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) Great Ormond Street Hospital Biomedical Research Centre (BRC) newsletter July 2014

Welcome to the July edition of our NIHR funded GOSH BRC newsletter, which is designed to highlight our notable activity.

A number of BRC supported staff have recently been recognised and honoured. Professor Paolo De Coppi was awarded a highly prestigious NIHR Professorship. This award enables outstanding early career academics to dedicate a fixed five-year period to translational research, strengthen their research leadership and develop research capacity in translational research to improve health. Dr Veronica Kinsler was awarded a Wellcome Trust Intermediate Clinical Fellowship to continue her work on the molecular basis of melanoma. Dr Chiara Bacchelli has been selected as the first Aurora Champion for UCL Institute of Child Health (ICH). Aurora is a new women-only leadership development initiative, which seeks to enable women to engage in leadership development at early stages of their careers.

ICH has achieved an Athena SWAN Silver Award, which recognises ICH's support of women in science.

The focus and work of the GOSH BRC on rare diseases has been given a huge boost by the recent announcement of a generous gift from a member of the Abu Dhabi Royal family to help GOSH - UCL realise it ambition to develop a Centre for Research into Rare Disease in Children. The gift of £60 million will go towards the building of a new centre to house clinical academic teams working on rare diseases at 20 Guilford Street which will open in 2018.

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

David Goldblatt
Director, NIHR Biomedical Research Centre
Director, Clinical Research and Development
Professor of Vaccinology and Immunology
Visit our website: http://www.gosh.nhs.uk/research-and-innovation/biomedical-research-centre-brc/

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NEWS

General news

BRC symposium and external advisory board visit on 13 and 14 May 2014

When the BRC was funded in 2012, it committed to establishing an external advisory board (EAB) with international leaders in their fields to provide oversight as to the performance and strategy of the GOSH BRC. The first meeting of the GOSH BRC EAB took place on 13 and 14 May 2014. The EAB, chaired by Professor David Williams of Boston Children's Hospital, successfully completed their first visit to the GOSH BRC. EAB members are: Professor Mary Rutherford of King's College Hospital, Dr Petra Kaufmann from the National Institute of Neurological Disorders and Stroke, Dr Kym Boycott from University of Ottawa, Dr Stephen W Scherer from the Hospital for Sick Children, Toronto and Dr Julia Dunne of NDA Regulatory Ltd. Recommendations made by the EAB are now being considered and we are planning for a further two visits in 2015.

Coinciding with the EAB visit, we held a BRC symposium attended by around 150 delegates. The symposium provided an overview of the type of research undertaken in each of the GOSH BRC's four themes, a poster exhibition showcasing a number of research projects supported by the GOSH BRC as well as a perspective on how young people view research and what they expect from rare diseases research. The keynote lecture was delivered by Professor David

Williams, who gave an overview of his research into human immunodeficiency and malignancies. Professor Sir Peng Tee Khaw, Director of the NIHR Moorfields BRC, closed the event with his vision for BRCs in the future.

NIHR rare diseases translational research collaboration meeting at UCL Institute of Child Health (ICH)

On 3 July, stakeholders who are part of the immunological and paediatric themes of NIHR rare diseases translation research collaborations (NIHR RD-TRC) came together to showcase their work. 53 people attended the meeting. An introduction on the aims of the NIHR RD-TRC and next steps was given by the operational director for the NIHR RD-TRC, Dr Marijcke Veltman.

Professor Lucy Wedderburn presented her group's work on juvenile dermatomyositis Professor David Sansom and Dr Siobhan Burns their work on common variable immunodeficiency and Professor Phil Beales gave an insight into deep phenotyping for ciliopathies. All speakers stressed the significance of NIHR RD-TRC funding in two areas to achieve patient benefit: 1) the bringing together of lots of individual research projects and 2) the importance of industrial collaborations. In the future significant bioinformatics expertise will be needed to make maximal use of the very precious datasets being generated through these projects.

