally, regulation of gene expression by TF could only be studied at the single-gene level. Recent advances in technology such as chromatin immunoprecipitation followed by high-throughput DNA sequencing (ChIP-seq) has made it possible to examine the genome-wide binding of TFs, enabling researchers to identify a plethora of TF binding events and revisit the concept that TFs bind only to canonical sequence motifs. There is growing evidence to suggest that TFs bind in a canonical and non-canonical manner. One example of this is GATA3, a member of the GATA zinc fingered DNA binding protein family, which has been shown to bind independently of its motif in T-cells. The aim of this project is to further understand GATA3-mediated TF binding events and their role in gene regulation in different cell lines. We developed a computational pipeline to analyse publicly available GATA3 ChIP-seq data from a human lung adenocarcinoma cell line (A549) and human breast adenocarcinoma cell line (MCF7). Surprisingly, we find that large proportion of GATA3 binding sites (48%) do not display a canonical motif. The enrichment of these motif-independent binding events in the vicinity of transcription start sites indicates that these sites are functional. In addition, we find that activation of genes associated with motif-independent and motif-dependent GATA3 binding is very similar suggesting that the different GATA3 binding modes are equally important. We are now carrying out further work to understand the functional role of this novel way of GATA3 binding in oncogenic transformation.

DR ANITA DAWES

Department of Physical Sciences, the Open University

Sponsored by the Science and Technology Facilities Council and the Open University

"Sooty snowballs": the role of polycyclic aromatic hydrocarbons in astrophysical ices

A Dawes

The space between the stars, the interstellar medium (ISM), is filled with gas, dust and radiation. Star formation begins in dense and extremely cold regions of the ISM called dense molecular clouds, where temperatures are so low (<-253°C) that almost all atoms and molecules (except hydrogen) "freeze-out" onto dust grains, forming ice. Chemical reactions in the ice produce progressively more complex molecules, which are expected to be locked into the ice until they are gently warmed and then returned to the gas, during the gravitational collapse that leads to star formation. However, even before this process begins, there are complex (desorption) mechanisms involved that unlock molecules from ices, without any heating. The cycling of molecular species between gas and solid phases is the most crucial feedback mechanism in the star formation process. Therefore understanding these desorption mechanisms is essential in building a picture of the star formation process, and is the basis for my research.

The aim of my project is to understand the role of large soot-like molecules known as polycyclic aromatic hydrocarbons (PAHs) on the desorption processes in interstellar ices. PAHs are ubiquitous in the ISM and are likely to be embedded in the ices, where they will absorb radiation and heat the surrounding molecules, causing them to desorb. I will use laboratory astrochemistry techniques to grow interstellar ice analogues and simulate both thermal (heating) and non-thermal (initiated by cosmic rays) processes that lead to desorption using two methodologies: temperature programmed desorption and electron stimulated desorption respectively.

I will subsequently exploit my laboratory data to search for observational evidence of the interplay between PAHs and interstellar ices in dense molecular clouds using archival data from infrared space telescopes (AKARI, Herschel, Spitzer and ISO).

DR MARGARITA FERNANDEZ-CHAS

King's College London

Sponsored by the Royal Academy of Engineering (July 2013 - July 2015)

Quantifying inter-species similarities and differences in cardiac cell functional heterogeneities between the rat and human: a simulation study

M Fernandez-Chas, SA Niederer, NP Smith

The effective pumping of blood around the body relies on the coordinated contraction of trillions of cardiac cells. Despite their common purpose, cardiac cell properties vary across the myocardium, with distinct transmural variations from endocardium to epicardium. These variations can be found in multiple species and understanding the functional differences in this variation between species is important for translating findings from one species to another.

The present study aims to simulate cardiac cell electrophysiology and calcium dynamics and quantify the spatial variations throughout the heart. An analysis of the regional variability of calcium concentration within the cells of the heart is presented for this purpose. The rationale of this analysis is to identify the differences in spatial variation between species at different locations across the myocardium.

There are a number of cardiac cell excitation–contraction coupling models available in the literature that characterise these properties of the single cell across the heart wall. Among them, the models of the adult rat and human heart have been used for our study.

It is of particular interest to identify how different these heterogeneities are in experimental animal models in contrast to the human heart. The analysis of these differences is presented in our study in terms of the dynamic response of these two spatial models. For this purpose, simulations are run for both models and a comparison of the frequency response of calcium concentration and action potential restitution, together with their response to external perturbations, is presented. These experiments will provide a quantitative description of the gradient in physiological function across the wall in rat and human preparations.

The outcome of this analysis will contribute towards a better understanding of the similarities between the rat and human hearts facilitating the effective translation of laboratory research into the clinical setting.

DR SHEILA FLANAGAN

Centre for Neuroscience in Education, Department of Psychology, University of Cambridge.

