University of Glasgow | College of Medical, Veterinary & Life Sciences

Glasgow Polyomics Launch Symposium

14th September 2012
Graham Kerr Building, University of Glasgow

Programme

Glasgow Polyomics
www.glasgow.ac.uk/polyomics

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Index

Foreword from the Head of College

It is my great pleasure to welcome you to the official launch of *Glasgow Polyomics*.

The College of Medical, Veterinary and Life Sciences, which was formed in 2010, is committed to supporting innovative projects that use experimental and analytical approaches that are at the forefront of biomedicine. With over 900 research staff and almost 6,000 students, ours is a large and successful College; it has an annual turnover of £170M and has attracted research awards worth £65M in 2010–11.

The basic and clinical research of the College revolves around the themes represented by its research institutes – Cancer Sciences; Cardiovascular and Medical Sciences; Infection, Immunity and Inflammation; Neuroscience and Psychology; Molecular, Cell and Systems Biology, and; Biodiversity, Animal Health and Comparative Medicine. The strong translational focus that is the hallmark of the College stems principally from fostering collaborations between groups that bring diverse methodologies and perspectives to bear on clinically important research questions. Our inter-disciplinary aims are further reflected in the fact that our life scientists are seamlessly integrated with clinical academics, engineers, statisticians and computing scientists.

As biomedical science has become more quantitative and data-rich, we have kept pace by investing in the staff, equipment and projects that allow cells, organisms or populations to be analyzed in a systems context. Technological progress allows us to dissect biological processes in unprecedented detail, and to integrate different layers of understanding towards obtaining a more holistic view of biological function, health and disease.

Glasgow Polyomics encapsulates this vision of a technologically advanced, multi-dimensional group. In this newly constituted facility, sensitive and high-throughput analytical instrumentation is operated by highly skilled staff to permit the collection and analysis of many omics datasets in order to assist both basic and applied research programmes across the life science disciplines.

Glasgow Polyomics brings together experts in genomics, transcriptomics, proteomics, and metabolomics who are supported by experienced bioinformaticians and software developers. Our aim is that biomedical researchers across the University and beyond will take advantage of the skills and instrumentation offered by this state-of-the-art facility, and that collaborating with staff at *Glasgow Polyomics* will help to strengthen existing investigations and to catalyze new research directions.

Tangible benefits of these fruitful interactions will be visible across the College, in the form of innovative projects that are robustly designed and executed, and in a broadening of the technical and knowledge base of our research groups.

I hope that you enjoy our symposium and seize the opportunity to interact with staff from *Glasgow Polyomics*.

Anna F. Dominiczak
OBE MD FRCP FRSE FMedSci
Regius Professor of Medicine,
Vice Principal & Head of College of Medical, Veterinary and Life Sciences

An overview of Glasgow Polyomics

Understanding any biological system invariably involves piecing together its structure or function from its constituent parts. For over a decade now, the means by which such parts can be collected has been transformed beyond imagination by the ability to obtain data on a large scale accurately and cheaply. This new means of gathering biological data in a high-throughput fashion is known as ‘omics’.

The birth of omics dates back to a quarter of a century ago, when advances in DNA sequencing technology made it feasible to contemplate the start of the Human Genome Project. Before long, genomics was joined by high-throughput technologies that characterize other levels of biological organization: epigenomics, transcriptomics, proteomics, metabolomics, lipidomics and glycomics, each of which aims to describe different parts of the cellular infrastructure. The entirety of these data sets defines the ‘polyome’, and so ‘polyomics’ describes the acquisition, characterization and integration of these datasets. *Glasgow Polyomics* was set up to respond to these transformations in the biomedical sciences — the role of our facility is to provide the equipment and expertise to generate and analyze polyomics datasets for the wider research community.

Omics technologies provide the means to examine traditional research questions on a vast scale. For example, we are now able to take global molecular snapshot of cells or tissues when these are perturbed, say, by a drug, by environmental stress, or by a genetic mutation. Through bioinformatics, omics datasets can be integrated, leading to powerful biological inferences — for instance, DNA variation can be related to variation at the RNA level, and to protein variability and changes in metabolite profiles.

As omics tools are very versatile they can be applied across the life sciences, from ecology to medicine. In fact, the unifying power of omics technologies allows these different areas to be combined — as exemplified by the study of the ecology and evolutionary dynamics of microbes that cause disease.

Omics approaches can also steer research into exciting new directions. Determining an individual’s unique personal polyome offers the opportunity to understand the molecular basis of disease and how medicines may be targeted to individuals at particular risk. In synthetic biology, the polyome of microbes can be manipulated to enable these organisms to generate high value chemicals including fuels and pharmaceuticals.

Glasgow Polyomics is equipped with state-of-the-art, next-generation DNA sequencing technology, and a fleet of mass spectrometers and nuclear magnetic resonance (NMR) technology to measure the proteome, lipidome and metabolome from any system. We work flexibly with users to generate and/or analyze data; we can work on projects in a service capacity or as full collaborators. We invest in tools that meet the needs of the research community — our team of bioinformaticians can develop tailored methods and software products to meet demand. We are also committed to disseminating omics knowledge more widely, and so run formal taught courses as well as personalized training sessions.

All aspects of the life sciences can be better understood in the context of their polyome. *Glasgow Polyomics* aims to allow all researchers in Glasgow and beyond to gain inferences about every aspect of life through understanding its component pieces and the principles that operate between them.

Michael P. Barrett
Professor of Biochemical Parasitology, Wellcome Trust Centre for Molecular Parasitology, Institute of Infection, Immunity & Inflammation, College of Medical, Veterinary & Life Sciences
and
Director, Glasgow Polyomics

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Proteomics: Richard Burchmore

Biomarker discovery: Bill Mullen & Harald Mischak

Software development: Fraser Morton

Glasgow Polyomics
Joseph Black Building,
University of Glasgow

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Glasgow Polyomics

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General information

Refreshments
Coffee and lunch breaks, and the drinks reception will take place in the Museum, which is located on the same floor as the auditorium.

Posters
Posters will be displayed throughout the day in the library on the first floor, and on the first floor landing.

Interacting with *Glasgow Polyomics* staff
Attendees who have scheduled appointments with *Glasgow Polyomics* staff should check the booking sheets at registration for information about the location of their meeting. Meetings will be held in two locations: in Lecture Theatre 2 (adjacent to the museum) and in the small meeting room (opposite the main lecture theatre). See the map on page 7 for details.

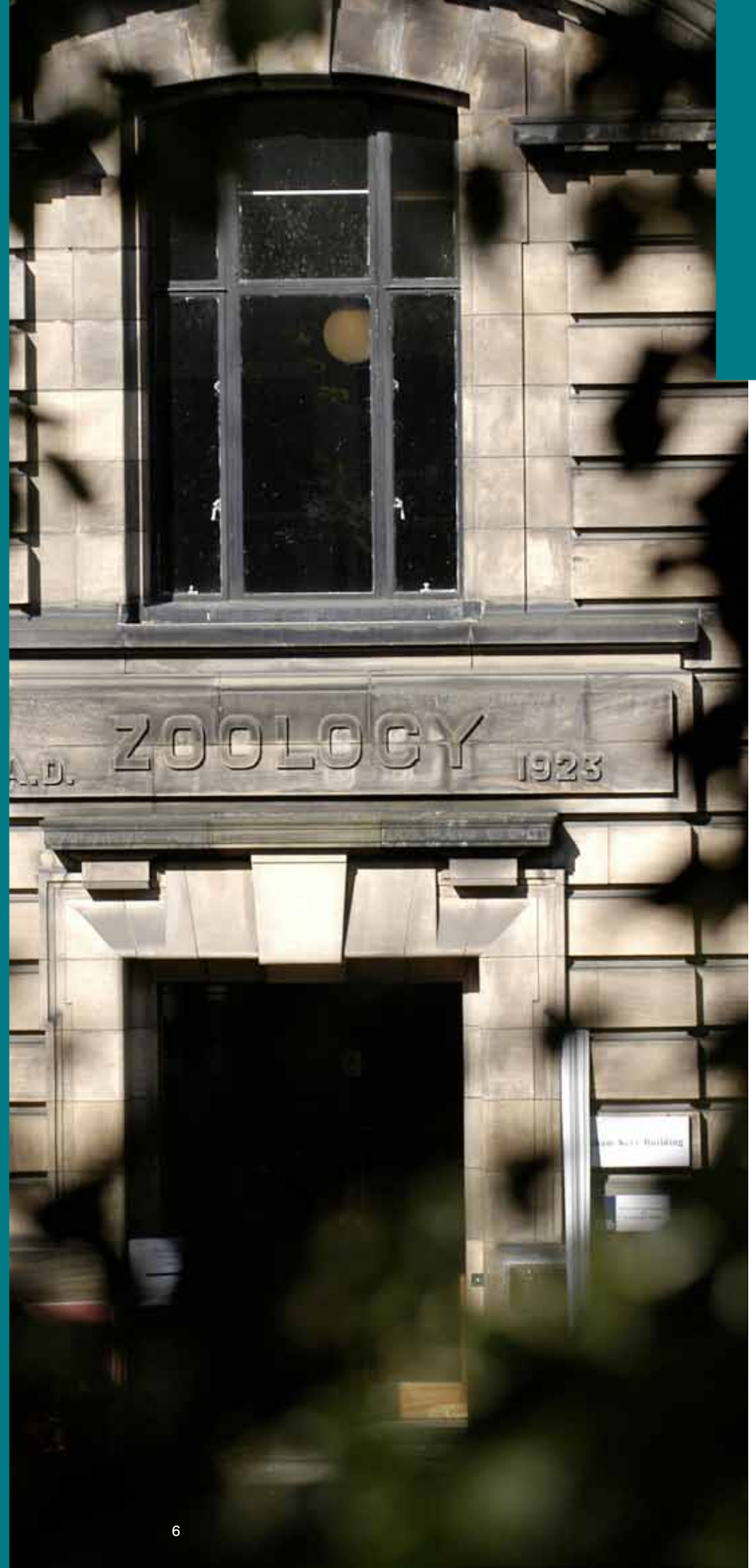
Staff members of *Glasgow Polyomics* are identifiable by a coloured sticker on their name badge. We would be delighted to meet you and answer any query.

Facilities
Toilet facilities can be found on the ground floor by the front entrance. A cloakroom is available in the small meeting room.

