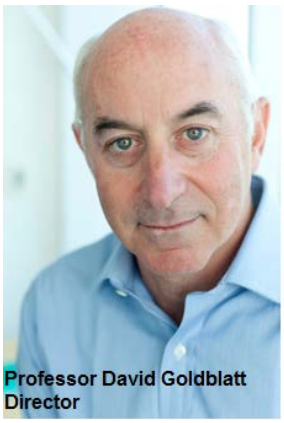
National Institute for Health Research

News from the The National Institute for Health Research (NIHR) Biomedical Research Centre at Great Ormond Street Hospital for Children NHS Foundation Trust and University College London

February 2015


Professor David Goldblatt
Director

Welcome to the February edition of our National Institute for Health Research (NIHR) Biomedical Research Centre (BRC) at Great Ormond Street Hospital (GOSH) for Children NHS Trust and University College London newsletter, which is designed to highlight our notable activity.

Our Special Feature this issue focuses on the lead role GOSH will take in coordinating the network of hospitals involved in the Genomics England '100,000 Genomes Project'. GOSH has been named as the Lead Organisation responsible for coordinating the recruitment of patients through the new network that will form the North Thames Genomic Medicine Centre.

We look forward to welcoming visual artist Sofie Layton, who has received an award from the Wellcome Trust, working with our children and young people on how they view and experience disease and more can be read in the general news section.

We are pleased to announce Professor Phil Beales, BRC theme lead, Molecular basis of childhood diseases, has been appointed as the Deputy Lead of the NIHR Paediatric Rare Disease Translational Research Collaboration (RD-TRC).

Congratulations also this month to Dr Ri Liesner who was identified by NIHR Clinical Research Network as a Leading Commercial Principal Investigator 2015. Dr William van't Hoff also received an award for 'Delivering Above and Beyond' and Professor Francesco Muntoni for 'Consistently Delivering to Time and Target and First Global or European Patient'. These awards were in recognition of theirs and importantly their teams' efforts in contributing to the successful growth and delivery to the NIHR Clinical Research Network Commercial Portfolio 2015.

The top team from the NIHR co-ordinating centre, led by Tony Soteriou, visited the GOSH BRC in December for very productive discussions which included a focus on industry engagement. They were followed on the same day by a visit from the NIHR Bristol Nutrition BRU to discuss increased collaboration (see general news). Now the BRC staff and faculty are busy preparing for our second International External Advisory Board visit which will take place in March, and will focus on the performance of two of our four themes, Diagnostics and Imaging and Novel Therapies.

I hope you enjoy reading this newsletter and as always welcome any thoughts and contributions you would like to make.

David Goldblatt
Director, NIHR GOSH BRC
Director, Clinical Research and Development
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Visit our website: http://www.gosh.nhs.uk/research-and-innovation/biomedical-research-centre-brc/

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SPECIAL FEATURE

GOSH named as key centre in 100,000 Genome Project

Great Ormond Street Hospital is set to play a lead role coordinating a network of hospitals involved in the Genomics England '100,000 Genomes Project'. GOSH has been named as the Lead Organisation responsible for coordinating the recruitment of patients through the new network that will form the North Thames Genomic Medicine Centre and, alongside other partnering London Trusts, will recruit participants to the project.

As well as giving blood for whole genome sequencing, participants will have blood samples stored for future metabolomic, proteomic, and RNA analysis. The project will focus on patients with Rare Diseases, co-ordinated across North Thames by Professor Maria Bitner-Glindzicz, and Cancer, co-ordinated by Professor Adrienne Flanagan. The project is unique and far reaching as it aims to follow-up research participants for life, by using electronic health records to continually update clinical data for ongoing research. For Rare Diseases,

the patients and ideally both parents, will have their whole genomes sequenced and will give consent to access to their full medical and scoial care records, past, present and future. For cancer patients, both the patient's blood and their tumour will be subjected to whole genome sequencing. By collecting and analysing these genetic samples and matching them with the symptoms and long-term outcome associated with these conditions, the genome project aims to position the UK as the first country in the world to sequence 100,000 whole genomes. The hope is that this will help researchers and clinicians better understand, and ultimately treat, rare and inherited diseases and common cancers. Over the last year GOSH, UCLH and Moorfields patients took part in a pilot study for the project, which involved providing blood samples to Genomics England (GEL) for detailed analysis.