Sponsored by the University of Cambridge (Oct 2012 - Sept 2014)

Music, rhythm and developmental dyslexia: an investigation into perceptual centres and amplitude envelope sensitivity

SA Flanagan, UC Goswami

Developmental dyslexia is a learning disorder marked by a severe difficulty with written language. Approximately 7% of children who are otherwise of normal intelligence are affected by developmental dyslexia, which can lead to impaired education and eventual quality of life. It is widely accepted that the core difficulty in developmental dyslexia is a deficit in the auditory processing of the pattern of speech sounds, so called phonological awareness. Children with dyslexia have difficulties with sub-word phonology, e.g. deciding which words rhyme. These difficulties may be due to subtle auditory impairments, even though children with developmental dyslexia usually perform normally on hearing screens. One auditory sensory shortfall found in children with dyslexia is with the processing of the rate of change of the amplitude envelope. The amplitude envelope represents the lowest frequency component of the speech signal, corresponding to stressed syllables. In music it is related to the beat or meter. It has been suggested that auditory temporal processing is achieved by the synchronisation of internal neural oscillators to external temporal structure. This may be mediated through the perceptual centres (P-centre) of a word or other sound token which corresponds to its psychological moment of occurrence. Producing a list of words at regular intervals (isochronously) is not simply achieved by having the onsets at regular intervals. The perceived rhythm of a series of acoustic tokens is affected by their acoustic structure. The major influence on P-centre is onset rise-time. This study compares the perception of P-centres by subjects with and without dyslexia, to determine a causal link between amplitude envelope sensitivity and developmental dyslexia, with the aim to achieve early detection and develop effective remediation based on music and rhythm.

DR DEBRA E. FREDERICKSON MATIKA

College of Science and Engineering, University of Edinburgh.

Sponsored by University of Edinburgh (Sept 2011- Sept 2013)

The role of zinc finger transcription factors in managing nitrosative stress during disease resistance processes in the model plant *Arabidopsis thaliana*

DE Frederickson Matika, G Loake

A change in cellular reduction–oxidation (redox) status is one of the earliest responses detected in the plant cell following challenge by a putative pathogen. Hydrogen peroxide (H_2O_2) and nitric oxide (NO) are rapidly triggered and activate a form of programmed cell death called the hypersensitive response (HR). Furthermore, H_2O_2 and NO production lead to the activation of complementary defence genes, underscoring the specificity of these reactive intermediates and implicating redox changes as fundamental to the development of the plant immune response. Zinc finger transcription factors (ZnTF) are proteins that regulate gene expression by binding to DNA and are highly redox-responsive. Using PCR, we have confirmed 'knockout' of several ZnTF genes and reduced expression ('knockdown') in RNAi lines. Inoculation with virulent *Pseudomonas syringae* shows several selected lines have increased susceptibility. Using the yeast-2-hybrid system we have demonstrated weak interaction with the negative regulator Topless (TPL). Furthermore, Electrophoretic Mobility Shift Assay (EMSA) investigation of DNA sequence recognition by one ZnTF shows that it may bind to its own promoter. Flag-tagged constructs of the ZnTFs will enable investigation of potential binding sites of the ZnTF and the effector genes operating under disease/NO stress through the powerful chromatin immunoprecipitation and sequencing (chIP-Seq) technique.

DR HILARY KAY

Department of Astrophysics, University of Manchester

Sponsored by the Royal Astronomical Society (Oct 2012 - Oct 2014)

Very late thermal pulses (VLTP) in evolved stars

H Kay, A Zijlstra

Stars such as the Sun undergo a sequence of rapid changes towards the end of their lives. Much of the star's outer material is ejected into space forming a planetary nebula (PN) and the dead remains of the star cool to become a White Dwarf (WD). However, around 10–20% of these stars are expected to undergo a very late thermal pulse (VLTP) where the residual helium re-ignites when the star is already cooling to become a WD. Very few examples of VLTP stars have been identified and the only case where we have been able to follow this evolutionary phase in detail is that of Sakurai's Object, which underwent a VLTP before 1996. However, the evolution of Sakurai's Object has occurred up to 100 times faster than early evolutionary models had predicted. Sakurai's Object is currently enshrouded by dusty material making it difficult to study at visible wavelengths. We have obtained observations at radio wavelengths with the e-MERLIN facility and the Jansky Very Large Array (JVLA), which can penetrate the dust. I will present preliminary measurements of the current radio flux from Sakurai's Object and another possible VLTP star. I will later be using these fluxes to model the emission and determine the current temperature of the central stars. This will allow me to calculate the reheating rate and therefore place constraints on current evolutionary models of the VLTP phase. I will also present measurements of the current sub-mm flux from Sakurai's Object, which has been determined from observations with the Atacama Pathfinder Experiment (APEX). This will be used to determine how dust production in Sakurai's Object has evolved.