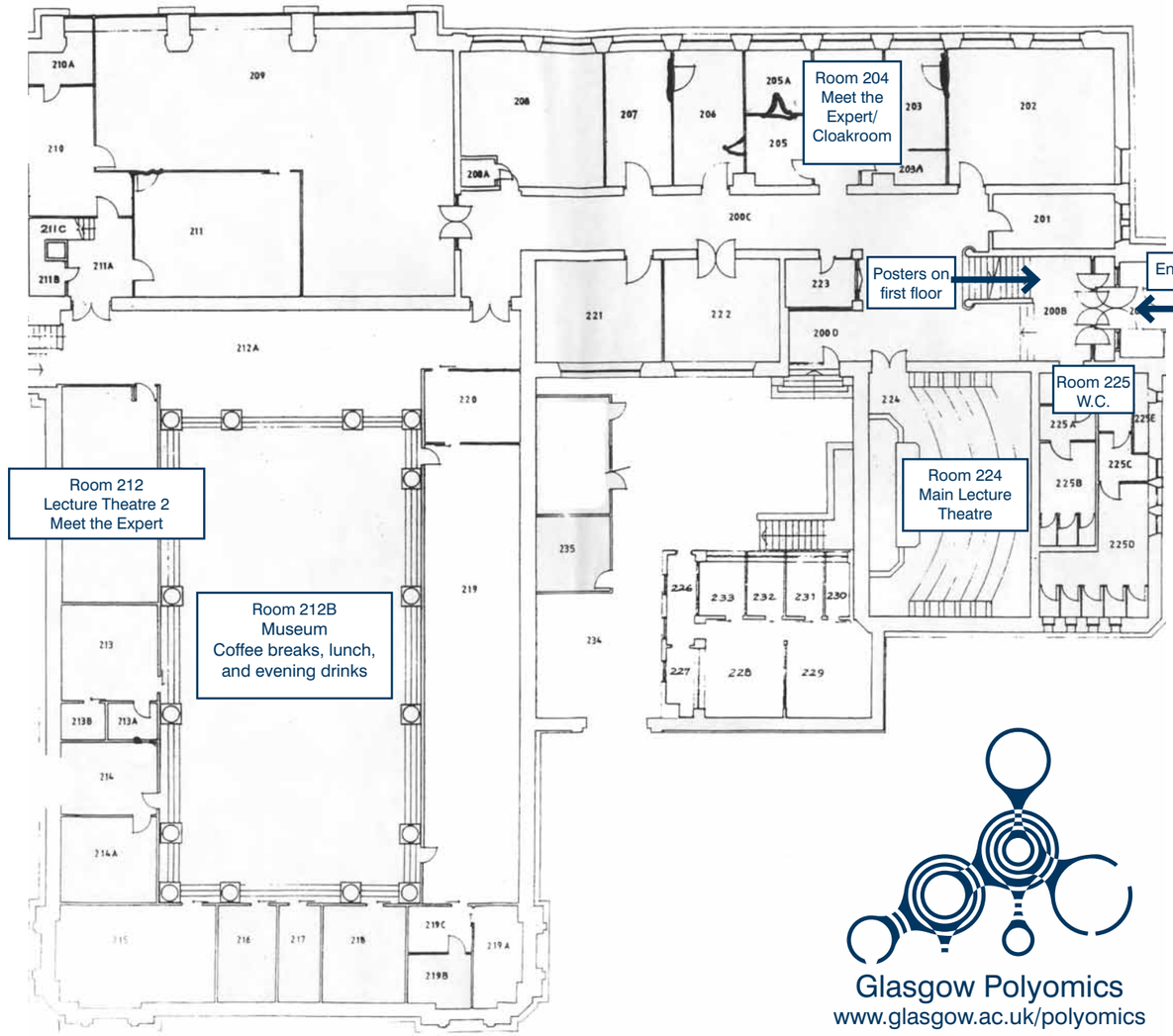
Acknowledgements
We gratefully acknowledge the support of the Wellcome Trust for this meeting. We are also indebted to Kathleen Doris, Lynne Kelly, Maggie Reilly and Lorna Kennedy for their invaluable and good humoured support.

The front cover image is reproduced with permission from shutterstock. Photos are reproduced with permission from the University Photographic Unit.

We are grateful to the following people for providing images to include in this programme booklet: Jing Wang (Affymetrix microarray chip showing *Drosophila* gene expression, p10); Graham Hamilton and Stephen Yarwood (ChIP peaks and associated genes mapped to the mouse genome, p11); Emanuela Sani, Pawel Herzyk and Anna Amtmann (histone modification profile over five *A. thaliana* chromosomes, detected with ChIP-seq, p12); Rainer Breitling and Richard Scheltema (heatmap representation of data from an Orbitrap LC-MS measurement of a complex sample, p15); Rainer Breitling and Andris Jankevics (bubble plot of an Orbitrap mass spectrometry data set, p17).



Ground floor of the Graham Kerr Building



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Programme

All presentations will take place in Lecture Theatre 1, on the ground floor of the Graham Kerr Building.

9:30am
Registration opens

'Meet the expert' sessions will run 9am–4pm in Lecture Theatre 2 and in the small meeting room of the Graham Kerr Building

9:45am–9:55am
Welcome address

Professor Anton Muscatelli, Principal and Vice-Chancellor

9:55am–10:05am
Overview of *Glasgow Polyomics*

Professor Mike Barrett, Director, *Glasgow Polyomics*

Session 1

Chair: Professor Mike Barrett

10:05am–10:50am
The cellular uptake of pharmaceutical drugs: a problem not of biophysics but of systems biology

Professor Douglas B. Kell, Research Chair in Bioanalytical Sciences, School of Chemistry and Manchester Institute of Biotechnology, University of Manchester, UK; Chief Executive and Deputy Chair of the Biotechnology and Biological Sciences Research Council (BBSRC)

10:50am–11:30am
Insights from *Plasmodium* metabolomics

Dr Manuel Llinás, Richard B. Fisher Preceptorship in Integrative Genomics, Princeton University, Princeton, New Jersey, USA

11:30am–11.50am
COFFEE BREAK AND POSTER VIEWING

Session 2

Chair: Professor Anna Dominiczak

11:50am–12:30pm
Life sciences at the tipping point

Dr Peter Silvester, President, Europe, Middle East & Africa, Life Technologies™

12:30pm–1:10pm
Cancer polyomics: from discovery to patient care

Professor Andrew V. Biankin, Head, Pancreatic Cancer Research, Garvan Institute, Sydney, New South Wales, Australia

1:10pm–2:30pm
LUNCH AND POSTER VIEWING

Session 3

Chair: Professor Andy Waters

2:30pm–3:10pm
Polyomics to dissect mechanisms regulating mesenchymal cells in cancer, development and adult tissue maintenance

Professor Nick Hastie, Director, MRC Human Genetics Unit; Director, Institute of Genetics and Molecular Medicine (IGMM), University of Edinburgh, UK

3:10pm–3:50pm
Using polyomics approaches to embrace the complexity of asthma

Professor William O. Cookson, Professor of Genomic Medicine, Imperial College London, London, UK

3:50pm–4:10pm
COFFEE BREAK AND POSTER VIEWING

Session 4

Chair: Fraser Morton

4:10pm–4:50pm
From biocuration to computational biology and bioinformatics: an example of integrative biology

Professor Ioannis Xenarios, Director, Swiss-Prot & Vital-IT, Swiss Institute of Bioinformatics, Center for Integrative Genomics, University of Lausanne, Switzerland

4.50pm–5:00pm
Poster prize presentation and Closing remarks

Professor Mike Barrett

5:00pm–6:30pm
DRINKS RECEPTION IN THE MUSEUM

Speaker abstracts

The cellular uptake of pharmaceutical drugs: a problem not of biophysics but of systems biology

Professor Douglas B. Kell, Research Chair in Bioanalytical Sciences, School of Chemistry and Manchester Institute of Biotechnology, University of Manchester, UK; Chief Executive and Deputy Chair of the Biotechnology and Biological Sciences Research Council (BBSRC)

It is widely assumed that pharmaceutical drugs and other xenobiotics enter cells by diffusion across phospholipid bilayer portions of their membranes, essentially according to their lipophilicity. This is not correct, and an abundance of evidence indicates that they get into cells by hitchhiking on carriers normally used for transporting intermediary metabolites [1-5]. Semantically encoded knowledge of metabolic networks [6] allows one to infer, as is the case [7], that successful drugs are more like metabolites than are typical library molecules. Understanding this makes the problem of modelling and understanding cellular drug uptake a problem of systems biology rather than one of biophysics.

1. Dobson PD, Kell DB: Carrier-mediated cellular uptake of pharmaceutical drugs: an exception or the rule? Nat Rev Drug Discov 2008; 7:205-220.
2. Dobson P, Lanthaler K, Oliver SG, Kell DB: Implications of the dominant role of cellular transporters in drug uptake. Curr Top Med Chem 2009; 9:163-184.
3. Kell DB, Dobson PD: The cellular uptake of pharmaceutical drugs is mainly carrier-mediated and is thus an issue not so much of biophysics but of systems biology. In Hicks MG, Kettner C (eds.): Proc Int Beilstein Symposium on Systems Chemistry. Berlin: Logos Verlag, 2009:149-168 - http://www.beilstein-institut.de/Bozen2008/Proceedings/Kell/Kell.pdf.
4. Kell DB, Dobson PD, Oliver SG: Pharmaceutical drug transport: the issues and the implications that it is essentially carrier-mediated only. Drug Disc Today 2011; 16:704-714.
5. Lanthaler K, *et al.* Genome-wide assessment of the carriers involved in the cellular uptake of drugs: a model system in yeast. BMC Biology 2011; 9:70.
6. Herrgård MJ, *et al.* A consensus yeast metabolic network obtained from a community approach to systems biology. Nature Biotechnol 2008; 26:1155-1160.
7. Dobson PD, Patel Y, Kell DB: "Metabolite-likeness" as a criterion in the design and selection of pharmaceutical drug libraries. Drug Disc Today 2009; 14:31-40.