Professor Lyn Chitty, clinical lead for the project, said: “This is a really exciting project and offers a great opportunity. We hope that by doing whole genome sequencing we will identify the underlying genetic cause for some rare diseases as well as potentially highlighting new treatments for cancer patients through a better understanding of the disease.”

“In the longer term this is a project that stands to transform the NHS. Ultimately, if we can make it affordable and efficient enough, whole genome sequencing could be used as one of the first lines of investigation to help clinicians diagnose diseases more quickly, as well as identifying the most appropriate treatment, without the need for numerous other tests.”

The above image was taken at a reception at Downing Street on August 1st 2014 to announce the signing of contracts between Genomics England and Illumina, the company who will do the sequencing for the project. From left: Professor Sir John Burn (Institute of Genetic Medicine, Newcastle), Professor Maria Bitner-Glindzicz (Rare Disease lead), Dr Ruth Jamieson (Strategic Coordinator Personalised Medicine, UCL), and Alastair Kent OBE (Genetic Alliance UK).

NEWS

General news

NIHR Great Ormond Street BRC seminar on 21 January 2015

The first seminar of 2015 took place in January and was chaired by Professor Adrian Thrasher, BRC theme lead for Gene, stem and cellular therapies. These seminars showcase the research taking place at the BRC and in the wider organisations of GOSH and ICH, as well as providing an opportunity for speakers and attendees to network with potential collaborators.

The first speaker, Dr Pascale Guillot, Senior Lecturer, Maternal and Fetal Health, gave an insight into stem cell therapy for the neonatal treatment of brittle bone disease. Talks followed by Steve Hart, Professor of Molecular Genetics, on targeting nanoparticles for the delivery of gene and siRNA therapies, Professor of Paediatric Oncology Kathy Pritchard-Jones on greater precision medicine in childhood renal tumours and Dr Chiara Bachelli, Head of Experimental & Personalised Medicine Section, Genetics and Genomic Medicine Programme, finished with ‘Personalised medicine: part, present and future’.

Our next BRC symposium will take place on Friday 22 May 2015, with speakers to be announced shortly on the events section of our website.

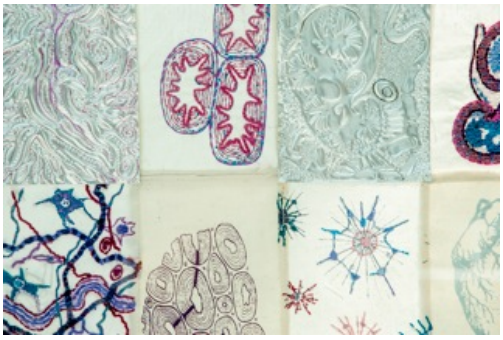
Opportunity to collaborate with NIHR Bristol Nutrition Biomedical Research Unit (BRU)

The NIHR Biomedical Research Unit in Nutrition, Diet and Lifestyle at University Hospitals Bristol NHS Foundation Trust and the University of Bristol opened in April 2012. The Bristol Nutrition BRU is funded to carry out research in experimental medicine over the next five years. It aims to translate knowledge developed from work on causal associations in nutrition, drawn from population and clinical studies, to develop interventions that improve the health of people with conditions related to poor nutrition. The Unit has five themes including Children with chronic disease, with most studies focussing on the modification of nutrition or physical activity.

Currently several new devices are being tested to monitor nutrition in children, with twelve ongoing projects and three completed projects in the children's theme. NIHR Bristol Nutrition BRU has the expertise in measuring features of eating (such as speed of eating) and physical activity in children, and can recruit children with common conditions to feasibility studies.

NIHR Bristol Nutrition BRU would welcome collaborations from members of the NIHR Great Ormond Street BRC. Details of the work of the unit, the unit's policies and the projects currently underway can be found on their website. Specific enquiries about collaboration with the children's theme should be directed to Professor Julian Hamilton Shield.

Wellcome Trust funds artist for collaborative BRC work



Sofie Layton, a visual artist with previous ART in Health (work) experience at Evelina Children's Hospital - Guys' and St Thomas', has been successful in obtaining Wellcome Trust funding of £29,925 to work with GOSH BRC Theme Leads and the hospital's arts programme GO Create! to explore how young people view their disease. The end product will be a CREATED Environment? (space) showing how children, young people and parents view disease. The NIHR Great Ormond Street BRC has also agreed to provide £5,000 towards the project, with £4,000 from the Blavatnik Family Foundation and £4,000 from GO Create! Sofie received excellent feedback from the Wellcome Trust, and in particular the collaboration of research scientists at GOSH with young people and their families in a creative way was applauded.