4 Daphne Jackson Fellows, to date, have gone on to become professors at universities in the UK

DR JANE E KING

Faculty of Life Sciences, University of Manchester

Sponsored by the Medical Research Council (April 2012 - April 2014)

Capsule gene expression during urinary tract infections by *Escherichia coli*

JE King, HAH Aal Owaif, IS Roberts

Urinary tract infections (UTI) are one of the most common human bacterial infections accounting for up to 3% of all general practice consultations in the UK. Uropathogenic *Escherichia coli* (UPEC) are the predominant cause of UTI. Studies have shown that upon infection of uroepithelial cells UPEC enter a complex developmental pathway involving the formation of intracellular bacterial communities (IBCs), which have biofilm like properties. The K1 polysaccharide capsule on the surface of UPEC is a key virulence factor and has recently been shown to be involved in IBC development. However, in the initial stages of infection during growth in urine it is likely that capsule expression is down regulated to promote attachment to uroepithelial cells indicating capsule expression may be regulated both spatially and temporally during UTI. To gain a better understanding of the expression of the capsule genes during UTI a green fluorescent protein (gfp) reporter strain has been constructed where gfp is under the control of the capsule gene promoter of the clinical isolate UTI89 (this strain has also been engineered to constitutively express dsRED). The resulting strain (UTGFP1dsRED) shows a slight (but significant) down regulation of gfp and hence capsule gene expression in pooled human urine (mimicking the initial stages of UTI) compared to growth in rich media. Infection of a bladder epithelial cell line with UTGFP1dsRED has allowed us to visualize strong capsule gene expression during IBC development. Furthermore a capsule deficient mutant shows impaired ability to produce IBCs confirming the importance of the capsule in this developmental process. Fluorescent microscopy of UTGFP2dsRED has also revealed heterogeneity in capsule gene expression within the clonal population. The mechanism for this heterogeneity is unclear but could indicate that capsule gene expression is under the control of a bistable switch. This hypothesis is under further investigation.

DR TZANKA KOKALOVA

School of Physics and Astronomy, University of Birmingham

Sponsored by the Science and Technology Facilities Council (April 2011- April 2013)

The 'Hoyley Grail' of nuclear physics

Tz Kokalova

Have you ever asked yourself "where did the elements we're made of come from"? We know that the elements have been forged in the stars, and that the average human body consists predominantly of two elements, oxygen and carbon. But what made it possible for the elements to be synthesised? The answer is surprising and very exciting, because the key to nucleosynthesis in stars relies on one particular state in one particular nucleus – the Hoyle State in carbon-12, named after Sir Fred Hoyle, who predicted its existence in 1953, from anthropological arguments. I call this state the 'Hoyley-Grail' of nuclear physics because even today, more than 50 years after the discovery of that state, we still don't know its precise underlying structure. Yet the structure of the Hoyle state affects the production of carbon-12 in stars by eight orders of magnitude. We know that the Hoyle state consists of three alpha particles, each containing two protons and two neutrons, but what the exact arrangement of those particles is, remains an open question. I will review the recent experimental results, the evidence needed, and the experimental tools that can be used, to finally answer this question.

DR LI LIU

Department of Chemistry, University of Leicester

Sponsored by the University of Leicester and private sponsorship (Jan 2013 - Jan 2015)

Breath fingerprinting by PTR-ToF-MS for rapid, non-invasive diagnostics

L Liu, IR.White, P Qualey, P Jefferd, S Kuppusami, AM Ellis, MR Sims, TJ Coats, PS Monks

A multidisciplinary project which encompasses non-invasive technology in order to rapidly assess metabolic and disease state by monitoring cardiovascular health, thermal- and hyperspectral- body imaging and breath sampling is being carried out at the University of Leicester. The diagnostic development unit's (DDU) pilot scheme involves patients administered to the Emergency Department at Leicester Royal Infirmary, UK with the 20 most common presentations and diagnoses. Preliminary results are presented from this pilot study into the potential of proton transfer reaction–time of flight–mass spectrometry (PTR–ToF–MS) for fingerprinting breath.

PTR–ToF–MS has only relatively recently been exploited in breath research. It is a direct MS technique capable of measuring multiple metabolite signals over a timeframe fast enough to characterise a full breath cycle. Here, it was used to analyse volatile organic compounds (VOCs) in breath sampled during both controlled single exhalations and normal, tidal breathing alongside simultaneous measurements of nitric oxide and carbon dioxide. Sample collection methods are under investigation to best facilitate breath measurements on critically ill patients and those suffering respiratory disorders.

Deconvoluting the complex mass spectra obtained during these studies yields sample population distributions for a variety of tentatively identified individual metabolites. However, in treating each subject's full breath mass spectral profile as a potential biomarker, patient groups could be discriminated through multivariate analyses. The results highlight both the challenges and the potential surrounding the deployment of this technology into the clinical environment towards real-time multi-marker measurement for non-invasive diagnostics.

DR TAMSIN MO MAJERUS

School of Life Sciences,
University of Nottingham

Sponsored by
University of Nottingham
and the Natural Environment
Research Council
(July 2013 - July 2015)

Understanding the genetic basis of adaptation is a fundamental aim in evolutionary biology

TM Majerus

A small number of well-understood examples suggest that similar genetic changes can result in parallel evolutionary outcomes, even across divergent taxa. Ladybirds are colourful and popular insects, as well as economically important biological control agents. They are fascinating models for studies including invasive species, reproductive strategies, sexually transmitted diseases, host–parasite interactions and male-killing. Yet despite exhibiting such phenotypic and behavioural characteristics that inevitably impact upon their survival and reproductive fitness, their genomes are largely unstudied.