Insights from *Plasmodium* metabolomics

Dr Manuel Llinás, Richard B. Fisher Preceptorship in Integrative Genomics, Princeton University, Princeton, New Jersey, USA

The genome of *Plasmodium falciparum* indicates that the metabolic pathways utilized by this organism are highly unique. Our laboratory has begun to characterize various aspects of parasite metabolism using high accuracy mass-spectrometry to simultaneously measure metabolites from complex cellular extracts from parasite-infected cells. The approaches we are using allow us to assay various aspects of the *P. falciparum* metabolome including the interaction of *Plasmodium* with the host red blood cell, metabolic fluxes through known biochemical pathways, and the genetic underpinnings of metabolic variability in the progeny of *Plasmodium* genetic crosses. Results from these studies are beginning to unravel the divergence of metabolism in *P. falciparum* and promise to provide unique avenues for future drug-intervention strategies.

Life sciences at the tipping point

Dr Peter Silvester, President, Europe, Middle East & Africa, Life Technologies™

Throughout history the democratization of key technologies has driven change that defined the era — from steam engines that powered the Industrial Revolution, to semiconductors that power the World Wide Web. While the 20th Century was defined by the physical sciences, the life sciences will shape the 21st Century, providing solutions to some of the major challenges facing the modern world: security, energy, food, and affordable healthcare. One technology has brought together physics and biology to drive understanding of the basis of life itself. The availability of fast, simple and inexpensive DNA sequencing will provide the engine to start the long promised genomic revolution.

Cancer polyomics: from discovery to patient care

Professor Andrew V. Biankin, The Kinghorn Cancer Centre, and the Cancer Research Program, Garvan Institute of Cancer Research, Sydney, New South Wales, Australia; The Australian Pancreatic Cancer Genome Initiative — International Cancer Genome Consortium (ICGC)

Pancreatic cancer (PC) is the fourth leading cause of cancer death in our society, with a mortality that virtually parallels its incidence, a median survival of < 12 months even with maximal therapy, and a 5-year survival rate of < 5%. The diversity of clinical outcomes and the molecular heterogeneity of histopathologically similar cancer types, incomplete knowledge of the genomic aberrations that drive carcinogenesis and the lack of therapeutics that specifically target most known genomic aberrations necessitates large-scale detailed analysis of cancer genomes to identify novel potential therapeutic strategies. As part of the International Cancer Genome Consortium, the Australian Pancreatic Cancer Genome Initiative, together with the Baylor College of Medicine and the Ontario Institute of Cancer Research we use exomic sequencing and copy number analysis to define the genomic aberrations that characterise a large, clinically focused and prospectively accrued cohort of patients with pancreatic cancer. We develop stratified, molecular-phenotype-guided therapeutic strategies using existing therapeutics that are either rescued, repurposed, in development, or are known to be effective in an undefined subgroup

of PC patients. These are then tested in primary-patient-derived xenografts and cell lines from the deeply characterised cohort mentioned bove. In addition, we are launching a clinical trial named IMPaCT (Individualised Molecular Pancreatic Cancer Therapy): this trial randomises patients with metastatic disease to either standard first-line therapy with gemcitabine, or to a molecular-phenotype guided approach using next-generation-sequencing strategies to screen for actionable mutations defined through the ICGC effort.

Polyomics to dissect mechanisms regulating mesenchymal cells in cancer, development and adult tissue maintenance

Professor Nick Hastie, Director, MRC Human Genetics Unit; Director, Institute of Genetics and Molecular Medicine (IGMM), University of Edinburgh, UK

There is considerable topical interest in mesenchymal cell biology, particularly in the context of stem/progenitor cells, and the reciprocal switches that may convert mesenchymal cells into epithelia and vice versa. Wilms' tumour is a paediatric kidney cancer that is a remarkable example of malignancy arising through disrupted development. Mutation in the Wilms' tumour gene, WT1, may lead not only to the eponymous tumour but also to severe glomerular renal disease, gonadal dysgenesis and heart problems. We have shown that WT1 is a key regulator of mesenchymal cell biology during development and in adult tissue homeostasis and repair. Whereas WT1 is required for the mesenchymal to epithelial transition (MET) that produces kidney nephrons, in the heart it is required for the epithelial to mesenchyme transition (EMT) that produces proliferating coronary vascular progenitors. Remarkably, deletion of WT1 in adult mice leads to acute multiple organ failure. Within 10 days, not only is kidney function impaired, but there is dramatic loss of body fat, bone, spleen and exocrine pancreas. Furthermore, there is growing evidence that WT1 is required for the response of tissues to damage. We hypothesize that these dramatic effects result from systemic and local, cell-autonomous effects of WT1 deletion mainly on mesenchymal cells, including stem/progenitor cells. WT1 is a transcription factor but evidence from our group suggests it also binds to RNA, regulating various post-transcriptional processes. To dissect the physiological, cellular and molecular processes by which WT1 exerts these vital functions, we are using a variety of omic technologies. These include genomic and transcriptomic analysis, by arrays and next generation sequencing, and proteomics using mass spectrometry and high throughput signalling arrays.

Using polyomics approaches to embrace the complexity of asthma

Professor William O. Cookson, Professor of Genomic Medicine, Imperial College London, London, UK

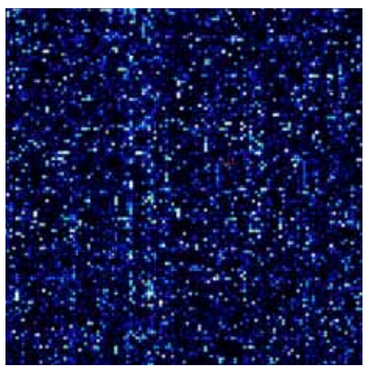
Asthma is a common syndrome that affects one child in 7 in the UK and 300 individuals worldwide. Asthma is due to a combination of partially understood genetic and environmental factors, and our group has been using genomic tools to unravel the basic mechanisms of disease. Genome-wide association studies (GWAS) have shown that genes underlying asthma susceptibility are often found in the bronchial epithelium and are thought to communicate epithelial damage to the adaptive immune system. Global measurements of gene expression and expression quantitative trait locus (eQTL) mapping have helped to assign function to GWAS top hits. Network analysis of gene expression and methylation patterns has identified cell-specific modules of genes that mediate asthmatic inflammation. Hubs in these networks define novel targets for therapeutic intervention. Asthma is rare in rural communities, and throughout the world a rich microbial environment is protective against asthma and against allergies. Our group has used metagenomic techniques to show that the airway microbiome differs significantly between asthmatic and normal subjects. Measurements of gene expression by next generation sequencing of airway biopsies and model systems of bacterial and epithelial cell co-cultures will allow direct understanding of the interactions between host and the microbiome. Although all these approaches provide formidable volumes of highly dimensional data, careful study design and appropriate analytic techniques are now leading to detailed mapping of the major pathways at work in asthma pathogenesis.

From biocuration to computational biology and bioinformatics: an example of integrative biology

Professor Ioannis Xenarios, Director, Swiss-Prot & Vital-IT, Swiss Institute of Bioinformatics, Center for Integrative Genomics, University of Lausanne, Switzerland

The presentation will focus on several examples that demonstrate the advantages of bringing together the expertise of biocurators, bioinformaticians, statisticians and biologists to address modern challenges in biology and/or medicine. The examples will be taken from the biology of social ants and from human genetics and oncology, and in each case the focus will be placed on the necessity and the benefits of gathering a wide range of expertise to successfully address research questions. The infrastructure requirements for such endeavours will be also highlighted.

The Swiss-Prot group is part of a large consortium comprising the Swiss Institute of Bioinformatics (SIB), the European Bioinformatics Institute (EBI) and the Protein Information Resource (PIR); these form a common project called the UniProt Knowledge Base. This project has supported the annotation of protein functions for more than a decade and is fundamental for the maintenance of biological knowledge. The Vital-IT infrastructure is the high performance and high throughput computing centre that provides the means and resources as well as the competency to perform present day computational challenges. Together, Swiss-Prot and Vital-IT constitute a unique resource for Swiss researchers and the international community.



Poster abstracts

Posters will be displayed on the first floor stair landing and in the library on the first floor. Poster presenters are requested to stand by their posters during coffee breaks and lunch.
Names in bold type below indicate presenting authors.
The winner of the poster prize competition will be announced at the end of the day.

1/ Development of MALDI-TOF platform to classify patients with diabetic nephropathy (DN) in a clinical setting, based on a panel of proteomic biomarkers.

Albalat, Amaya; **Stalmach, Angelique;** Bitsika, Vasiliki; Husi, Holger; Siwy, Justyna; Golovko, Igor; Persson, Frederik; Mischak, Harald
University of Glasgow, UK

INTRODUCTION: The use of capillary-electrophoresis coupled to mass spectrometry (CE-MS) applied to urinary proteomics has resulted in the discovery of novel biomarkers of chronic conditions such as acute kidney disease (AKI), chronic kidney disease (CKD), coronary artery disease or diabetic nephropathy (DN). Although a robust technical platform, CE-MS requires technical experience and is expensive and time consuming, preventing its application in routine clinical settings.

OBJECTIVE: This study aims at establishing an alternative analytical platform (MALDI-MS) which would be acceptable in a clinical setting, to assess an already existing biomarker panel by CE-MS.

METHODS: We used urine samples of healthy volunteers (n = 20) and DN patients (n = 20). Their urinary peptide profile was first analysed using CE-MS and we use the DN-biomarker panel [1] to classify and ensure the presence of relevant peptides. The method development for MALDI-MS focused on the choice of target plate and pre-fractionation methods to establish an acceptable dynamic range of concentrations which would accommodate patient sample variances and ensure clinical applicability. Emphasis on the reproducibility of signal intensities was addressed to ensure the detection of a dynamic range of peptides in a linear fashion.

RESULTS: Sample preparation adapted from the CE methodology on an Anchorchip plate using the dried droplet method was able to detect a significant number of peptides, some of which corresponded to the DN biomarker panel published by Rossing et al. [1], with good mass accuracy. The development of an in-house algorithm based on Visual Basic commands was applied to determine the normalised intensities from the range of dilutions, by linear regression analysis. This algorithm was capable of detecting the range within which peptides behave linearly (slope of the regression line close to 0), with a good fit of the data (78-80% of the r2 values above 0.8). Subsequently, a biomarker model was designed based on the selection of 16 samples (n = 8 cases and n = 8 controls), and tested in the remaining subset (n = 32). The area under the ROC curve was 0.857 ($p < 0.0001$) with a sensitivity of 100% and a specificity of 71.4%, for a criterion value of <=0.

