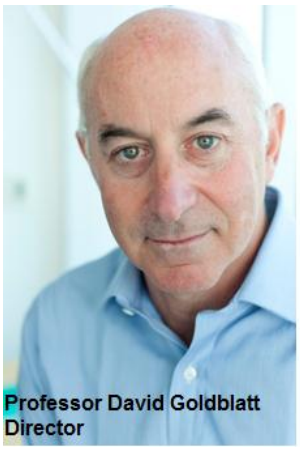
National Institute for Health Research

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

National Institute for Health Research (NIHR) Biomedical Research Centre newsletter January 2014


Professor David Goldblatt
Director

Welcome to the third edition of our newsletter. This is our way to share with you initiatives that our NIHR Biomedical Research Centre (BRC) has supported, as well as news and successes from our faculty members, often in collaboration with other organisations.

At the end of 2013 we approved funding for two new high-impact research programmes, which will build on our existing commitments to translate our research into patient benefit. Further details of which can be found in the general news section.

In our November 2013 edition, you read about our participation in the Genomics England 100k pilot. The project will see the sequencing of 100,000 patients in the next five years. Knowledge gained will lead to improved diagnosis and personalised care. Together with University College London (UCL) Hospitals and Moorfields Eye Hospital, we have worked to collect 650 samples since the end November. This huge effort involved opening the Great Ormond Street Hospital (GOSH) Somers Clinical Research Facility over several weekends in November and December with recruitment now continuing through routine clinics in January.

I would like to take this opportunity to congratulate Professor Neil Sebire, NIHR BRC Diagnostics and Imaging theme lead, on having been invited to become a Fellow *ad eundem* to the Royal College of Obstetricians and Gynaecologists. Please read more about this in the general news section.

In this edition you will read about research breakthroughs, including the discovery of the genetic cause of a novel childhood onset neuromuscular disease, the development of new diagnostic tests for primary ciliary dyskinesia and primary immune deficiency, and the first ever treatment option for motor neuron disease. Our special feature this month includes an update on our Athena SWAN silver award application.

David Goldblatt
Director, NIHR Biomedical Research Centre
Director, Clinical Research and Development
Professor of Vaccinology and Immunology

Visit our new website: http://www.gosh.nhs.uk/research-and-innovation/biomedical-research-centre-brc/

NEWS

General news

NIHR congratulates GOSH on first global recruits

We were extremely pleased to hear that research teams at GOSH recruited the first global patients to four multi-centre studies, including the first two patients to a Summit PLC sponsored phase Ib study. The treatment under investigation is this phase Ib study is a compound capable of up-regulating the production of utrophin, a protein that can compensate for the lack of dystrophin, which cannot be produced in boys with DMD. This treatment could slow or even stop the progression of this devastating condition. Read the full press release by Summit PLC for more information. This is a significant achievement and shows the dedication of the research and research support teams in the Trust.

Royal College of Obstetricians and Gynaecologists honours NIHR BRC theme lead


Professor Neil Sebire

Professor Neil Sebire, NIHR BRC Diagnostics and Imaging theme lead, on having been invited to become a Fellow *ad eundem* to the Royal College of Obstetricians and Gynaecologists (RCOG).This award acknowledges major contributions made to the specialty and to the wellbeing of women, for example he has developed minimally invasive perinatal autopsy. Further, Professor Sebire is a recognised world expert on trophoblastic disease pathology and is involved in several RCOG expert groups as pathology representative. He has also recently contributed to the forthcoming World Health Organisation (WHO) Guidelines on trophoblastic disease pathology.

NIHR BRC funds high-impact proposals

The NIHR BRC is funding two high-impact proposals. Professor Phil Beales' project will use an all-inclusive OMICS approach (including genomics, proteomics or metabolomics) to initially investigate a small number of disease cohorts. Its outcomes are expected to inform diagnostics and treatment options of rare diseases. This pilot project complements research funding through NIHR Rare Diseases Translational Research Collaborations. The second project led by Dr Waseem Qasim will feature in our next newsletter.