Research has shown that colour-patterns can influence survival and reproductive fitness. Ladybirds are an excellent model system to investigate colour pattern control, with many species exhibiting high levels of polymorphism in the colour-patterns of their wing-cases. The two-spot and ten-spot ladybirds, *Adalia bipunctata* and *Adalia decempunctata*, are particularly well-suited, with over 200 different forms being described. Although little is known about the genetic basis of this polymorphism, breeding experiments show its inheritance is consistent with the segregation of alleles (variants) at a single (super) gene. It is also well understood in an ecological context, with several evolutionary forces important in maintaining colour-pattern variation, including mimicry, thermal and industrial melanism, and sexual selection. Bright, contrasting colours also serve as warning colours as ladybirds are toxic or distasteful to potential predators.

Restriction-site associated DNA (RAD)-sequencing is being used to investigate this question. Identifying sequenced markers that segregate with different phenotypes will allow construction of a linkage map of the region controlling colour pattern and investigation of whether the same genetic regions and changes are involved in both species. In addition, the same data will provide markers linked to sex and will serve as the foundation for future research into the basis of male-killing, a common phenomenon in several insect species which has dramatic consequences for reproductive success.

DR BEATE NÜRNBERGER

Institute of
Evolutionary Biology,
University of Edinburgh

Sponsored by the
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Research Council
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A genome-wide assessment of evolutionary divergence in hybridising fire-bellied toads

B Nürnberger, A Fijarczyk, J Szymura, M Blaxter

Speciation is the source of all organismal diversity on earth. It is the process by which evolutionary lineages become so distinct that they can no longer interbreed so that gene exchange between them ceases. Spectacular species radiations, for example of cichlid fish in African lakes, demonstrate that this process can be completed in a relatively short time span (~10,000 years). At the other end of the spectrum are taxa that continue to hybridise despite profound evolutionary divergence. A case in point are the European fire-belled toads *Bombina bombina* and *B. variegata*. Despite their ancient lineage split (~5 million years BP) and their adaptation to different habitats, they produce abundant fertile hybrids to this day in narrow zones of contact wherever their species ranges adjoin. We have generated de novo assemblies of their transcriptomes in order to develop a large battery of genetic markers. It will be used for a genome-wide dissection of the evolutionary forces that govern the current hybrid zone dynamics and that should explain why speciation is so protracted in *Bombina*. The datset also allows us to decipher past evolutionary processes. Over the course of several glaciation cycles, both species ranges have repeatedly contracted and re-expanded. It appears likely that hybridisation occurred episodically during inter-glacial periods. We employ coalescent analyses to detect these signals of past hybridisation and gene exchange. As outgroups we use transcriptomes from the nearest relative (*B. orientalis* from Korea) and from B v . scabra (a Balkan subspecies). These are used, respectively, to control for different rates of evolution among genes and as a non-hybridising control.

DR RURAMAYI
M. NZUMA-MSWAKA

Institute of Global Food Security,
Queens University Belfast

Sponsored by the
Society for Chemical Industry
(June 2013 - May 2015)

Generation of novel binders for *Campylobacter jejuni* using phage display and recombinant antibody technologies

R Nzuma-Mswaka, IR Grant

Campylobacter is the most commonly reported cause of food-related illness in humans. *Campylobacter jejuni* is particularly associated with raw poultry products. Current detection methods for *C. jejuni* are time-consuming and not sensitive enough, making intervention control measures along the food chain ineffective to date. The development of faster, cheaper and sensitive detection methods is a priority. Novel *C. jejuni*-specific peptide binders with the ability to distinguish *C. jejuni* from other Campylobacter species will be generated using a powerful technique known as phage display biopanning. These phage display-derived binders will then be used to develop and optimise a novel immunomagnetic separation method (IMS) for selective capture and concentration of *C. jejuni* enhancing its detection from poultry processing samples.

DR MARGARET O'HARA

School of Physics
and Astronomy,
University of Birmingham

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Sciences Research Council
(Nov 2012 - Nov 2014)

Breath analysis in liver disease - volatile organic compounds (VOCs) as possible markers of cirrhosis

M O'Hara, C Mayhew, P Brown, A Holt, T Shah, J Neuburger

Analysis of volatile organic compounds (VOC) in human breath has been proposed to improve diagnostics in various medical applications. In the present study, a proton transfer reaction mass spectrometer (PTR-MS) was used to analyse VOCs in breath samples obtained from 21 patients with liver disease and 14 healthy controls. PTR-MS is a highly sensitive mass spectrometric technique which can measure VOCs in mixed gas samples. Analysis is direct with no need for pre-concentration. Patients had cirrhosis, hepatitis C, neuroendocrine disease and liver tumours. The samples were obtained during liver clinics at the Queen Elizabeth Hospital, Birmingham. Samples were collected in Teflon bags and were analysed on the same day. Sample bags were heated to 40°C during measurement to prevent condensation.