Molecular basis of childhood disease theme news

NIHR Great Ormond Street BRC funded GOSgene helps identify a novel centrilolar gene

The NIHR Great Ormond Street BRC funded gene discovery facility, GOSgene has supported the identification of new gene, CENPF (a novel centriolar disease gene) in kindred with an embryonic lethal ciliopathy phenotype and in a patient with primary microcephaly. Mutations in microtubule-regulating genes are associated with disorders of neuronal migration and microcephaly. Regulation of centriole length has been shown to underlie the pathogenesis of certain ciliopathy phenotypes. The recent publication in the *Journal of Medical Genetics* uses a next-generation sequencing approach to identify CENPF as a new centriolar disease gene implicated in severe human ciliopathy and microcephaly related phenotypes.

Bogue Fellowship awarded to Genetics and Genomic Medicine programme PhD student

Lydia Leon, a PhD student supervised by Professor Gudrun Moore, has been awarded a grant under the UCL Bogue Fellowship scheme. In autumn 2015 Lydia will travel to Virginia Commonwealth University in the United States to carry out additional research for her PhD exploring links between bacterial infection, the maternal immune system and preterm birth risk. Lydia will work in Professor Gregory Buck's lab learning and conducting a state of the art protein quantification assay that has been specifically designed by

the team in Virginia for pre-term research. Professor Buck's group have recently received a highly prestigious grant as part of the NIH Human Microbiome project for the establishment of the MOMS-PI (Multi-Omic Microbiome Study-Pregnancy Initiative).

Novel therapies for childhood disease theme news

Frensenius medical care award to support clinical trial

Dr Rukshana Shroff has been awarded a grant of €60,000 from Fresenius Medical Care to support the Kidney Research UK funded study "The effects of Hemodiafiltration (HDF) vs conventional Hemodialysis (HD) on growth and cardiovascular markers in children". Dr Shroff's team is studying children on dialysis across more than 20 sites in the EU, including 6 in the UK. They will compare two different dialysis modalities: HDF and HD. HDF is a newer type of dialysis that achieves better removal of toxins and excess fluid than HD. Children on HD die of heart disease, and if results of this study show reduced cardiovascular morbidity, HDF may be adopted as the preferred dialysis modality in children.

New neuromuscular clinical trial opens in Somers Clinical Research Facility

The Somers Clinical Research Facility (Somers CRF) will be supporting SKIP-NMD, in a new clinical trial to test a genetic therapy in boys with Duchenne muscular dystrophy (DMD). The underlying cause of DMD is a mutation in the gene for dystrophin, an essential protein involved in muscle fibre function. This investigational therapy is designed to skip exon 53 in the dystrophin pre-mRNA and restore the ability to make a functional, though shorter, form of the dystrophin protein. SKIP-NMD is funded by the European Seventh Framework Programme FP7 and involves 10 research institutions and muscle centres from France, Italy and the UK.

The exon skipping therapy could potentially be used to restore dystrophin production in about eight percent of boys with Duchenne muscular dystrophy.

Professor Francesco Muntoni, BRC theme lead for Novel Therapies for translation in childhood disease and the Chief Investigator and SKIP-NMD Project Coordinator from UCL Institute of Child Health & GOSH said, "It is certainly pleasing to see that the long-term collaboration with our European partners from London, Paris, Newcastle, and Rome – and with Sarepta in the U.S. – has come to fruition with the dosing of the first patient recruited into the dose escalation part of the study. This project, which started two years ago, enters now into the in-patient phase in which we aim to demonstrate safety of this new antisense oligonucleotide. This is a trial in which, for the first time, we will use novel ways to better assess the efficacy of this new molecular patch. The study will both tell us how safe this new drug is and use several ways to measure its efficacy."

More information on the trial is available in Sarepta Therapeutics' press release.