GOSH BRC trainees win prizes at NIHR Doctoral Research Training Camp in July

The Doctoral Training Research Camp was organised by the NIHR for NIHR funded doctoral students. This year's training camp focused on giving practical training in the preparation and presentation of a funding proposal to an expert panel.

Five GOSH BRC doctoral students attended the event and two were awarded prizes. Aysha Patel won 'Best Oral Presentation' and Sonja Soskic was part of a group winning first prize for 'Best Health Research Funding Application'. Please visit our website for a full account of the training camp.

First annual GOSH BRC trainee day

On the 26 June, the inaugural GOSH BRC trainee day was held. The aim of the day, organised by the GOSH BRC Training team, was to allow 20 GOSH BRC trainees to network, hear about fellow trainees work and learn more about NIHR BRC funding.

GOSH BRC trainees presented details of their projects ranging from gene therapy to tissue engineering to the developments in personalised medicine. Read the full article by GOSH BRC trainee Dr Yvonne Majani on our website.

GOSgene team joins superheroes fundraising event for Rare Disease UK

GOSgene team and family with Ruth Jamieson fundraising for rare diseases

GOSgene is a GOSH BRC funded initiative that works to improve diagnostic testing and supports genetic counselling through facilitating rapid gene identification in uncharacterised genetic diseases.

Staff from GOSgene joined in a fundraising event in support of Rare Disease UK (RDUK), a "national alliance for people with rare diseases and all who support them". Over £1,000 were raised by GOSgene. RDUK believes that everyone living

with a rare disease should be able to receive high quality services, treatment and support.

ICH achieves Athena SWAN Silver Award in May 2014

ICH has received a Silver Award from the Athena SWAN Charter in May 2014. This award is especially important to us as a BRC, since Chief Medical Officer, Professor Dame Sally Davies, indicated that from 2016 the NIHR will only shortlist applications for BRC status from institutions holding such an award.

Athena SWAN Awards recognise success in developing employment practices to further and support the careers of women in science, technology, engineering, maths and medicine departments in academia. An independent report has confirmed that the Charter has a positive impact on gender equality and working culture in institutions. We would like to acknowledge and thank the 'self-assessment' team coordinated by Dr Shamima Rahman for having achieved this result with their fantastic application.

The team has identified key challenges for women's careers in science, promotes existing good practices within ICH and has also created new support structures. Thanks to the team, there is now have an annual ICH academic careers' day, a Mums' and Dads' group and a postdoctoral forum. All events have produced benefits for all staff, not only women. More information can be found on the ICH website.

Molecular basis of childhood disease theme news

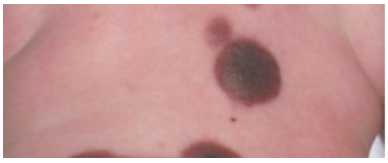
Arthritis Research UK funding won to evaluate a new treatment option for a rare form of vasculitis

Dr Brogan and an international team of experts at a meeting in September 2013 to derive prior opinion to help with the design of the Bayesian randomised controlled trial, MYPAN

Dr Paul Brogan, a GOSH BRC supported researcher, has won an Arthritis Research UK grant to investigate a different treatment option for children suffering from polyarthritis nodosa - a drug called mycophenolate mofetil (MMF). PAN is a rare form of inflammatory blood vessel disease (vasculitis) that results from an autoimmune response. PAN presents insidiously with fever, arthritis, skin rash, and abdominal pain, amongst other symptoms. Its current standard treatment is cyclophosphamide (CYC) in combination with high dose corticosteroids; however this drug has serious long-term side effects.

Dr Brogan will lead a multi-centre international study including the clinical trials unit based at the University of Liverpool and the paediatric rheumatology international trials organisation. The study aims to reduce the PAN disease burden, particularly infection, nausea, and potentially late problems such as infertility and malignancy. The results of this trial would bring immediate and direct clinical benefits to children with PAN. As PAN is very rare, it could take over 60 years to recruit enough patients using the standard frequentist (objective probability) trial methodology. Therefore, the MYPAN trial will adopt a special type of design called Bayesian methodology. The team believe that this type of study design could help clinical trials for any disease where sample sizes are anticipated to be small.