Breath samples from patients were compared to those from healthy controls to identify possible biomarkers. A peak at molecular mass 137 (*m/z* 137) was significantly higher in 10 patients with cirrhosis: 1010 (1160) (mean (SD), units are normalised counts per second) v 195 (112) in other liver disease and 99 (45) in normal controls. Of those cirrhotic patients, *m/z* 137 was particularly high in 4 patients who also had encephalopathy 1180 (859). *m/z* 137 is probably a monoterpene as a fragment at *m/z* 81 was also observed which is typical for monoterpenes. Other possible markers were *m/z* 183 for neuroendocrine disease: 713 (776) v 94 (142) other liver disease and 121 (153) normal controls.

Sample sizes were small and the data had a wide distribution but these findings warrant further investigation. Future studies are proposed in which larger numbers of patients with cirrhosis are sampled. In order to investigate whether this marker is particular to encephalopathy, as opposed to cirrhosis in general, a study is planned in which patients hospitalised with acute encephalopathy supply breath samples during the course of treatment.

DR FRANCES PEARL

Breakthrough Breast
Cancer Research Centre,
Institute of Cancer Research

Sponsored by the
Medical Research Council
(July 2011 - July 2013)

Assessing the druggability of DNA damage response (DDR) proteins

F Pearl, B Al-Lazikani

The almost universal development of genomic instability that accompanies tumourigenesis has brought the pathways that mediate the DNA damage response (DDR) to the fore as targets for development of new approaches to the treatment of a wide range of cancers. However, unlike the protein-kinase signaling pathways that have been the focus of much anti-cancer drug development in the past decade, the proteins that make up the DDR are very diverse in structure and function, and there is a need for major effort in target definition and identification before these pathways can be fully exploited.

To help support these drug discovery activities we have assembled a comprehensive dataset of proteins involved in the DDR. These have been systematically analysed using a wide range of data to define both their genetic vulnerability to mutation and to identify their suitability for functional inhibition by small molecule drugs – 'druggability'. These data include: chemical screening data, gene expression data, mutational data, functional annotation, 3D structure, and analysis of interaction networks. The ultimate aim of this study is to identify 'druggable' points of intervention within the DDR pathways, on which drug discovery can be most effectively focussed.

4 out of 10 Daphne Jackson Fellows are supported by one of the five research councils that fund STEM research

DR MARINA PTUSHKINA

Institute of Human Development, University of Manchester

Sponsored by the Medical Research Council (April 2013 - April 2015)

Ancient conservation of cell survival networks revealed in fission yeast expressing human GR

M Ptushkina, T Poolman, D Ray

The glucocorticoid receptor (GR) is a ligand activated transcription factor and a member of the superfamily of nuclear receptors (NR). The GR is essential for stress response in mammals, regulating energy metabolism, and immunity, mediating these effects by binding specific DNA sequences in the genome, and recruiting a diversity of other proteins. The quiescent GR is located in the cytoplasm, in a chaperone complex with hsp90/hsp70 .

Yeast are valuable unicellular eukaryotic model organisms with significant genetic and protein homology to mammals. The fission yeast *Schizosaccharomyces pombe* (*S.pombe*) is a good model for cell stress response, and cell fate research. We propose that ancient stress response pathways are conserved from such yeast, and can be identified using the human GR as a genetic probe. We applied three distinct stressors; heat, osmotic stress, and DNA damage. Responses were tracked by measuring cell proliferation. The first studies exposed wild-type and GR transgenic yeast to heat stress. Wild-type yeast cannot proliferate at 39°C, but the GR transgenic yeast were able to grow, and showed a highly significant rescue effect. This occurred in the absence of added ligand, and indeed yeast do not synthesise GR binding steroids. I investigated the effects of adding a highly potent synthetic GR ligand, dexamethasone. This strikingly abolished the survival effect, revealing the presence of a ligand binding dependent switch in GR function. I went on to study osmotic stress with sorbitol, and DNA damage stress with methylmethane sulfonate (MMS). In both cases transgenic GR offered a marked protective effect on the yeast. These data reveal a striking apoGR functional effect to protect yeast from cellular stress.

To pursue the mechanism I have measured GR effects on the yeast proteome, which have revealed marked changes. I am now determining if the mechanism requires regulation of the yeast transcriptome, or is mediated by cross-talk with yeast proteins.

DR CAROLINE SCOTT

Weatherall Institute of Medical Research, University of Oxford

Sponsored by the Medical Research Council (May 2012 - May 2014)

The role of alpha thalassemia mental retardation X-linked protein (ATRX) in genome stability at the MS32 microsatelite

C Scott, C Jelinska, D Higgs, R Gibbons

The major source of genomic instability that leads to disease comes from errors in DNA replication, repair and recombination; at certain regions within the genome these processes are thought to involve ATRX. Mutations in ATRX are associated with a severe syndromal form of intellectual disability known as ATR-X syndrome. Recently our lab has shown the remodelling protein ATRX binds to G rich repetitive regions of the genome and in the absence of ATRX the replication of DNA is perturbed and DNA damage is observed, suggesting that these repetitive regions present a problem for the cell to replicate.