BRC seminar on 28 November 2013

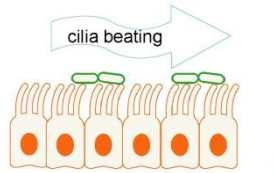
The first in a series of NIHR BRC seminars was well received as an excellent opportunity to find out about research supported by the BRC. The aim of the seminar series is to promote future collaborative work between groups and individuals to maximise NIHR BRC infrastructure. The event was chaired by Professor Francesco Muntoni, and speakers included Dr Haiyan Zhou on 'Developing RNA-based novel therapy for childhood diseases', Dr Hywel Williams on 'Centre for Translational Genomics – GOSgene: Update and future directions', Dr Waseem Quasim on 'Engineered T-cell therapies' and Professor Lyn Chitty on 'New approaches to prenatal diagnosis'. The next BRC seminar will be taking place on 25 February 2014, please see events section.

Molecular basis of childhood disease theme news

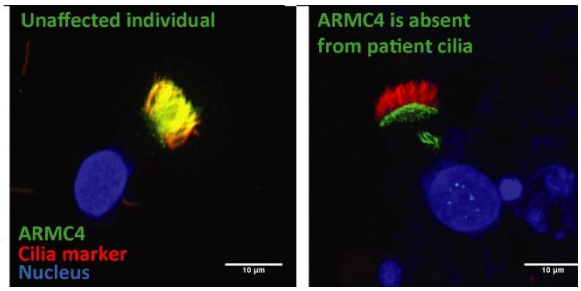
GOSgene team identify genetic cause of a rare bone and brain development disorder

A potential target for therapies to treat rare and more common conditions like osteoporosis has been discovered, which would bring great patient benefit. The key enzyme that is involved in bone development and maintenance was found by teams led by Professors Gudrun Moore and Phil Beales. Their findings were published in the journal *Nature Genetics*. Please read the GOSH press release for more information.

First use of whole-genome sequencing to diagnose primary ciliary dyskinesia (PCD)



Ciliated epithelia are a motile surface keeping airways clear

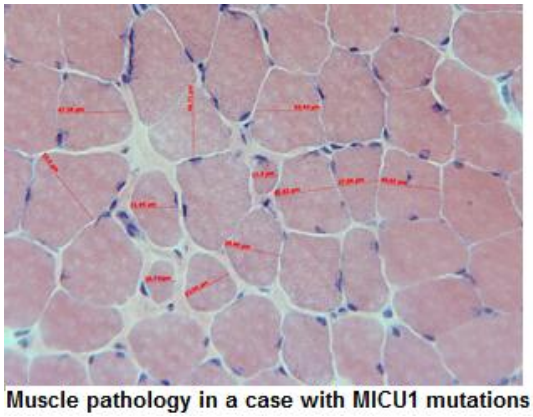


PCD is responsible for a number of symptoms, including neonatal respiratory distress, chronic respiratory infections, inflammation of the sinuses, and destructive lung disease. It affects one in every 15,000 to 30,000 births. A study led by UCL Institute of Child Health (ICH) researcher Dr Hannah Mitchison and facilitated by the GOSgene team illustrated that this technique can be used to identify gene mutations causing PCD. The full article was published in the *Journal of Medical Genetics*. More publications involving the BRC funded GOSGene team, may be accessed here:

Novel therapies for childhood disease theme news

Vitamin B 2 (riboflavin) provides first ever treatment option for a type of motor neuron disease
A collaborative clinical study co-ordinated by GOSH has shown encouraging treatment results for Brown-Vialetto-Van Laere syndrome, a rare neuromuscular disorder that causes the breakdown of muscle and nerve tissue. Next generation sequencing has proven instrumental in identifying one of the defective genes – a riboflavin transporter – suggesting that riboflavin supplementation could provide therapeutic benefit for patients with the disorder. The research supporting this study was led by the UCL Institute of Neurology's Professor Henry Houlden and NIHR BRC theme lead Professor Francesco Muntoni. Contributions were made by the GOSH metabolic team of Professor Peter Clayton and Dr Shamima Rahman. Findings were published in the journal *Brain*. Further details are available on the UCL news pages and at the GOSH press release.