Collaborative treatment programme providing hope for congenital melanocytic nevus sufferers



GOSH BRC supported Dr Veronica Kinsler is collaborating with the Beatson Institute in Glasgow to find a medical treatment for congenital melanocytic naevi (CMN), which in 15 percent of severe cases leads to fatal melanoma. CMN are large moles occurring in 1 in 20,000 infants, and can be associated with other problems such as neurological abnormalities, which is then called CMN syndrome. The charity Caring Matters Now has funded Dr Kinsler's research costs for this study. Dr Kinsler said: "This condition is currently untreatable, so our collaboration to test medical treatments in a laboratory model of CMN syndrome is very exciting, and an

important first step in developing new treatments for patients". Sky news were featuring one of Dr Kinsler's patients in a recent feature on how patients help drive research.

Two BRC funded researchers attend the Eureka Course for Translational Medicine

Dr Chiara Bacchelli and Dr Wendy Heywood, two BRC funded researchers have attended an Eureka Course for Translational Medicine in Sicily this year. The mission of the organisers of this event, the Eureka Institute for Translational Medicine, is to develop a community of translational medicine professionals that will help drive the discovery of new ways to help diagnose and treat patients. The course covered the regulatory and business side of translational medicine, clinical trial design and the value of academic and industry partnerships. Having returned to their working environments, the two researchers will endeavour to build collaborations and disseminate their knowledge to colleagues working in the same field across UCL.

Novel therapies for childhood disease theme news

Two patients recruited at GOSH to natural history study of ultra-rare metabolic disorder


Dr Sophia Varadkar

Molybdenum cofactor deficiency (MoCD) type A is an ultra-rare metabolic disorder that, untreated, results in neurological damage and eventual death within a few months of birth.

Up to 40 centres across the world are participating in a natural history of MoCD study that will inform future therapeutic trials. Within only a few weeks of the study opening at GOSH, a team led by Dr Sophia Varadkar, has achieved the recruitment of two patients to the trial. Instrumental to the robust and swift feasibility and set- up as well as the successful recruitment was the support provided by the GOSH BRC funded Somers Clinical Research Facility (Somers CRF) and the NIHR Clinical Research Network: North Thames (Children's division), who are currently hosted within the Somers CRF. Dr Sophia Varadkar: "I am enormously grateful to you all in the Somers CRF. You have made the whole process clear, guided us through it and been so professional and pro-active at every step". The contribution made by GOSH to this this study sponsored by Alexion Pharma International Sàrl hopefully will facilitate the understanding of this disorder and inform future development of novel treatments.

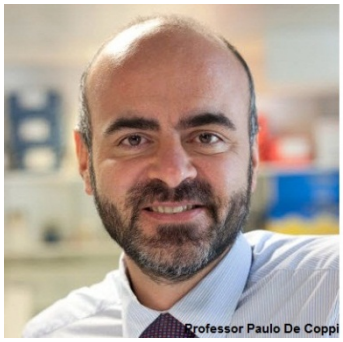
Novel experimental therapy for Duchenne muscular dystrophy found to be safe following a phase 1b study


Professor Francesco

Duchenne muscular dystrophy (DMD) is a severe progressive neuromuscular condition caused by mutations in the DMD gene, which results in the inability to produce a protein called dystrophin. As dystrophin is involved in reinforcing muscle structure, its' absence leads to muscle degeneration and eventual death. DMD affects around 1 in 5,000 boys born in the UK. A drug called SMT C1100, produced by UK biotech company Summit plc, is aimed at increasing the production of a dystrophin-like protein called utrophin. SMT C1100 is orally bioavailable (absorbed) and has the potential to treat all patients with DMD, regardless of the underlying dystrophin gene fault.

Earlier this year a phase 1b study sponsored by Summit plc has confirmed the first safety and tolerability in 12 DMD boys studied in UK. The data of the recently concluded phase 1b study is being analysed to decide the best way to take forward this utrophin modulator drug to a phase 2 trial. GOSH was one of the four UK sites participating in this phase 1b trial. BRC theme lead Professor Francesco Muntoni was both the local lead and the Chief Investigator. More information about this trial can be accessed through the full Summit press release.