To investigate the role of ATRX on genome stability I will focus on the G-rich tandem repeat MS32 microsatellite, which is a known target of ATRX and is prone to length instability. To conduct this study I have now established a robust and reliable protocol to amplify and detect MS32 from 0.1ng of gDNA template. There is considerable variation in the size of this repeat in individuals as amplified using this small pool polymerase chain reaction (PCR) technique which is identical to the gDNA bands seen with Southern blotting. The aim will be to use small pool PCR to assess the number of microsatellite bands across multiple PCR reactions to determine if there has been expansion or contraction of the microsatellite in comparison with the progenitor alleles in cell lines where ATRX has been reintroduced. An important resource for these experiments is the clonal line, named 22/3 which has been derived from U-2OS cells (ATRX null) into which a tetracyclin inducible ATRX transgene has been introduced. This cell line will be used to determine the effects of ATRX expression on MS32 microsatellite instability by addition and removal of doxcyclin.

42 Daphne Jackson Fellows are currently in post at 30 universities around the UK

DR SRISIVANE SIVANESAN

Department of Mechanical Engineering and Mathematical Sciences, Oxford Brookes University

Sponsored by Oxford Brookes University and the Engineering and Physical Sciences Research Council (Nov 2012 - Nov 2014)

Three-dimensional image reconstruction algorithm for electrical impedance mammography based on the method of fundamental solutions

S Sivanesan, L Marin, C Sebu

The paper is devoted to the development of a computationally efficient three-dimensional image reconstruction algorithm for electrical impedance tomography (EIT) which could be used to identify the size and the location of breast tumours in real-time. The mathematical analysis of breast cancer detection leads to the inverse conductivity problem of EIT on unbounded three-dimensional domains, precisely the lower half space. The inverse problem under consideration is to find the conductivity distribution of the lower half space from measurements of the current, and of the corresponding potential, on the surface.

The proposed algorithm is based on the method of fundamental solutions and is designed to be used for conductivity reconstruction from data collected by the mammographic sensors designed by the EIT group at the University of Mainz, Germany. The EIT devices developed in Mainz consist of a planar sensing head of circular geometry. The latest prototype consists of 12 large outer electrodes arranged on a ring of radius 4.4cm where the external currents are injected, and a set of 54 point-like high-impedance inner electrodes where the induced potentials are measured.

The algorithm will be initially tested using simulated data. To this end, EIDORS, an existing software package for solving the forward problem of EIT was modified and adapted to our geometry and then used to generate the simulated data

DR GEMMA SWEENEY

Department of Chemistry, University of Huddersfield

Sponsored by the University of Huddersfield and the Engineering and Physical Sciences Research Council (July 2013 - July 2015)

Mechanistic studies of iridium(iii) catalysed amine racemisation

G Sweeney, M Page

Many compounds exist in different mirror-image forms, called enantiomers. Following the devastating effects of the use of thalidomide as a mixture of both its enantiomers in the 1950s, all compounds with pharmaceutical or agrochemical potential must be tested in all their enantiomeric forms. Current methods used to separate pure forms from a mixture of enantiomers (a racemic mixture) on an industrial scale can be inefficient because often a kinetic resolution (e.g. a diastereomeric recrystallisation) is employed for operational simplicity. However, this means the maximum yield is limited to 50%, which has a considerable impact on the economic viability of the procedure. It is now possible to combine the kinetic resolution with a simultaneous racemisation (whereby enantiomers can interconvert) to give a theoretical yield of 100% in a procedure known as dynamic kinetic resolution (DKR). Professor Mike Page has recently discovered a novel catalyst, pentamethylcyclopentadienyliridium(III) iodide dimer [IrCp*I2]2 which successfully racemises amines with low catalyst loading, under extremely mild conditions, and within a few hours at 400°C. Furthermore the racemisation has been successfully coupled to an enzyme-catalyzed acylation to give overall a 90% conversion to the product with an enantiomeric excess (ee) of 96% on a 1g scale. On a 3g scale, the isolated yield of product was 82% in 96% ee.

Here I propose to investigate the mechanism of this catalytic method for the synthesis of chiral amines using this novel catalyst, with the aim of catalyst and process optimisation. By understanding how the catalyst racemises amines it should be possible to optimise the catalyst to enable improvement in substrate scope. I plan to investigate the mechanism of this process in three ways; by studying the pre-equilibrium step (using NMR), by studying the catalytic steps (using isotopically labelled substrates and intermediates), and by catalyst structural modification.

DR CAROLINE M TAYLOR

Centre for Child and Adolescent Health, University of Bristol

Sponsored by the University of Bristol (Feb 2012 - Feb 2014)

Effects of maternal lead levels on pregnancy outcomes: the ALSPAC study

CM Taylor, J Golding, AM Emond

The results of previous studies on the associations of prenatal blood lead levels (BLL) with pregnancy outcomes such as birthweight and preterm delivery have been inconsistent. Our aim was to study these associations in a large cohort of mother–child pairs in the UK.