CONCLUSIONS: Data indicates that MALDI is associated with certain challenges and the work highlights the difficulties and considerations to take into account when translating research outcomes from bench to bedside. Nonetheless, we have successfully developed a methodology that allows the classification of patients with DN with good accuracy using MALDI-MS. This methodology could be used in a clinical setting upon validation of these results.

REFERENCES 1. Rossing K, Mischak H, Dakna M, Zürbig P, Novak J, Julian BA, Good DM, Coon JJ, Tarnow L, Rossing P. Urinary Proteomics in Diabetes and CKD. J Am Soc Nephrol 2008; 19: 1283-1290.

2/ IDEOM: IDentification and Evaluation Of MS-based metabolomics data.

Darren J. Creek*, Andris Jankevics^$, Karl E.V. Burgess^, Rainer Breitling^, Michael P. Barrett^
University of Melbourne, Australia; ^University of Glasgow, UK; $University of Groningen, The Netherlands

Mass spectrometry (MS) focused metabolomics allows rapid and sensitive detection of many low molecular weight metabolites in a single experiment, providing a promising tool for the global phenotypic analysis of biological systems. Meaningful interpretation of the complex data generated by this approach currently poses a major bottleneck, restricting widespread application of MS-based metabolomics. IDEOM (http://mzmatch.sourceforge.net/ideom.php) is a user-friendly application for the analysis and interpretation of MS-based metabolomics data. IDEOM facilitates all necessary processing steps including peak picking, noise filtering, metabolite identification, statistical analysis and data visualisation. IDEOM is operated through a graphical user interface in Microsoft Excel, making it accessible for biologists without specialist informatics expertise. Data processing is automated either within Excel VBA, or through open-source packages in R (XCMS and mzMatch.R), and further metabolic pathway analysis is accessible by export to freely available web applications. IDEOM provides advanced noise filtering and metabolite identification for high resolution LC-MS, enhancing data interpretation by the removal of many false identifications that traditionally hinder untargeted analysis. Extensive annotation of biochemical and analytical metadata in IDEOM simplifies the analysis of all types of MS data, and can be applied to untargeted, targeted and/or stable-isotope labelled metabolomic analyses. The software is demonstrated by application to the pathogenic parasite *Trypanosoma* brucei for the identification of active metabolic pathways and determination of the mode of action of trypanocidal compounds.

3/ The Scottish Metabolomics Facility.

Karl Burgess, Stefan Weidt, Suzanne Eadie, Isabel Vincent, Darren Creek, Mike Barrett
University of Glasgow, UK

The Scottish Metabolomics Facility (ScotMet) was founded in 2009 with a grant from SULSA to the Universities of Glasgow and Strathclyde. Now part of Glasgow Polyomics, ScotMet builds on long-standing expertise in separations technology, mass spectrometry, bioinformatics and systems biology at both centres. Scotmet's facilities include liquid chromatography-accurate mass spectrometry, gas-chromatography-mass spectrometry, nuclear magnetic resonance, and a novel bioinformatics pipeline to provide comprehensive analysis of the metabolome of any biological system. ScotMet provides a world-class facility with a focus on systems biology. Experts in metabolomics work alongside leaders in the fields of genomics, proteomics and bioinformatics who can provide training, sample analysis and collaboration on experimental design and data handling.

4/ MzMatch/mzMatch.R: an open source software for the sequential processing and analysis of mass spectrometry data.

Jankevics, Andris*^; Chokkathukalam, Achuthanunni^; Breitling, Rainer*^
***University of Groningen, The Netherlands;**
^University of Glasgow, UK*

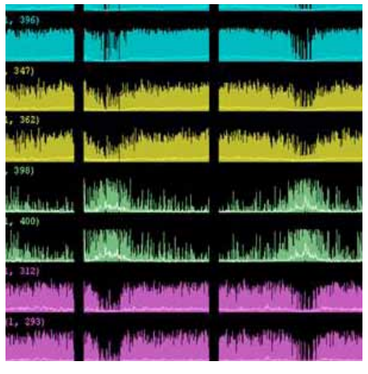
Liquid Chromatography Mass Spectrometry (LC-MS) is a powerful and widely applied method for the study of biological systems, biomarker discovery and pharmacological studies. LC-MS measurements are, however, significantly biased by several factors, including: (1) ionisation suppression/enhancement, interfering with the correct quantification of analytes; (2) detection of large amounts of derivative ions, increasing the complexity but not the information content; and (3) machine drift during extensive sample sequences, altering mass and quantification accuracy. Here we present our efforts to produce a customizable pipeline for mass spectra calibration [1], processing [2], filtering [3-5], annotation [3], statistical analysis and visualization. The benefits of such a processing pipeline include an easy "rewind" option to roll back to intermediate steps in the data analysis and increased verifiability of the performance of the analytical methods. The developed approaches have provided us with a fuller understanding of the information content of our observations and a better assessment of the metabolites detected in the analyzed data sets [6]. Currently we are extending the pipeline to include advanced techniques such as Bayesian statistical models and stable isotope labelling studies. We illustrate the application of the mzMatch pipeline in a variety of large metabolomics studies, ranging from work on bacterial cell extracts [7,8] to human biofluids and cancer cells.

REFERENCES [1] Scheltema RA, Kamleh A, Wildridge D, Ebikeme C, Watson DG, Barrett MP, Jansen RC, Breitling R (2008) Proteomics 8 (22):4647–4656. [2] Scheltema RA, Jankevics A, Jansen RC, Swertz MA, Breitling R (2011) Anal. Chem. 83 (7):2786-2793 [3] Scheltema RA, Decuypere S, Dujardin JC, Watson D, Jansen RC, Breitling R (2009) Bioanalysis 1 (9):1551-1557. [4] Jankevics A, Merlo ME, de Vries M, Vonk RJ, Takano E, Breitling R (2011) Metabolomics In Press, DOI: 10.1007/s11306-011-0341-0. [5] Creek DJ, Jankevics A, Breitling R, Watson DG, Barrett MP, Burgess EV (2011) Anal. Chem. 82 (22): 8703-8710 [6] Jankevics A, Merlo ME, de Vries M, Vonk RJ, Takano E, Breitling R (2011) Proteomics 11 (24):4622-4631 [7] Merlo ME, Jankevics A, Takano E, Breitling R (2011) Bioanalysis 3:2443–2458. [8] Nguyen QT, Merlo ME, Medema MH, Jankevics A, Breitling R, Takano E (2012) FEBS Lett. 586(15):2177-2183

5/Biomarkers of immune function of the bovine nasal mucosa.

M. Faizal Ghazali, N. Nicholas Jonsson, R. Burchmore, P. David Eckersall
University of Glasgow, UK

INTRODUCTION: Bovine nasal secretion has not been well characterised but may provide useful indicators of immune function and status. The aim of this study was to undertake a biochemical and proteomic analysis of normal bovine nasal secretion, with a view to identification of biomarkers for immune function of the bovine nasal mucosa.
METHODOLOGY: Nasal secretions were collected from thirty eight clinically healthy Holstein-Friesian cows aged 2-5 years on the University of Glasgow Cochno Farm. The nasal secretions were examined for biochemical composition using an automatic biochemical analyzer, protein concentration using a Bradford assay and IgA and IgG concentrations using specific ELISAs. Sections of bovine nasal mucosa were prepared for histological study and endogenous alkaline phosphatise stained with an enzyme specific kit. The nasal secretion proteome was separated with 2-dimension electrophoresis followed by SDS-PAGE on 4-12% polyacrylamide gels and stained with Coomassie blue. Protein spots were excised and subjected to tryptic in-gel digestion. Samples were then analysed using MALDI-TOF/TOF mass spectrometer. Analysis of the MS and MS/MS spectral data was performed using SwissProt database version 57.15.
RESULTS: Biochemical analysis revealed that alkaline phosphatase (ALP) activity was higher in all nasal secretion samples, with a median of 1193 U/L (range: 144 - 2392 U/L) compared to the reference range for bovine serum which is 20-280 U/L (laboratory reference range). Other biochemical analytes were within or near the reference range for serum. The concentrations of IgA and IgG in nasal secretion were between 0.45 to 1.82 g/L and 0.17 to 1.88 g/L respectively. Histological study confirmed a high presence of ALP activity in the bovine nasal epithelium and serous gland of the nasal mucosa. Proteomic investigation revealed seven major proteins in bovine nasal secretion. Serum proteins: albumin, fibrinogen, apolipoprotein A1s and serotransferrin were identified in the nasal secretion. In addition, lactotransferrin, an anti-bacterial protein known to occur in secretions such as milk and saliva, odorant binding protein, known to be involved in scent recognition and glutathione-S-transferase, an enzyme capable of detoxifying noxious compounds were putatively identified.
CONCLUSION: This is the first study to show that ALP is synthesized and secreted from the nasal epithelium. Its function in this tissue is not clear, although might be related to the known effect of alkaline phosphatases on the lipopolysaccharides of Gram-negative bacteria. Proteomic analysis of the nasal secretion has revealed the high abundance of proteins in this fluid. This will enable the development and validation of biomarkers in this fluid to study the pathophysiological responses of the host against respiratory diseases.



6/ Extending a dynamic model of trypanosome metabolism: challenges for iterative systems biology.

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BACKGROUND: Systems biology is widely described as an iterative process, where models are used to form hypotheses predicting biological behaviour, which can be tested by wet lab experiments, and the obtained data is subsequently used to improve the initial model leading to new hypotheses and the next round of experimentation. Here we demonstrate the surprising challenges faced in the modular extension of a successful and well-curated model, the Bakker model of energy metabolism in the tropical parasite *Trypanosoma* brucei, by a single additional pathway.
METHODS: The current model of trypanosomal glycolysis was modularly extended with the pentose phosphate pathway, using a combination of literature derived and measured parameter values. Reverse genetics was used to test hypotheses that were postulated during the iterative process of model extension.
RESULTS: Incorporation of the pentose phosphate pathway, partly localized in a unique organelle called the glycosome, into a model of *T. brucei* glycolysis caused a lethal imbalance in bound phosphates in the glycosome. Two mechanisms to relieve this problem were explored: (i) the presence of a glycosomal ATP:ADP antiporter, and (ii) the presence of a ribokinase enzyme working in the direction of ribose production. The ribokinase hypothesis was tested experimentally, and catalytic activity and reverse genetics support a previously unexpected essential role of ribokinase in *T. brucei*. Furthermore, the resulting model was capable to mimic regulation of the pentose phosphate pathway by the amount of oxidative stress, and predicts why 6-phosphogluconate dehydrogenase is an essential enzyme.
CONCLUSIONS: The modular extension of a dynamic model as demonstrated here will be used for further extending the current model with the trypanothione pathway. Crucial in the model building process has been to stress the model and find conditions where the model breaks. This is of general interest for extension of any dynamic model of metabolism.