UCL and University of Leeds collaboration finds novel mechanism responsible for childhood onset neuromuscular disease


Muscle pathology in a case with MICU1 mutations

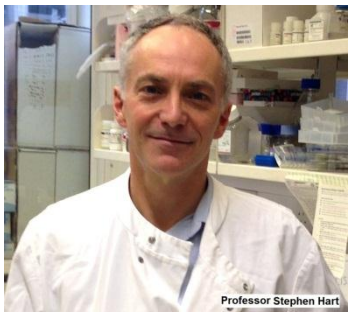
The gene responsible for childhood onset neuromuscular disease with associated brain involvement has recently been identified. The disease is characterised by muscle weakness, learning difficulties and progressive involuntary reflexes and movement. A genetic technique called exome sequencing has shown that particular mutations in a gene called MICU1 are responsible for this novel condition. This demonstrates potential to use the technique to identify new ways to diagnose and find new targets for treatment. The research team included NIHR BRC theme lead Professor Francesco Muntoni, and findings were published in the journal *Nature Genetics*. You can read more in the full UCL press release.

GOSH recruiting patient to trial investigation into medication for Duchenne muscular dystrophy (DMD)
GOSH has opened recruitment to a phase Ia trial looking at DMD patients with a mutation around location 53 in the DNA for the dystrophin protein. In this Prosensa Therapeutics B.V.-sponsored trial, eligible DMD patients receive systemic administrations of an antisense oligonucleotide developed by Prosensa and aimed at inducing exon 53 skipping. This is hoped to restore dystrophin expression and to improve muscle condition in DMD patients. Learn more about this trial.

Multi-centre nephrology study with potential to improve life expectancy in children on dialysis
Dr Rukshana Shroff has received funding from Kidney Research UK (KRUK) for an international study comparing two different types of dialysis and their effects on growth and cardiovascular outcomes in children. The study is a collaboration between all 13 paediatric nephrology centres in the UK and approximately 20 sites across European Union countries will collaborate to deliver the study. The results hope to inform which dialysis type improves the child's cardiovascular health and improve life expectancy. Further details can be found in the KRUK press release.

Gene, stem and cellular therapies theme news

Discovery of efficient delivery of therapeutic agents in the brain



Safe and efficient delivery of gene therapies to the brain has long been a major problem because the blood-brain barrier is very effective at allowing only specific molecules from the blood and into the brain. Supported by the BRC, Professor Stephen Hart (a Professor in Molecular Genetics at ICH) and his colleagues have developed a new, specially coated form of very small synthetic particle for gene delivery called an anionic nanoparticle. This nanoparticle is delivered to the brain by a precise form of injection through the skull using a very narrow needle, a procedure called convection enhanced delivery. A single injection of the nanoparticle achieves widespread dispersal for improved gene delivery. This represents real potential for the development of treatments for a wide variety of serious neurological diseases, ranging from neurodegenerative diseases to brain tumours. Read the full article in the journal *Biomaterials*.

BRC-funded researcher sharing expertise on manufacture of investigational medicinal products

Dr Karen Buckland (a NIHR BRC funded translational scientist in the gene and cellular therapies laboratory at GOSH and ICH) gave a short presentation at the 18th stem cell users group meeting (SCUG), held at Guy's Hospital on 22 November 2013. Dr Buckland described the use of CD34+ stem cells for manufacture of investigational medicinal products as part of NIHR BRC-funded clinical trials that are investigating gene therapy for primary immune deficiencies and recruiting at GOSH. The SCUG convenes twice a year as a forum for discussion of processing of bone marrow cells among UK research groups to share expertise and best practice. Topics covered included techniques, regulatory affairs and laboratory management. Altogether, sharing expertise and best practice will bring about patient benefits.