Pregnant women resident in the Avon area of the UK were enrolled in the Avon Longitudinal Study of Parents and Children (ALSPAC). Whole blood samples were collected and analysed by inductively coupled plasma dynamic reaction cell mass spectrometry (n=4285). Self-completion postal questionnaires were used to collect data on lifestyle, diet and environmental factors during pregnancy. Data collected on the infants included anthropometric variables and gestational age at delivery. Statistical analysis was carried out with SPSS v18. Regression models were adjusted for covariates including maternal height, smoking, parity and sex of the baby.

The mean BLL was 3.67±1.47 (median 3.41, range 0.41–19.14) µg/dl. BLL were significantly higher in women delivering low-birthweight babies (<2500 g; 3.89±2.55 vs 3.65±1.46 µg/dl, p=0.024), but not preterm babies (<37 weeks; 3.85±1.66 vs 3.66±1.45 µg/dl, p=0.053). Increasing BLL was significantly associated with reductions in birthweight, head circumference and crown–heel length (p=0.013, p=0.028 and p=0.026, respectively). BLL ≥5 µg/ml significantly increased the risk of preterm delivery (p=0.013) or having a low-birthweight baby (p=0.044).

There was an adverse effect of BLL on pregnancy outcomes in this group of women, with reductions in birthweight, head circumference and crown–heel length, and an increased risk of preterm delivery and low birthweight, in adjusted regression models. This could have important long-term effects on the physical and neurological development of the child.

DR DIVYA TIWARI

Department of Engineering Photonics, Cranfield University

Sponsored by the Royal Academy of Engineering (July 2013 - July 2015)

Optical fibre long period grating (LPG) sensors for atmospheric monitoring of carbon dioxide

D Tiwari

Optical fibre long period gratings (LPGs) coated with functional nanomaterials provide a promising platform for the fabrication of sensors with high sensitivity that offer specific response to targeted chemical species. In work pioneered at Cranfield, it was shown that the LPG transmission spectrum exhibits a high sensitivity to the optical properties of coatings deposited onto the surface of the optical fibre. This research aims to develop a chemical sensor for atmospheric monitoring of CO_2 at carbon capture and storage sites (CCS). The refractive indices of phenol and *p*-nitrophenol exhibit dependemce on the concentration of CO_2. By coating the cladding of the section of optical fibre containing the LPG with nanoscale films of these materials and tracking their influence on the LPG transmission spectrum, a sensitive tool can be developed for monitoring CO_2 concentration. Optimisation of sensitivity performance will be achieved by the appropriate choice of LPG and coating parameters.

Rising CO_2 concentration in the atmosphere has led to increasing ocean acidification and is a contributing factor to climate change and rising global temperatures. About 55% of CO_2 is created by fossil fuel based industries and power stations, and if the world is to maintain its dependence on fossil fuels then CCS is a necessary technology for tackling raising atmospheric CO_2. To ensure that there is no unintended CO_2 release from storage sites, atmospheric monitoring tools are installed. But with these techniques many significant problems remain unsolved: (1) cross-sensitivity to other gas species, such as water vapour, (2) thermal calibration drift, and (3) heavy weight. The proposed sensor aims to address some of these limitations.

REBECCA WARD

Department of Engineering, University of Cambridge

Sponsored by the Royal Academy of Engineering (April 2011 - April 2013)

Cutting carbon emissions from building energy consumption at the Royal Botanic Gardens, Kew

R Ward

A methodology for the analysis of building energy consumption to support decision making for building retrofit and energy supply strategy has been developed and applied to a representative case study involving buildings at the Royal Botanic Gardens, Kew. The methodology requires selection of the appropriate building simulation tools dependent on the nature of the primary energy demand. Development of a stand-alone model to simulate heat flow in botanical glasshouses has been required, together with simulation of the power demand for buildings with high equipment density and occupancy-led operation in a way which captures the stochastic nature of the demand. Application of the methodology to the buildings at the Kew site illustrates the potential reduction in energy consumption at the building scale achievable from the application of retrofit measures deemed appropriate for heritage buildings. The potential benefit to be gained from energy micro generation and supply at the district scale has also been investigated using an energy demand optimisation tool for the highest consuming cluster of buildings at Kew, resulting in an optimised energy supply strategy for the cluster.

DR RACHEL WHITE

Institute of Medical Sciences, University of Aberdeen

Sponsored by the University of Aberdeen (April 2012 - April 2014)

Is dysregulation of pH in articular chondrocytes the key to understanding osteoarthritis?

R White, S Yin Yong, R Aspden

Osteoarthritis (OA) is the most common musculoskeletal ailment and it is estimated that 85% of people by the age of 75 will show clinical or radiological evidence of OA, although only 60% will be symptomatic. Traditionally, OA has been seen as a degenerative disease of articular cartilage but tissue growth is a key characteristic in the early stages. Other than analgesia, there is no established pharmaceutical therapy.