GOSH, UCL Hospital and Royal Free Hospital collaborating to develop novel oesophagus replacement therapy



Every year round 250 births occur, where the infants do not have a complete oesophagus. Those infants are unable to swallow or feed and suffer from long-term health issues requiring full-time care. Developing an oesophagus replacement therapy would allow these children to be able to swallow.

Professor Martin Birchall at UCL Hospital Professor Paolo De Coppi at GOSH are coleading the project. Professor De Coppi is leading the development of a novel therapy involving the building of an oesophageal tissue from amniotic stem cells. Once the oesophageal tissue development phase has been completed, the next stage will be for the therapy to go to clinical trial. Funding for the development of the therapy and the clinical trial is provided by UK Stem Cell Foundation and Cell Therapy Catapult with support from UCL Business plc. Please read the GOSH press release and Cell Therapy Catapult press release for more detail.

Professor De Coppi has recently been awarded a prestigious NIHR Professorship.

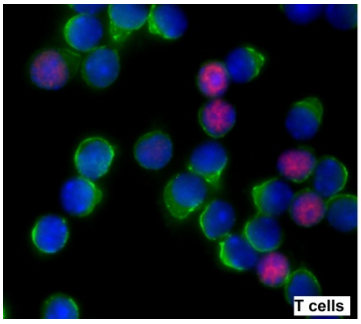
Medical Research Council awards grant to develop novel antisense oligonucleotide therapy for spinal muscular atrophy

A Medical Research Council (MRC) translational research grant (ref: MR/L013142/1) has been awarded to a collaboration led by Professor Matthew Wood at Oxford University and involving our GOSH BRC novel therapy theme lead, Professor Francesco Muntoni, University of Cambridge and Newcastle University. The three-year award of £1,008,202 will facilitate the clinical development of an advanced antisense oligonucleotide therapy for spinal muscular atrophy (SMA). SMA is one of the most common genetic diseases, which causes childhood mortality and is currently incurable.

Professor Muntoni' s research team has recently reported the promising therapeutic potential of antisense oligonucleotide in spinal muscular atrophy in a pre-clinical study using a SMA transgenic mouse model. This work was previously funded by UCL's Therapeutic Innovation Fund, which is supported by the three NIHR BRCs at University College London. This type of therapy is already successful in treating Duchenne muscular dystrophy and has shown the enhanced efficacy in organ-targeting delivery (French Muscular Dystrophy Association program grant to Professor Muntoni).

Gene, stem and cellular therapies theme news

New therapy for leukaemia being developed through collaboration between UCL, Imperial and Cell Therapy Catapult



Acute myeloid leukaemia (AML) is a type of cancer that affects white blood cells called myeloid. In AML, non-functioning myeloid cells are produced that will not fight infection, hence leaving the patient with a diminished immune system. A new therapy discovered by Imperial and UCL scientists involves the genetic modification of the cancer patient's immune T-cells, so that the modified T-cells specifically recognise and destroy tumour cells when infused back into the body.

At our GOSH BRC funded Gene and Cell Therapy Facility, Dr Waseem Qasim and Professor Adrian Thrasher will lead the manufacture of the cell therapy product. Cell Therapy Catapult will sponsor the multi-centre clinical trials led by Professor Hans Stauss and Dr Emma Morris at the Royal Free Hospital, UCL Hospital and other UK centres. To expedite this exciting new therapy, UCL Business, Imperial Innovations and the Cell Therapy Catapult have formed a joint venture, Catapult Therapy TCR Limited, which will assume responsibility for its further development. For more information on the joint venture formed, please visit the UCL news website.