Diagnostics and imaging in childhood disease theme news

New diagnostic test developed for primary immune deficiency (PID)

PID occurs in 1 in 500 people and is characterised by an impaired immune system that is unable to mount an immune response to pathogens. A collaboration between the North East Thames Regional Genetics Service laboratory based at GOSH and the GOSH Immunology laboratory has resulted in the development of a Next Generation Sequencing panel for PID. This panel screens for 72 immunodeficiency genes and has a sensitivity of 98 percent. It is faster and more cost effective than sequential gene screening and is now being transferred into routine diagnostic use. To date, 19 previously undiagnosed patients now have a confirmed molecular diagnosis enabling optimal therapy as well as family screening and counselling. The pilot study was part funded by the NIHR BRC and this work was selected as an oral presentation at the UK Primary Immunodeficiency Network Forum 2013 and was presented at the winter meeting of the British Paediatric Allergy, Immunology and Infectious Diseases Group. The results are now being submitted for publication.

Potential for new diagnostic test for kidney disease in paediatric Fabry disease and juvenile diabetes patients

ICH researchers have discovered two very sensitive biomarkers that can predict presymptomatic kidney disease in a patient's urine. These biomarkers have been developed into a rapid, multiplexed urine test by GOSH chemical pathology. The NIHR BRC-funded GOSomics facility has supported this work led by Dr Kevin Mills, which was recently published in the *Journal of Proteome Research*. There is great potential to use this non-invasive test to look at many other types of kidney disease, including as a non-invasive test for kidney rejection in patients that have undergone transplantation and who currently require serial kidney biopsies. Other benefits to patients include the early diagnosis of kidney disease and the ability to monitor enzyme replacement therapy in Fabry patients.

Nuclear imaging expertise in cancer diagnosis and therapy being taken abroad

One of the NIHR BRC's objectives is the dissemination of expertise to national and international research centres. A good example is Dr Lorenzo Biassoni, a Consultant in Nuclear Medicine at GOSH, who recently presented his work at conferences in Pakistan and India. He talked about using imaging techniques such as metaiodobenzylguanidine (MIBG), single-photon emission computed tomography (SPECT) and X-ray computed tomography (CT) scans for both diagnostic and therapeutic use in paediatric solid tumours.

SPECIAL FEATURES:
Athena SWAN
and
Translational Research Manager for Great Ormond Street Hospital and UCL Institute of Child Health

UCL Institute of Child Health Athena SWAN application

The ICH has submitted an application for an Athena SWAN Silver award. Athena SWAN promotes gender equality in the biomedical academic work force, and their Silver award recognises that actions are being taken to address challenges in this area and that these actions are having an impact. From 2015, the award will be one of the eligibility criteria for receiving future funding from the NIHR. The outcome of the application is expected in spring 2014.

The application was led by Dr Shamima Rahman (Reader in Paediatric Metabolic Medicine), supported by a Self-assessment team (SAT) consisting of both academic and non-academic members at different career stages. The team included Professor Rosalind Smyth (ICH Director), Professor Maria Bitner-Glindzicz (Professor of Clinical and Molecular Genetics), Professor Jane Sowden (Professor of Developmental Biology and Genetics), Professor Jenny Morgan (Professor of Cell Biology) and Dr Elisa Fassone (Postdoctoral Research Associate) among many others.

Data was collected about staff and students in order to inform the application. Two critical career crunch points were identified, where support should be given to female staff: for clinical staff there was a loss of female representation at lecturer level, and for non-clinical staff there was a drop in numbers of women at lecturer and at reader career stage.