7/ Development of a high throughput combinatorial microarray platform for identifying novel glycolipid targets in inflammatory neuropathies.

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Glycolipid targets for autoantibodies have been firmly implicated in the pathogenesis of various autoimmune neuropathies, including the motor axonal variant of Guillain Barré syndrome (GBS), Fisher syndrome, and IgM paraproteinaemia; however, identification has remained elusive for other clinical subtypes. The field of anti-glycolipid antibody research has predominantly focused on screening antisera against single glycolipid species, however recent research has demonstrated that pairs of structurally distinct glycolipids interact to form heteromeric complexes that create neo-epitopes for autoantibodies in neuropathy cases. When considering serum screening methods for identification of heteromeric complex binding, current ELISA techniques are completely impractical, being handling-intensive, insensitive and wasteful of scarce reagents. To address this, we have developed a combinatorial microarray screening methods that is based on a refinement and miniaturization of our current combinatorial glycoarray assay which has already been successfully employed to identifying new antigenic targets in inflammatory neuropathy.

8/ A transcriptomic based approach to the detection of recombinant human erythropoietin doping.

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The use of recombinant human erythropoietin (rHuEpo) is prohibited by the World Anti-Doping Agency. An OMICS-based longitudinal screening approach has the potential to improve further the sensitivity of current detection methods such as the Athlete Biological Passport.
AIM: To assess the effects of rHuEpo on blood gene expression profiles in order to identify a "molecular signature" of rHuEpo doping.
METHODS: 19 trained males received rHuEpo injections of 50 IU/kg body mass every two days for 4 weeks. Blood was obtained 2 weeks before, during and 4 weeks after administration. RNA was extracted from blood stabilized in Tempus RNA tubes, amplified, labelled and hybridized to Illumina HumanHT-12v4 Expression BeadChips. Expression data was analyzed using RankProducts with a 5% false discovery rate.
RESULTS: rHuEpo worked effectively as confirmed by the ~20% increase in total haemoglobin mass (947 ± 112 vs. 1138 ± 137 g, $p < 0.001$). Data for 9 subjects is presented. Relative to baseline, 110 and 1859 genes were differentially expressed 2 days after the first injection and during the last 2 weeks of administration, respectively. 1516 and 496 genes were differentially expressed 2 weeks and remained differentially expressed 4 weeks after administration, respectively. Using an additional 2 fold-change threshold, we identified a signature pattern of 18 genes up-regulated during rHuEpo and subsequently down-regulated at 2 and 4 weeks after administration.
CONCLUSION: These results provide the strongest evidence to date that OMICS technologies such as gene expression have the potential to add a new dimension to the Athlete Biological Passport in terms of specificity and sensitivity for drugs detection, not confined only to rHuEpo.

9/ Examination of molecular basis of gametocytogenesis in malaria parasites.

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Gametocytogenesis in *Plasmodium* is a critical step for completion of the parasite life-cycle and represents a major population bottleneck. A progressive decrease in gametocytogenesis has been observed following prolonged culture *(P. falciparum*) and mechanical passage *(P. berghei)* of bloodstream forms. This loss of gametocytogenesis is not associated with gross genetic variations; however, smaller mutations remain undetected or unaddressed and certain, possibly multiple genetic loci may control various steps in gametocytogenesis and these are the loci that become mutated and positively selected during repeated asexual multiplication. We explored the hypothesis that the loss of gametocytogenesis is reflected in the parasite genome organization at genome sequence and/or epigenetic level. Ten parallel infections of mice with *P. berghei* ANKA clone 820 (produces RFP in female and GFP in male gametocytes) were set up. The parasites were asexually maintained in mice for about 52 weeks by weekly mechanical passages to

naïve mice. Each week, gametocytemia was monitored with Giemsa-stained smears and FACS and the parasites were cryopreserved. Three out of potential ten lines became Gametocyte Non-Producers (GNPs) during the passage period. The GNPs and the parental producer lines were sequenced using the Illumina platform and comparatively analyzed for SNPs/indels. Data analysis reveals one and the same single gene which is uniquely mutated in each of the 3 GNP lines. Evidence from pre-existing GNP lines also supports the involvement of this gene in gametocytogenesis. However, other identified point mutations that might have a role in gametocytogenesis are also being scrutinized. Gene knockout studies of the identified gene using a variety of approaches produced the GNP phenotype. Complementation studies in the knockouts and the natural mutants are ongoing and a more detailed biochemical and cell biological characterization of the gene will be presented.

10/ Effects of recombinant human erythropoietin on targeted blood metabolomic profiles in endurance trained individuals.

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BACKGROUND: OMICS-based longitudinal screening approaches have the potential to improve further the sensitivity and specificity of the Athlete Biological Passport (ABP) enforced by the World Anti-Doping Agency.
AIM: To assess the effects of repeated recombinant erythropoietin (r-HuEPO) administration on blood metabolomic profiles in order to identify a potential metabolic trend related to r-HuEPO doping.
METHODS: 20 aerobically trained men (mean ± SD, age: 26.5 ± 5.0 yr, body mass: 74.8 ± 7.7, height: 179.5 ± 5.4 cm) received r-HuEPO injections of 50 IU.kg-1 body mass every two days for 4 weeks. Blood samples were obtained 2 weeks before, during rHuEpo and 4 weeks after administration. Plasma samples from 9 subjects (n=84) were analyzed by using LC-MS (Exactive Orbitrap) in both positive and negative mode to quantify some 400 unique metabolites (i.e. targeted profiling). Data were normalized and subjected to multivariate statistical analysis, incorporating 'date order' and 'participant' factors into the model and thus enabling comparison of the targeted sample spectrum between conditions (pre-, during and post-r-HuEPO administration).
RESULTS: The perturbation involving r-HuEPO worked effectively as confirmed by the ~20 % increase in total haemoglobin mass at the end of the r-HuEPO administration (947 ± 109 vs. 1131 ± 131 g, $p < 0.001$). Separation of each condition was achieved after careful modelling. Principal component analysis (PCA) confirmed clustering between each phase as well as a distinct separation of post-r-HuEPO from pre- and during administration. The adapted multivariate model incorporates 'date order' (continuous) effect and 'participant' (factorial) effect; this approach allows for clear differentiation and trend separation of the post r-HuEPO phase.
CONCLUSION: These preliminary results support the notion that the abundance of targeted metabolites in blood could facilitate the identification of r-HuEPO doping and potentially add a new dimension to the ABP.

11/ PfGail: A parasite quantitative trait locus controlling *Plasmodium falciparum* infectivity in *Anopheles gambiae* mosquitoes.

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The prevalence (% infection) and intensity (number of oocysts per mosquito) of infection in *A. gambiae* mosquitoes have been measured for 20 progeny clones from the 3D7 x HB3 genetic cross of *P. falciparum.* These clones have also been genotyped using a custom-built Affymetrix molecular inversion probe 10K malaria SNP array with a coverage of ~1 SNP per 3 kb to generate a genetic map. We have used a quantitative trait locus (QTL) approach to map the parasite loci contributing to differences in prevalence and intensity of infection. Here we present data showing that a major locus on chromosome 12 contributes both to prevalence and infection intensity phenotypes. This locus, which we have named *P. falciparum gambiae* infectivity locus 1 (PfGail1), is responsible for 94% and 44% of the observed variation in infection intensity and prevalence respectively. The locus contains 27 open reading frames. Analysis of expression of the 27 ORFS in *P. falciparum* gametocyte, ookinete and oocyst material revealed only 8 genes expressed in these stages, thus narrowing down the candidate genes. Further details of the 8 loci will be presented. This study demonstrates for the first time a single parasite QTL having a major effect on mosquito infection in *P. falciparum.*

12/ Deep re-sequencing of *DPYSL2* exons reveals novel variation in splicing and exon usage patterns in schizophrenia patients and controls.

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Dihydropyrimidinase-like 2 *(DPYSL2)* is an emerging candidate risk gene for schizophrenia. We and others have shown association of *DPYSL2* gene variants with schizophrenia in case-control association studies and our data show that *DPYSL2* is differentially expressed in the prefrontal cortex of schizophrenia patients (compared with controls) and in a rodent PCP model of cognitive deficits. Further, we have revealed allele-specific transcript levels associated with exonic SNPs in *DPYSL2*. Recently, it emerged that differential expression of *DPYSL2* protein in brain regions with clinical relevance to schizophrenia is one of the most reproducible findings across proteomic studies. *DPYSL2* transcripts were sequenced from overlapping RT-PCR products generated from RNA isolated from post mortem prefrontal cortex of schizophrenia patients (n=18) and controls (n=18). Indexed libraries were generated from pooled RT-PCR products from each individual's sample and paired-end sequencing was performed on the Illumina Genome Analyzer II. The data underwent quality control measures using an automated pipeline, then were aligned to the reference genome sequence using Tophat and further analysed using custom scripts. Exonic variants were screened using the Genome Analysis Toolkit. Splice site variation was identified by Tophat and custom scripts and visualised in the UCSC Genome Browser. Approximately 500,000 indexed sequence reads of 85 nucleotides were generated per sample. Novel alternative splicing patterns at the 5' end of the gene, multiple novel exons or exon boundaries and novel transcript isoforms involving exon skipping were identified. Analysis of the functional consequences of the transcript variation we have revealed is ongoing, and RT-PCR is being used to validate the findings.

13/ Metabolomic profile associated with hepatic insulin resistance in nondiabetic subjects: results from the RISC study.