BRC funded Gene and Cell Therapy Facility and Great Ormond Street Hospital Children's Charity supporting development of a stem cell gene therapy trial for in children with Sanfilippo disease


Professors Bobby Gaspar and Adrian Thrasher

Sanfilippo disease or mucopolysacharidosis-IIIA (MPSIIIA)) is a genetic disease caused by the lack of an enzyme responsible for breakdown of the glycosaminoglycan heparan sulphate (HS). The resulting build-up of HS throughout the body means that children with the condition mainly suffer from neurological disease. Further in life, progressive dementia and severely disturbed behaviour characterise the condition and death usually occurs in the mid-twenties. There are no effective treatments.

The aim of the study is to prepare stem cell gene therapy for a clinical trial in children with MPSIIIA by 2016. The benefit to patients from this technology is likely to be a lifelong therapy, which could help to improve brain disease. Any improvement in neurological symptoms in this patient population would be beneficial. GOSH BRC funding will be used to optimise the pre-clinical transduction process, which is important to ensure the stem cell therapy can work. The GOSH BRC leads are Professors Adrian Thrasher and Bobby Gaspar. Great Ormond Street Hospital Children's Charity (the charity) is funding plasmid production and GMP vector manufacture of this project. This award has been made under the charity's national call on rare disease research to Dr Brian Bigger at the University of Manchester.

Diagnostics and imaging in childhood disease theme news

First large-scale genetic association study of drug response in childhood arthritis, funded by SPARKS with additional support from the BRC, provides clues about predictability of medication response

Juvenile idiopathic arthritis (JIA) is a condition that causes inflammation of the joints in children. Uncontrolled JIA can cause irreversible damage to joints and other tissues. A drug called methotrexate (MTX) forms the standard first course of treatment of this disease. For reasons that are unknown, treatment responses to MTX differ between patients.

A study led by Professor Wedderburn in collaboration with health research centres in Manchester, Birmingham, the Netherlands and Czech Republic has discovered a potential explanation for the differences in treatment response. Three novel genes have been identified as being likely to be associated with response to MTX. This study published in '*The Pharmacogenomics Journal*' (*Nature* group) is the first of its kind for JIA, both in terms of its large scale and comprehensive cover of the genome. Future work can now look at using this study to develop genetic risk models for MTX response prediction.

Significant funding received for fetal surgery research

UCL has received a £10 million award from the Wellcome Trust and the Engineering and Physical Sciences Research Council to develop better tools, imaging techniques and therapies for fetal surgery research. Improved fetal surgery will benefit around one-in-a-hundred babies in the UK that are born with a severe birth defect.

GOSH surgeons will play a key role in the research leading the development of improved ways to deliver stem cell therapies to the unborn baby in the womb, working on better surgical imaging techniques and improving precision during surgery. The overall project lead, UCL's Professor Sebastien Ourselin said: "Our aim is to combine less invasive surgical technologies with stem cell and gene therapies to treat a wide range of diseases in the womb, with considerably less risk to both mother and baby." Professor Paolo de Coppi, consultant paediatric surgeon at GOSH and the local lead at GOSH, added: "As the safety of foetal surgery increases, it is possible that many of the operations that we currently perform on newborn babies at

Great Ormond Street will become fetal procedures. That's very good news for a child's long term outlook, because the earlier we can correct a serious defect in a growing fetus, the better the outcome is likely to be for the child and their future development." To read the full stories, please see GOSH press release and UCL news.

SPECIAL FEATURES

Somers Clinical Research Facility

The Somers Clinical Research Facility (Somers CRF) provides specialist day care accommodation for children and young people taking part in clinical research studies. It is a state of the art, purpose-built facility, which is available to all GOSH and ICH staff undertaking clinical research, in particular early phase and experimental medicine studies. As well as a dedicated space for clinical research, there are a team of research nurses and data managers, a play specialist, a trial pharmacist, admin team and preparation laboratory.

The GOSH BRC award from the NIHR provides the 70 percent of the revenue costs with 30 percent being supported from commercial sources. There are currently over 70 active research studies taking place in the facility, covering over 20 different clinical specialties and half of studies are sponsored by industry. One of the Somers CRF recent successes is that two of the studies they have delivered have led to the clinical development and approval of a drug called VIMIZIM as a treatment for Morquio A syndrome. Six children were recruited into both studies, which we have been running in the Somers CRF since November 2010. There are currently over 20 new studies at different stages of set-up and 84 percent of these are industry sponsored.