In a pilot study, selected gene expression in tissue samples from patients with OA and osteoporosis (OP) were compared. The gene, *SLC9A3R1* which encodes for a member of the sodium/hydrogen regulatory factor protein family (NHERF1) was found to be differentially expressed. NHERF1 plays a role in tumour suppression and intracellular pH (pHi) regulation by acting on the sodium/hydrogen exchanger (NHE). We are investigating whether a decrease in NHERF1 causes a change in the pHi of chondrocytes and causes chondrocyte proliferation. The aim of the project is to test the hypothesis that dysregulated expression of NHERF1 is a key part of the abnormal behaviour of articular chondrocytes. This will be achieved by the following objectives comparing articular cartilage from patients with OA with tissue from patients with OP or amputations: a) examine NHE and NHERF1 expression in articular chondrocytes; b) measure the pHi of articular chondrocytes; c) determine the severity of OA in samples by using the OARSI histological scoring system.

The methods used to achieve these objectives include histology, immunohistochemistry and laser scanning confocal microscopy. All methods and techniques have been fully optimised and this is the first study to identify NHERF1 and NHE expression in human articular cartilage and measure pHi in single isolated chondrocytes using the fluorescent dye, BCECF. Experiments are now underway to determine differences between OA samples and controls, and measure NHE and NHERF1 gene expression.

DR ZOULIKHA ZAIDI

Institute of Pharmaceutical Science, King's College London

Sponsored by King's College London and the Medical Research Council (April 2013 - April 2015)

Can mathematics provide a quantitative understanding to link drug administration and drug effect in asthma?

Z Zaidi, B Forbes, T Coolen

Asthma is a chronic and complex disease which affects about five million people in the UK, causes about 1300 deaths a year, and puts a huge financial burden on the health services. Developing drugs that provide relief from the airway constriction in this disease is a challenge for pharmaceutical firms in the sense that it is very expensive, lengthy, and requires empirical proof of safety and efficacy.

Drug delivery/discovery researchers use cell-culture experiments, animal models and human clinical trials to assess or predict the drug effect in the airways. Among the limitations of these approaches are inter-laboratory variability, interspecies variation and the complexity of disease/clinical investigations. Moreover, it is well known that pharmacological results obtained from animal models do not always translate to humans. This has led to a search for alternatives to replace/reduce animal use. For example, researchers are increasingly using mathematical modelling/simulation-approaches that use the principles of biological science and the latest tools in computer technology.

Drug action is initiated according to its concentration in the airways and its molecule specific properties, whereas its biological effects and their magnitude are dependent upon complex and highly variable biological factors such as homeostatic mechanisms (systems responsible for regulating cell/body normal condition and function).

In this work, we aim to integrate drug knowledge and information from experimental data, to uncover the complex interactions of the most relevant messaging systems that are responsible for initiating relaxation of the airways. We will use mathematical modelling to do the detective work.

DR DALIA ZAKARIA

Cellular and Molecular Medicine, University of Bristol

Sponsored by the University of Bristol (Sept 2010 - Nov 2013)

Epithelial–dendritic cell interplay in the shaping of the immune response to *Niesseria meningitidis* and *N. lactamica*

D Zakaria, D Hill, N Williams

Group B *N. meningitidis* is a major cause of septicemia and meningitis for which no universal vaccine is currently available. These bacteria can be carried asymptomatically in the back of the throat without causing disease. However, such bacteria can cause devastating disseminated infections while close relatives of these organisms (*N. lactamica*) colonise the same site without causing any disease. The aim of this study is to build picture of the differences between commensal and pathogenic neisserial species and the immune responses they evoke at the epithelial–dendritic cell (DC) interface. DC act as sentinels of the immune system by expressing functional proteins that enable them to penetrate epithelial barriers to sample antigens. Initially, the profiles of products (cytokines) expressed by epithelial cells (16HBE) following their interactions with wild (Nm) and capsule deficient (Nm-c) strains of *N. meningitidis* and *N. lactamica* (Nl) were studied. The transwell system was used to allow cellular differentiation presenting both apical and basolateral surfaces, better representing the in vivo epithelial state. Enzyme linked immunosorbant assay of the cutlutre supernatant post-infection revealed that some cytokines (IL-6, IL-8, TNF-α and TGF-β) were released at both apical and basolateral surfaces of 16HBE cells challenged with Nm-c, Nm or Nl except for TNF-α which was produced only at the apical surface. Other cytokines assayed for (Il-10, Il-4, Il-12, Il-23 and TSLP) were not present at detectable levels at either the apical or basolteral sides of the 16HBE monolayer following infection by Nm or Nl. We observed that Nm-c and Nl were able to stimulate larger amounts of cytokines compared to Nm. In addition, Nm traversed the 16HBE monolayer in greater numbers compared to Nl. The effects of cytokines released by epithelial cells following infection with *Neisseria spp*. on the differentiation and function of DC will be investigated subsequently.

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