Gene, stem and cellular therapies theme news

GOSH gene therapy labs support new Phase 1 trial for Epidermolysis Bullosa

Epidermolysis bullosa is a debilitating blistering skin disease that causes serious health problems in children and adults. The Sohana Research Fund and DEBRA recently awarded funding of £500,000 to researchers at UCL ICH and Guys Hospital/King's College London (KCL) to undertake Phase 1 testing of a new therapy using gene modified fibroblasts taken from patients with the condition. A lentiviral vector designed and produced by the ICH team, led by Dr Waseem Qasim and Dr Wei Li Di, has already been manufactured by the team using GMP facilities at KCL and has been shown in modelling experiments to restore missing anchoring fibrils in human skin. Processes to isolate, engineer and expand fibroblasts have been finalised in the GOSH gene therapy labs. A first in man clinical trial will be conducted by Professor

John McGrath, a world leading expert in the condition and is expected to open later in 2015.

The ICAT Trial - Immunotherapy with CD25/71 Allodepleted Donor T-cells

The two major causes of morbidity and mortality in patients undergoing matched, unrelated haematopoietic stem cell transplant (HSCT) for haematological malignancy are infection and graft versus host disease (GVHD). These side-effects also have a significant cost implication on transplant units. By infusing doses of donor T-cells depleted of the alloreactive fraction at intervals post-transplant, the ICAT Trial aims to safely improve post-HSCT immunity in patients without contributing to the risk of GVHD. The ICAT trial, funded by the Medical Research Council (MRC), is dependent upon the support of the GOSH Immunology and Cell Therapy Laboratory, who have helped with the development of the procedure, have undertaken some of the monitoring of the patients, and offer their facilities and equipment for the processing and analysis of patient and donor cells. Our BRC-funded Quality Assurance Officer supports and oversees this trial.

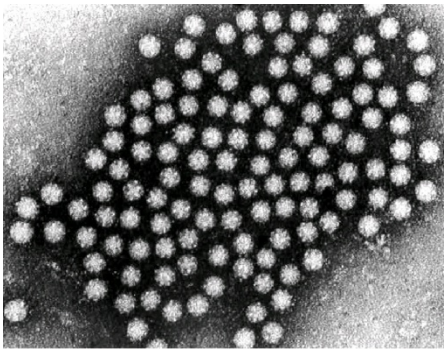
Diagnostics and imaging in childhood disease theme news

Biomarkers of clinically aggressive disease in relapsed medulloblastomas identified

BRC supported Consultants Drs Antony Michalski, Darren Hargrave and Thomas S. Jacques, in collaboration with the Northern Institute for Cancer Research, Newcastle University, contributed towards the recent publication in *Cancer Cell* identifying P53-MYC interactions at medulloblastoma relapse as biomarkers of clinically aggressive disease may be targeted therapeutically.

This high impact paper shows medulloblastomas develop altered biology at relapse, which predicts outcome and cannot be detected at primary diagnosis. The data in this paper supports the incorporation of biopsy at relapse into routine clinical practice and thus directing palliative care and the development of improved treatment strategies.

New virus found to cause dangerous brain infection



Work funded by the BRC has discovered a newly recognised virus, which shows similarities to viruses found in bats, mink and sheep that may be the cause of a severe brain infection in children, whose immune systems are low. Teams at GOSH, along with colleagues at UCLH, identified a new astrovirus, HAstV-VA1/HMO-C-UK1(a), which is highly divergent from human astrovirus (HAstV- 1-8) genotypes, but closely related to VA1/HMO-C astroviruses, which is likely to be the cause of encephalitis in these patients. It was discovered using a new technique which enables scientists to examine all the genetic material in a sample for viruses, rather than testing for a specific type. The finding, published in *Clinical Infectious Diseases*, could lead to a greater number of children with encephalitis being diagnosed and treated where they couldn't be previously.

Infection in Cystic Fibrosis (CF) patients is found not to be contagious

Researchers at GOSH have found that an infection that was thought to be able to pass from patient to patient with cystic fibrosis seems not to be transmitted between children in hospital. The team looked at 16 children with CF who contracted the *Mycobacterium abscessus* infection over a 10 year period and who had come into contact with each other at the hospital either as an inpatient or in CF clinic. They found that each child and young person had different strains of the bacteria, despite many opportunities to transmit the bacteria over many years and therefore this infection couldn't have been passed between these patients. One sibling pair tested did show the same strain but the infection they developed occurred 12 years apart, suggesting other causes are likely to be at play.

Further work is now needed to better understand the nature of the source of these bacteria, so we can

better understand how and where they are caught in the first place.