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Hepatic insulin resistance (Hep-IR) is the major determinant of elevated fasting plasma glucose (FPG) and therefore characterizes subjects at risk for type 2 diabetes. Since the assessment of Hep-IR requires tracer infusion, we used untargeted global metabolomic analysis to identify potential biomarkers in a nondiabetic population. The RISC cohort comprised 1,222 nondiabetic, normotensive European subjects (age 44±8 years (mean±SD) [range 30-60], BMI 25.5±4.1 kg/m2, [range 16.9-43.9]) phenotyped for glucose tolerance by OGTT, peripheral insulin resistance (by euglycemic hyperinsulinemic clamp), and Hep-IR index (validated against tracer infusion in a subgroup of 380 subjects). In the entire cohort we measured by mass spectrometry (Author WG, www.metabolon.com) a panel of metabolites and correlated them with Hep-IR index, liver enzymes AST/ALT), and fatty liver accumulation assessed using the recently validated fatty liver index (FLI). After adjusting for centre, sex, and age, the metabolites that remained independently associated with Hep-IR index by multiple linear regression analysis were: H-hydroxybutyrate and creatine in a positive manner (partial r = 0.12 and 0.17 respectively), and J-hydroxybutyrate, oleoyl-LPC, AST/ALT, linoleoyl-lysophosphocholine (LPC), and glycine in a negative manner (partial r = -0.16, -0.15, -0.15, -0.13, -0.07, p=0.01-0.0001). Similar correlations were found also when ln(FLI) was used as dependent variable: H-hydroxybutyrate, creatine, and palmitoyl-LPC correlated in a positive manner (partial r = 0.12, 0.15 and 0.07), J-hydroxybutyrate, linoleoyl-LPC, AST/ALT, serine and glycine, in a negative manner (partial r = -0.23, -0.22, -0.20,-0.09, -0.05, p=0.01-0.0001).
CONCLUSION: In nondiabetic subjects, metabolites associated with oxidative stress and metabolic overload are new biomarkers for hepatic insulin resistance and fatty liver.

14/ Absolute metabolite concentrations and metabolic changes associated with oxidative stress and different stages of cell growth in *Trypanosoma brucei*.

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Human African trypanosomiasis (HAT) is a neglected tropical parasitic disease in sub-Saharan Africa caused by the protozoan parasite, *Trypanosoma brucei* (*T. brucei*) and transmitted by tsetse flies. It is fatal if untreated so effective drug treatment is necessary. New drugs are urgently required to eliminate the disease and so discovery of new targets for chemotherapy is of great importance. LC-MS based metabolomic studies enable simultaneous measurement of a number of the small molecule metabolites in biological systems and can give information on how drugs perturb metabolism. However, although the relative quantification of metabolites gives us information regarding cell responses, absolute metabolite concentrations are critical to perform metabolic flux analysis and ultimately construct a quantitative mathematical models of metabolic flux. Quantitative modelling will play a critical role in developing optimised anti-parasite drugs. In order to obtain absolute concentrations, uniformly (U)-13C-labelled *E. coli* extract can be used as an internal standard to overcome non-linear responses in MS with labelled metabolites behaving identically to their unlabelled forms in sample extract. Therefore, absolute intracellular concentrations of metabolites can be calculated by adding known amounts of U-13C-labelled cell extract prior to the extraction procedure. *T. brucei* bloodstream forms at different stages of cell growth in culture were analysed using LC-MS for metabolite profiling and absolute quantitative analysis. A total of 58 metabolites were absolutely quantified and key mass ions were determined by using univariate and multivariate analyses from the MS data. We then use this approach to reveal not only metabolic changes caused by different cell densities but also metabolic responses to oxidative stress.

15/ Roles of metabolism in the development of resistance to trypanocidal drugs.

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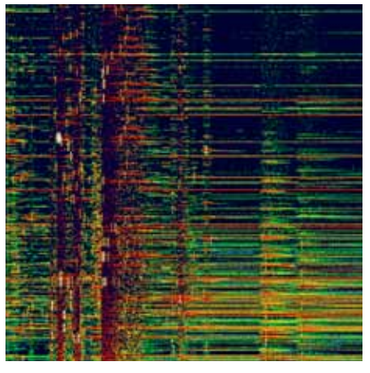
Metabolomics offers a means of rapidly identifying mechanisms for drug resistance. Isometamidum, homidium and diminazene are the three veterinary drugs used to treat animal trypanosomiasis, a disease that decimates livestock in Africa. Isometamidium is active against *T. congolense* and *T. vivax* in domestic animals. It is also used against *T. brucei* and *T. evansi* causing the disease in horses, camels and donkeys. It is mainly used for prophylactic purposes. Drug resistance to veterinary drugs is prevalent in 17 African countries out of 37 in which animal trypanosomiasis is endemic. In these countries 50 to 70 million animals are at risk from the disease. Drug resistance to isometamidium chloride (ISMM) is more common than to the other two drugs. Despite these drugs being in use for a long time, their mode of action and mechanisms of resistance has just begun to emerge or is yet to be worked out. The reduction in the mitochondrial membrane potential has previously been proposed to play a role in ISMM and ethidium bromide resistance. Here we set out to use metabolomics, to identify the role of energy metabolism in ISMM resistance development in both bloodstream form (BSF) and procyclic form (PCF) of *T. brucei*. *T. congolense* shares aspects of its metabolism with both of these forms of *T. brucei* that grow readily in in vitro culture. ISMM resistance was selected more readily in BSF than in PCF *T. brucei.* Loss of the mitochondrial genome (the kinetoplast) and reduction in the mitochondrial membrane potential, accompanied resistance in BSF while resistance has been exceptionally difficult to select in PCF. The metabolomic comparison of wild type and derived ISMM resistance clones is currently in progress.



16/ Discovery based metabolomics reveals novel host and parasite mechanisms in *Plasmodium*.

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An untargeted discovery based metabolomics study to compare metabolomes of host erythrocytes and *Plasmodium berghei* asexual and sexual stage parasites showed that reticulocytes offer a richer environment than normocytes for parasites to grow and may offer redundancy to some parasite genes in intracellular stages owing to species specific compensation in *Plasmodium* species preferentially invading reticulocytes. Also, a potential new source of energy in exflagellating male gametocytes was identified during the metabolomics study indicating that glycolysis may be supplemented by other metabolic reserves during gamete formation.

17/ A Bayesian approach to metabolite peak identification in liquid chromatography mass spectrometry experiments.

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In recent years, the use of liquid chromatography coupled to mass spectrometry (LC-MS) has enabled the high-throughput profiling of the metabolic composition of biological samples. However, the resulting surfeit of data poses problems, with extensive processing needed in most cases to make sense of the mass of information. Recent efforts have provided much relief in this regard [1, 2], but much work remains in improving the accuracy and reliability of these automated techniques. Here, we present a novel computational technique that is designed to deal with a problem inherent in MS data, that of detecting (and potentially removing) derivatives of a substance of interest, which are created as artefacts of the technology and tend to make up roughly 80% of detected signals. Our technique uses a Bayesian statistical model, that not only identifies derivatives, but automatically clusters them in order to increase the detection power for the peak of interest. The arbitrary thresholds and unstable maximum operators of currently used greedy algorithms are eschewed in favour of a statistical clustering treatment that inherently tolerates noise in both the peak intensities and peak shapes. Also, because of the use of the Bayesian paradigm, a measure of confidence in the derivative detection can be given. This technique can be easily incorporated into existing open processing pipelines, such as mzMatch, in order to increase the accuracy of the analysis by eliminating spurious base-peak detections. It can also be easily joined to previous work on Bayesian metabolite identification [3].

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18/ Insights into childhood SCID-X1 gene therapy induced leukemias.

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Gene therapy for SCID-X1 disease has been hampered by the emergence of lymphomas where the therapeutic virus had inserted near the gene *LMO2*. From studies in murine models it has been suggested that frequent vector activation of *LMO2* is due to oncogenic collaboration with the therapeutic gene (*IL2RG*) or to disease-specific perturbation of hematopoiesis. We explored these hypotheses further by examining retroviral leukemogenesis in *Il2rg*-deficient or *IL2RG* transgenic mice. While the *IL2RG* transgene had relatively minor effects on the wild-type background, we found that *Il2rg* deficiency conferred an increased leukemic susceptibility, an expanded spectrum of tumour phenotypes and atypical marker expression. Highly sensitive analysis of proviral integrations by nrLAM-PCR and next generation sequencing revealed the complex structure of MLV-induced lymphomas where both major and minor clones display strong evidence of selection driven by viral integration. Moreover, the Il2rg null background favored recruitment of target genes including *Zmiz1*, *Lfng*, *Runx3*, *Sfpi1/PU.1*, *Ccnd2* and *Ikzf1*. Increased susceptibility and skewed gene targeting was retained despite post-natal reconstitution of the murine lymphoid system by *IL2RG*. While recruitment of *Lmo2* was rare, our results suggest that underlying disease plays a role in the susceptibility to leukemia on the background of *Il2rg* deficiency, important for the future development of safer gene therapies.

19/ The genetic basis of adaptive craniofacial divergence.

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Divergence in craniofacial characteristics is a hallmark of many adaptive radiations, and can play a determining role in resource use. The African rift-lake cichlids offer one of the most dramatic examples of adaptive radiations in vertebrates, and display a plethora of craniofacial phenotypes. The ability to hybridize these recently derived species provides a unique opportunity to determine the genetic basis of craniofacial phenotypes. We created hybrids for genetic mapping by crossing species displaying 1) an exceptionally wide jaw for scraping algae, to 2) a species with a narrow jaw for 'plucking' filamentous algae. Using next-gen sequencing we created a high density linkage map and identified a number of candidate genes related to jaw width. In tandem we also performed a population genomic comparison between wide and narrow jaw species collected from the wild. Cross referencing between data sets shows that loci related to jaw width are also under the influence of natural selection. These findings provide an important inroad into the genetic basis of adaptive craniofacial divergence which may also have relevance for analogous human syndromes.

20/ Genome-wide association study approach in elite Jamaican athletes to identify common genetic variations associated with world class athlete status.