To address these career crunch points, an action plan has been drawn up (led by Professor Jane Sowden) and a number of initiatives are already underway. A new appraisal style will be introduced and a 'Mums and dads' support group (MADS) has been created, led by Dr Philippa Mills and Professor Maria Bitner-Glindzicz. In June 2013, the first ICH Academic Careers Day was held, targeting female students and postdoctoral researchers. Also in 2013, a NIHR BRC researcher was nominated by the SAT and chosen by UCL to participate in the Aurora leadership programme, a female-only leadership training programme. Future plans include a maternity support fund, a move towards external speaker gender balance, and holding a high proportion of events in core hours (between 10am and 4pm).

Future meetings of the Athena SWAN SAT team will be held bi-monthly and a call for new members will be issued soon. If you are interested in finding out more or getting involved, please contact Shamima Rahman (ICH SWAN champion), Chris Thalasselis (ICH SWAN administrator) or email the SAT directly.

Translational Research Manager appointed for GOSH and UCL ICH

We are pleased to introduce Dr Fiona Chan-Porter, a Translational Research Manager from the Translational Research Office (TRO) at Maple House, UCL. The post is partially funded through our NIHR BRC and UCL.

Dr Chan-Porter's remit is to be the first point of contact for researchers of GOSH and ICH who wish to access translational research support from the TRO. Support includes identifying translatable opportunities, advising on project progression strategy and accessing suitable funding. The TRO also provides project management expertise to steer awarded programmes towards successful endpoints.

Fiona will be based at the GOSH/ ICH Research & Development office on Monday and Friday between 10:00–16:00, and she can be contacted at f.chan-porter@ucl.ac.uk

PATIENTS AND THE PUBLIC

Patient and public involvement (PPI) in scientific research
Erin Walker, PPI lead GOSH/ICH**,** will hold a PPI seminar on 25 March 2014 between 12.00–13.00 Leolin Price Lecture Theatre, ICH. Erin is also available for 1:1 advice, please e-mail Erin Walker.

Research Awareness week at GOSH in May 2014
International Clinical Trials day, which is held on 20 May each year to commemorate the day that James Lind began his trials into the causes of scurvy. James Lind is generally considered to be the originator of clinical trials because he was the first to introduce control groups into his experiments. If you are interested in being involved please contact Nicola Logue.

EVENTS

20 February 2014, 14.00−17.45
Crick symposium: rare diseases
Beveridge Hall, Senate House, Malet St, London
Chair: Philip Beales, UCL (GOSH UCL NIHR BRC theme lead)
Tess Harris, President, PKD International: Personal experiences of living with rare diseases
Tim Aitman, Imperial College London: The new genomics and precision medicine
Nick Wood, UCL: Genetics of neurodegenerative diseases
Michael Simpson, King's College London: Genomics and rare diseases
Veronica van Heyningen, University of Edinburgh Western General Hospital: Genes
Matt Hurles, Wellcome Trust Sanger Institute: Deciphering developmental disorders
Fran Platt, Oxford University: Development of a small molecule therapy for lysosomal disorders
Francesco Muntoni, UCL ((GOSH UCLNIHR BRC theme lead): RNA therapies of neuromuscular diseases.
Register for the event on eventbrite.

25 February 2014, 12.00−13.30
BRC seminar series
Kennedy Lecture Theatre, ICH
Chair: Professor Neil Sebire
Dr Kevin Mills: Proteomics, metabolomics and lipdomics capability of GOSomics
Dr Miho Ishida: The analysis of methylomes and exomes in Silver-Russell Syndrome patients
Dr Manju Kurian and Dr Paul Gissen: Translational research for neurometabolic syndromes of childhood
Dr Karen Price: Use of 3D systems to understand normal human kidney development and disease
Lunch will be served in the winter garden from 13.30.
Please RSVP to Danielle.wagner@gosh.nhs.uk

28 February 2014, 12.00−13.00
How to get NIHR grant funding
Leolin Price Lecture Theatre, ICH
Speaker: Professor David Armstrong, Director, Research for Patient Benefit Programme

13 May 2014, 11.00–17.30
BRC symposium
Kennedy Lecture Theatre, ICH