BRC supported Kathryn Harris, a Clinical Scientist at Great Ormond Street Hospital and lead researcher on the paper says, “This result is important as it steers research away from looking at this infection as being transmissible. This means that we can start exploring other avenues and possible causes which could lead to simple interventions that could be put in place in order to prevent infections in the future.”

This research is published in the journal *Clinical Infectious Diseases*

PATIENTS AND THE PUBLIC

Otto Wolff lecture

On 8 December, Dr William van’t Hoff and members and facilitators of two NIHR Young Person’s Advisory Groups (YPAG) and Zara Todd, facilitator of the former VIPER group for children and young people with disabilities, were invited to present an Otto Wolff lecture. Their lecture, entitled ‘Involving Children and Young People to Improve Our Research’, was well attended and the young co-presenters received praise on their presentation, and their work in the YPAG. Further information on the work of VIPER, can be found here.

INVOLVE newsletter

We are working with INVOLVE, the national organisation for Patient and Public Involvement in Research, which supports the active public involvement in NHS, public health and social care research, and is funded by the NIHR. INVOLVE invited Dr Erin Walker and the CRN: North Thames YPAG to contribute an article for their upcoming Spring newsletter on children and young people’s involvement in research. This formed part of the basis for the December YPAG meeting, and it is anticipated the article will be published in the spring on the INVOLVE website.

If you have a research study that you would like to present to the YPAG for their input (for example how information leaflets are worded, or to comment on the design of a study, or your dissemination plan), please contact Dr Erin Walker (BRC joint Lead for Patient and Public Involvement and Engagement in Research).

TRAINING

Appointment of Clinical Research Nurse Practice Educator

Congratulations to Cassie Brady who has recently commenced the new post of Clinical Research Nurse Practice Educator. Cassie will be based in the Somers Clinical Research Facility and will use her experience as a Research Sister in the CRF to support Clinical Research Nurses around the Trust in continuing to integrate research with clinical care. This work will sit alongside that of Dr Kate Oulton, Senior Research Fellow/NIHR Clinical Academic Programme Lead: Nursing and AHP Research.

Academic Inquiring Minds forum January 2015

January saw the first meeting of Academic Inquiring Minds (AIM) - a forum of support, critical debate and networking for nurses and AHPs who have a PhD and current or aspiring PhD students. There was interesting discussion about the risks associated with conducting research with children and young people

and strategies to minimise these. Anyone wishing to join this forum, which meets every 3 months, should contact Dr Kate Oulton.

NIHR funded Masters in Clinical Research

Calls are now open for nurses and AHPs wishing to apply for the NIHR funded Masters in Clinical Research. You must have 1 year's clinical experience and a 2.1 degree (hons) to apply. Contact Dr Kate Oulton for more details.

EVENTS

Mini Symposium – NIHR Translational Research Collaboration 6 May, UCL

The purpose of this symposium is to familiarise attendees with the unique opportunities provided by the 100,000 Genomes project and to share the exciting results of the first gene discoveries. Individual sessions include Coagulation and Platelet Rare Diseases and Stem Cell, Immune and Myeloid Rare Diseases. For more information, visit our events section.

Get Involved in Research Awareness Week: 18-22 May 2015

Research Awareness week is taking place 18-22 May here at GOSH to coincide with International Clinical Trials Day on 20 May. On Tuesday 19 May there will be a 'research trail' to encourage children and families to visit different parts of the hospital where they can take part in activities to learn more about research and how it helps develop child health care. If anyone would like to get involved in this event, or has any ideas about activities to raise awareness of the research that happens at GOSH, please contact Ruth Nightingale, Joint Lead for Patient and Public Involvement and Engagement in Research or Nicola Logue, in the Joint Research and Development Office.

NIHR Great Ormond Street BRC Symposium Date Friday 22 May 2015

The 2015 BRC symposium will highlight the excellent science and translational impact of the work conducted within the BRC. A programme will be available shortly on our events section.

Translation of Research into Practice Conference Friday 19 June 2015

The Centre for Outcomes and Experience Research into Children's Health, Illness and Disability (ORCHID) is holding a conference in conjunction with the BRC and LSBU entitled, 'It's the translation of research into practice that counts: examples from nurses and AHPs'. Friday 19th June, Leolin Price Lecture Theatre, ICH. Contact Dr Kate Oulton to book your place or visit our events section for more details.