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BACKGROUND: Elite human athletic performance is a multifactorial polygenic trait and previous candidate gene studies have been inconclusive. We performed a genome wide association study of athletic performance in a cohort of elite Jamaican athletes and matched controls to identify common genetic variants associated with this trait.
METHODS: Ninety-five Jamaican sprinters including world record holders, world champions, Olympians and winners of other major events and 102 Jamaican controls were genotyped using the Illumina® Human OmniExpress (with 730,525 markers/sample)/Omni1-Quad BeadChips (with 1,134,514 markers/sample). Standard GWAS quality control and population stratification correction was applied to the genotyping data. Association analysis was performed using an additive model.
RESULTS: After quality control steps, 462,661 single nucleotide polymorphisms (SNPs) on 88 sprinters and 87 controls were available for analysis. The genomic control inflation factor was 1.076. Nine SNPs in 6 regions showed association with P-value < 5x10-5. These hits are listed as follows in the order of SNP numbers, chromosomal locations, odds ratios and P-values: SNP (1) 8q24.3, 2.95, 9.75x10-6; SNP (2) 19q13.2, 0.33, 1.22x10-5; SNP (3) 19q13.2, 0.31, 1.72x10-5; SNP (4) 6q21.3, 3.59, 2.54x10-5; SNP (5)-(7) 8q24.3, 2.65, 2.74x10-5; SNP (8) 16p13.1, 3.80, 3.73x10-5; SNP (9) 13q34, 0.25, 4.06x10-5.
CONCLUSIONS: Nine SNPs crossed a threshold P-value of 5x10-5. Further validation of these signals in independent cohorts is ongoing. Replicated SNPs will be taken forward through fine-mapping and functional studies to identify a mechanistic basis of athleticism.

21/ mzMatch-ISO: an extension of mzMatch for the identification and relative quantification of isotope-labelled mass spectrometry data.

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Stable isotope labelling experiments have recently gained increasing popularity in global metabolomics studies providing unique insight into the dynamics of metabolic fluxes, beyond the steady-state information gathered by routine mass spectrometry. Here we describe mzMatch-ISO, a new extension to mzMatch.R that can be used for the rapid and reliable identification and relative quantification of isotope peaks in C-labelled mass spectrometry (MS) data. mzMatch.R was introduced recently as an open-source software toolbox for the MS data processing, and is the underlying platform for user-friendly software such as IDEOM. mzMatch-ISO can perform both targeted and untargeted profiling for labelled metabolites. In both these approaches, missing monoisotopic and related isotope peaks of individual samples are gap-filled from the raw data, while stringent filters exclude peak sets that are not reproducibly labelled. The outputs of mzMatch-ISO are plots that highlight trends in labelling and a table containing the area under each isotope peak in each sample for each metabolite. While the latter can be used for further statistical analysis, the former provide a convenient visual representation of the quality and quantity of labelling. For each metabolite identified four different types of plot are provided that show — a) the isotope peaks of each monoisotopic peak in each sample group; b) the ratio of monoisotopic and labelled peaks; c) the average peak area of monoisotopic and labelled peaks in each sample group; and d) the trend in the relative amount of labelling in a predetermined isotope. The power of mzMatch-ISO is demonstrated on tissue resolved 13C labelled metabolome data from cancer cells.

22/ A polyomic approach to understanding the regulatory switch between attachment and motility in *Escherichia coli* O157:H7.

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Enterohaemorrhagic *Escherichia coli* O157:H7 is a human gut pathogen that causes severe foodborne disease. It is estimated that there are over 100,000 cases annually in the US alone, with over 3000 resulting in hospitalisation and a small number of fatalities. *E.coli* O157:H7 relies on motility and attachment to seek out a favourable environment for pathogenesis and subsequently colonise host cells via its main virulence factor, the Type 3 Secretion System (T3SS). Despite O157:H7 pathogenesis being well characterised, the regulatory mechanisms behind the switch from motility to attachment (and vice versa) via environmental signalling remain poorly understood. Our lab has previously identified a novel membrane transporter protein, YhaO, which is essential in the regulation of virulence via the T3SS. The substrate of YhaO, D-serine, is toxic to O157:H7 and transport of this substrate also appears to initiate the switch to motility. This project uses a polyomic approach to understand the regulatory mechanism of YhaO on O157:H7 pathogenesis, including RNAseq transcriptomics to globally identify the regulatory switches involved in motility activation and metabolomics to understand the toxicity of D-serine. We show that D-serine dramatically affects several amino acid pools in the bacteria and alters the expression of a number of key virulence regulators resulting in a switch from the attached infectious state to a motile state.

23/ Proteome and metabolome profiling in the stroke-prone spontaneously hypertensive and congenic rat strains.

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OBJECTIVE: The stroke-prone spontaneously hypertensive rat (SHRSP) is an excellent model of human essential hypertension. Previous work identified *S1p1* and *Vcam1* as candidate genes for salt-sensitivity, in chromosome 2 congenic strains. Additionally, studies on sphingosine-1-phosphate (S1P) stimulated VSMCs demonstrated up-regulated pro-inflammatory signalling through S1P1 in SHRSP, compared to WKY normotensive rats. This study aims to investigate potential effects of altered S1P1 - VCAM1 signalling on blood pressure (BP) regulation, using high-throughput proteome and metabolome screening of WKY and SHRSP in combination with the SP.WKYGla2a and WKY.SPGla2a reciprocal chromosome 2 congenic strains.
DESIGN & METHODS: Mesenteric primary VSMCs from 16 week-old male rats were stimulated with S1P for 30 minutes. Proteome profiling was conducted using triple stable isotopic labeling by amino acids (SILAC), in two experiments [(A) WKY : WKY.SPGla2a : SHRSP, (B) WKY : SP.WKYGla2a : SHRSP]. Separation of labeled tryptic peptides by LC-MS/MS was followed by quantification and identification of proteins using MaxQuant and statistical analysis on Perseus. For the metabolome screening of WKY : SP.WKYGla2a : SHRSP (n=4/strain), labeling-free analysis employed HILIC-MS for metabolite separation. The IDEOM in-house software package was used for identification and quantification of metabolic changes. To explore relevant biological pathways / processes the data was uploaded to Ingenuity Pathway Analysis (IPA) and filtered for fold change (FC: +/- 1.3, proteome analysis) or FDR<0.05 (metabolome analysis).
RESULTS: Proteomic analysis: from a total of 1998 proteins identified 254 were differentially expressed between SHRSP versus WKY. 172 of them were in common with SP.WKYGla2a versus WKY. Several of the common proteins, generally up-regulated in SHRSP, are implicated in oxidative stress processes associated with BP regulation; hypertrophy (natriuretic peptide receptor C - NPR3), fibrosis (collagen type XI alpha 1 - COL11A1) and S1P/S1P1 signalling (caveolin-1 - CAV1). Metabolomic analysis: from the 743 metabolites identified in total, ~20 were significantly changing in each of the comparisons between S1P-treated versus control cells. Free radical scavenging was one of the highly affected networks. In specific, metabolites that reduce oxidative stress, such as 5,6,7,8-tetrahydropterin, hydrocortisone and taurine, were increased in S1P-stimulated WKY cells. On the contrary, metabolites associated with increased oxidative stress, such as hypoxanthine, inosine and kynurenic acid, were increased in stimulated SHRSP but reduced in stimulated SP.WKYGla2a cells, such as xanthine. This could imply a negative association of S1P signalling with the oxidative stress and activation of protective ROS scavenging mechanisms in the S1P-stimulated WKY and SP.WKYGla2a but not in the SHRSP.
CONCLUSIONS: Combination of high throughput proteome and metabolome comparisons with construction of chromosome 2 reciprocal congenic strains allows identification of significantly modulated molecules during S1P stimulation that could be related to altered sphingosine signalling and BP regulation. Integration of this data with transcriptomic studies will provide insights into the pathophysiology of hypertension and facilitate construction of computational dynamic networks relevant to the human essential hypertension.

24/ Genome wide loss of methylation in senescent cells as a potential precursor to aberrant methylation of cancer cells.

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Senescence is an irreversible proliferation arrest which can be caused by activated oncogenes, DNA damage and damage/shortening of telomeres. Senescence is understood to act as a prevention of cellular transformation by blocking cell proliferation and promoting immune clearance whilst also contributing to ageing via the inflammaging phenotype. Previous studies have shown methylation changes in both cancer and aged cells however the methylome of senescent cells has not been investigated in detail. We present whole-genome bisulphite sequencing of senescence using a replicative senescence model. DNA was extracted from proliferating and senescent cells and bisulphite treatment was used to convert unmethylated cytosines to uracils whilst leaving methylated cytosines unmodified. The resulting DNA is then sequenced and the methylation status of individual CpG dinucleotides can be inferred. Methylation changes do not appear to regulate global gene expression as hypomethylation of genes occurs mostly at those genes which are already transcriptionally repressed. We show that the genome is primarily hypomethylated in senescent cells and that it predominately occurs within partially methylated non-genic regions. These regions are late-replicating and are associated lamins. DNMT1 is a key DNA methyltransferase, which acts at the replication fork to methylate the hemimethylated DNA that is created as a result of replication. We have observed that DNMT1 is mislocalised in cells approaching senescence, specifically, large DNMT1 foci, associated with late replication, which are present in young proliferating cells disappear in pre-senescent cells. However, DNA replication still occurs in the absence of DNMT1. These findings suggest this mistargeting of DNMT1 prevents the methylation of these late replicating sequences during replication which leads to the observed hypomethylation of these sequences during senescence. Finally, we compared the methylation changes in senescence with those in colon cancer and observe striking overlap of the senescence and cancer methylomes. We hypothesise that as cells approach senescence they acquire the hypomethylated methylome described here and that cancer cells which have escaped the senescence barrier retain the senescent methylome attained before transformation.

25/ Next-generation sequencing and integrative genomics analysis in the Stroke-prone Spontaneously Hypertensive and Wistar Kyoto Rats.

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INTRODUCTION: The stroke-prone spontaneously hypertensive rat (SHRSPGla) is an excellent model for human cardiovascular disease. A genome wide scan between SHRSPGla and normotensive Wistar Kyoto (WKYGla) rats identified quantitative trait loci (QTL) on chromosomes 2, 3 and 14 for blood pressure, pulse pressure and left ventricular mass index, respectively. These QTLs were validated by the construction of chromosome 2, 3 and 14 congenic strains. This study aims to identify candidate genes which contribute to the SHRSPGla phenotype by the analysis of the SHRSP and WKY genome sequence, and gene expression patterns modified by age in tissues that are known to be relevant to the pathogenesis of cardiovascular disease. Genes will be prioritised that are positional (map to the congenic intervals) and found to harbour protein coding genetic sequence variants.
METHODS AND MATERIALS: Illumina raw paired-end reads from the SHRSPGla and WKYGla were mapped to reference genome of Brown Norway (BN) using Burrows Wheeler Aligner. Genome Analysis Toolkit was used to discover variants call between the SHRSPGla and WKYGla. Ensembl Variant Effect Predictor tool was used to annotate and functionally categorise the effect of next generation sequencing (NGS) sequence variants. Sanger direct sequencing data from 3 genes on chromosome 2 were compared to NGS data for quality control. Ingenuity pathway analysis (IPA) was used to provide insights into the impact of SHRSPGla and WKYGla genomic variants on pathways and disease. Significantly differentially expressed positional candidate genes identified by Partek® Genomics Suite in kidney or heart tissue which contain sequence variants such as non-synonymous coding, stop gain, frame shift coding SNPs (single nucleotide polymorphisms) or INDELs (insertions and deletions of DNA segments) was prioritised.
RESULTS: More than 90% of reads were mapped to reference genome of SHRSPGla at 20x and WKYGla at 26x coverage. Genomic difference distribution of 1,163,332 SNPs and 213,130 INDELs between SHRSPGla and WKYGla were not uniform and higher in intergenic/intronic regions compared to exonic regions. IPA biological interpretation of SHRSPGla and WKYGla genomic variants implicate networks, diseases and pathways that regulate cardiovascular disease. The quality control result shows that NGS variants data detected 29 SNPs and INDELs out of 34 variants found from capillary sequencing data. Significantly differently expressed genes in kidney or heart tissue that associated with 769 non-synonymous coding, 5 stop gained, 24 frame shift coding SNPs and INDELs within the congenic regions prioritised 10 candidate genes. One of the identified candidate genes, Gstm1, was previously validated as positional and functional candidate for hypertension in SHRSPGla.
CONCLUSION: We have shown that the integration of sequence variants and gene expression data between SHRSPGla and WKYGla has implicated positional candidate genes in the chromosome 2, 3 and 14 congenic intervals and can contribute to the understanding of the genetic determinants of the SHRSPGla blood pressure and cardiac phenotypes.

26/ Application of lipid array technology for autoantibody detection in human peripheral neuropathy.

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Measurement of anti-GM1 IgM antibodies in multifocal motor neuropathy (MMN) sera is confounded by relatively low sensitivity that limits clinical usefulness. A newly developed combinatorial glycoarray able to identify antibodies to 45 different heteromeric glycolipid complexes and their 10 individual glycolipid components was applied to a randomly selected population of 33 MMN cases and 57 normal or disease controls. Comparison with an enzyme-linked immunosorbent assay (ELISA) was conducted for selected single glycolipids and their complexes. By ELISA, 22/33 MMN cases had detectable anti-GM1 IgM antibodies, whereas 19/33 MMN samples were positive for anti-GM1 antibodies by glycoarray. Analysis of variance (ANOVA) revealed that of the 55 possible single glycolipids and their 1:1 complexes, antibodies to the GM1:galactocerebroside (GM1:GalC) complex were most significantly associated with MMN, returning 33/33 MMN samples as positive by glycoarray and 29/33 positive by ELISA. Regression analysis revealed a high correlation in absolute values between ELISA and glycocarray. Receiver operator characteristic (ROC) analysis revealed insignificantly different diagnostic performance between the two methods. However, the glycoarray appeared to offer slightly improved sensitivity by identifying by identifying antibodies in 4 ELISA-negative samples. The use of combinatorial glycoarray increased the diagnostic sensitivity of anti-glycolipid antibody testing in this cohort of MMN cases, without significantly affecting specificity, and may be a useful assay modification for routine clinical screening.

27/ MetExplore 2.0: Collaborative platform for building, analyzing, simulating and improving metabolic networks.

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The availability of complete genome sequences for several organisms offers an invaluable resource for the reconstruction of biochemical networks in organisms at the genome scale level. These genome-scale networks are essential for high-throughput “omics” data interpretation, and they can be converted into metabolic models for simulating the operation of cellular metabolism in response to different stimuli. By integrating metabolomics datasets with genome-scale metabolic networks and enabling graph analyses, the first release of MetExplore [1] offered to the community a powerful network-mining platform to comprehensively understand the metabolic capacities of an organism’s metabolism, and to identify potential drug targets. Within the new release of Metexplore, in silico metabolic simulations are now possible. MetExplore 2.0 allows the import, annotation and modification of metabolic networks, thereby enabling users to track missing, false or stoichiometrically badly-defined reactions, and ensuring highly consistent reconstructed models. In addition, MetExplore 2.0 enables the curation of metabolic models by several users in a collaborative way. The metabolic networks used to establish models can be duplicated from the MetExplore database or imported from external SBML files. Secondly, flux balance analysis (FBA) functions have been introduced in MetExplore 2.0 to simulate carbon flux distributions in metabolic networks under different environmental/genetic conditions. The strength of MetExplore is to provide a user-friendly tabular view that helps to fill in the FBA parameters by facilitating the selection of reactions by their names, their substrate and product metabolites, their genes or, the metabolic pathways to which they belong. The FBA-based functions provided in MetExplore 2.0 are computed using the SurreyFBA library and include i) computing of optimal functions, ii) knock out analysis, iii) robustness analysis, iv) identification of essential and live reactions, and v) flux variability analysis (FVA) . For the latter analysis, calculated flux distributions can be mapped on the network by directly launching the visualization tool Cytoscape. MetExplore also provides an original function that allows differences between two sets of FVA data calculated for two different conditions to be displayed graphically and interrogated.

The new release of MetExplore is the first web server that offers collaborative reconstruction, graph analysis and flux analysis within the same framework. This all-in-one pipeline accelerates analysis and avoids errors due to file exchanges between various platforms. Moreover, no programming skills are needed to perform complex analyses. It is particularly well suited for metabolic engineering and synthetic biology because addition or removal of (novel) metabolic capabilities, as well as the analysis of the effects of these changes, can be performed easily.
MetExplore has been running since June 2009. It has been visited 1048 times by 415 distinct visitors and has been intensively used and tested by the authors of this paper and by members of four international laboratories: Lyon University (France), Glasgow University (United Kingdom), LNCC (Brazil), ETH (Switzerland).
Web server address: http:/www.metexplore.fr

REFERENCE [1] Cottret, L.; Wildridge, D.; Vinson, F.; Barrett, M. P.; Charles, H.; Sagot, M.-F. & Jourdan, F. (2010), 'MetExplore: a web server to link metabolomic experiments and genome-scale metabolic networks.', Nucleic Acids Res 38 (Web Server issue), W132-W137.

28/ The plasma proteome and acute phase proteins of broiler chickens with gait abnormalities.

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Acute phase protein (APP) concentrations change in response to infectious, inflammatory, stressful traumatic or neoplastic events, the magnitude of change often proportional to the severity of the event(s). As such APP measurements are used as disease biomarkers and for prognostication. This investigation characterised the APP changes that occur due to gait abnormalities in broilers and further detailed the serum proteome with the view of establishing new biomarkers and biomarker profiles for disease and welfare. Plasma concentrations of APPs ceruloplasmin, PIT54 and ovotransferrin from 43 Strain A and Strain B broiler chickens aged 35-36 days with gait score 3 (obvious gait defect) or gait score 1 (normal) were measured using automated biochemical analyser and ELISA using established methods. To investigate acute phase reactive (APR) plasma gait 3 broilers results were ranked and samples with the highest APP concentrations selected for 2-dimentional electrophoresis. Healthy broilers with low concentrations of the same APPs were used as controls (non-APR serum). Proteins spots were excised from the gels and analysed using MALDI-TOF mass spectrometry.
Serum concentrations of ceruloplasmin ($P \leq 0.001$), PIT54 ($P \leq 0.05$), ovotransferrin ($P \leq 0.05$) were significantly higher in gait 3 than gait 1 broilers. There were clear differences in the protein profiles of the APR and non-APR plasma. Of the established APPs, PIT54, OVT, α1-acid glycoprotein, fibronectin, fibrinogen and haemopexin were identified in both APR and non-APR plasma. Other proteins identified in multiple spots in APR plasma and not the non-APR, require further characterising to further aid the development of biomarker profiles.

2012
Upcoming training courses in omics

Metabolomics Software Workshop
20–21 September 2012

A two-day workshop on analysing LC-MS metabolomics data with IDEOM and mzMatch software.

• **IDEOM workshop:** Thursday 20th September 2012 (registration fee = £50).
• **mzMatch workshop:** Friday 21st September 2012 (FREE registration)

Target group:
The IDEOM Workshop is suitable for all metabolomics researchers, particularly biologists.

The mzMatch Advanced Data Analysis Workshop is suitable for specialist metabolomics analysts, particularly analytical chemists and bioinformaticians.

Venue: Bioinformatics Research Centre, Joseph Black Building, University of Glasgow

Date: 20–21 September 2012, 10am–5pm

Computers: Bring own laptop or book a desktop

Maximum number of participants: 18

Registration:
• For day 1 only, or both days:
Darren Creek, darrencreek@gmail.com (registration fee = £50)

• For day 2 only: Andris Jankevics, andris.jankevics@gmail.com (FREE registration)

For more information see:www.gla.ac.uk/colleges/mvls/research/gpf/metabolomicsdataanalysisworkshop/ or follow the link from the *Glasgow Polyomics* website (www.glasgow.ac.uk/polyomics)

An Introduction to Omics
29–30 November 2012

A two-day course aimed at familiarizing course participants with the basis and application of various omics disciplines: genomics, transcriptomics, metabolomics, proteomics, and bioinformatics.

Each of the omics disciplines will be covered by a lecture and a practical session.

By the end of the course users should understand, for each omics level: the basis of the discipline, the instrumentation used to generate high-throughput biological data, key applications, and how to visualise the resulting data using popular software packages.

Participants will also be aware of how different large-scale data sets can integrated in order to obtain better biological inferences, and appreciate the nature of other modern challenges in bioinformatics.

Target group:
Research students and staff who wish to deepen their understanding of high-throughput data generation and analysis.

Venue: Jura teaching lab, Level 4 Annexe, University Library

Date: 29–30 November 2012, 9:30am-5pm

Maximum number of participants: 20

Registration:
Contact Tanita Casci (Tanita.Casci@glasgow.ac.uk)

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