If you are interested in using the Somers CRF for your clinical study, please contact the operations manager, Mrs Eleanor Rolle-Marshall.

Clinical Academic Programme Lead appointed for GOSH and ICH

Dr Kate Oulton, a Senior Research Fellow from the Centre for Outcomes and Experience Research in Children's Health, Illness and Disability (ORCHID), has been appointed as the Clinical Academic Programme Lead: Nursing and Allied Health Research. This part-time post is funded through our BRC and will work together closely with Lorraine Hodsdon, Head of Nursing Clinical Research.

Dr Oulton's remit is to co-ordinate the nursing and allied health research training plan at GOSH and ICH and she will be the first point of contact for nurses and allied health professionals who wish to pursue a clinical academic career. Support will include research career advice, identifying research training opportunities, advising on study design and dissemination, accessing suitable funding and facilitating peer support.

Dr Oulton will be based in the ORCHID office on Level 4 of York House on Monday, Tuesday and Thursday between 10:00–16:00, and she can be contacted on 0207 8297822, kate.oulton@gosh.nhs.uk.

ORCHID run drop-in sessions every Tuesday from 12.00– 14.00 for general research advice. No booking required.

PATIENTS AND THE PUBLIC

First research awareness week at GOSH

International Clinical Trials Day was celebrated by GOSH BRC staff through organising a Research Awareness Week in May. The aim of Research Awareness Week was to increase awareness of research taking place at GOSH amongst patients, families and staff. Several events and activities took place across the Trust throughout the week, including displays and seminars in the Lagoon, an open afternoon in Lung Function and sessions in the Hospital School, facilitated by Stuart Adams and his team in the labs and Erin Walker, our Patient and Public Involvement and Engagement (PPI/E) in research lead.

On International Clinical Trials day, patients and their families were asked to give feedback on what they thought about research. Many families came forward to tell us their stories and how grateful they were for the work that goes on at GOSH and the difference it has made to their child and family life. Research Awareness Week is just one step we are taking to further embed research in the clinical environment.

If you are interested in being involved with research communications or have any ideas about raising the profile of research in your area, please contact Nicola Logue.

Hospital school lesson on research

Dr Erin Walker (BRC lead for PPI/E in research) led a school lesson with inpatients from key stages 3 and 4 on the importance of paediatric experimental medicine. Topics covered were: what research is, why research involving children and young people is necessary, who carries out research, different research methods and an introduction to research ethics. Students completed a matching quiz to learn important terms and definitions in research, to get an idea about the language used in clinical trials. The lesson was well received by students and staff, and it is anticipated the lesson will run again.

PPI consultancy

Individual consultancy on the PPI can be arranged with Erin Walker. If you are preparing a grant application, or want to implement PPI in a current research project, please email Erin Walker to arrange a meeting.

GOSH BRC Open Day and London Science Festival
15 November 2014, 10:00 – 16:00, UCL Institute of Child Health

The aim of this day is to increase the general public's understanding of medical research, illustrate how it changes lives and inspire interest in a career in biomedical research. The day will include a variety of events, including hand-on activities, seminars, posters and lab tours. For more information on a draft schedule for the day, please visit our GOSH BRC events page.

If you want to get involved, please contact Erin Walker.

EVENTS

13–14 September 2014, Ashridge Business School, Hertforshire

Residential National Paediatric Academic Trainee Weekend

- An excellent opportunity for 40 academic paediatric trainees to develop their research skills in a weekend course supported by the GOSH BRC.
- The innovative programme includes facilitated interactive work in small groups on grant proposals, the peer review process, ethics review, and presentation skills.
- This will be a great opportunity to network with fellow paediatric trainees and academic leaders in paediatrics.
- Please visit the events page on the GOSH BRC website to view the draft programme.
- Acceptance to the weekend will be competitive, please e-mail Danielle Wagner to check current availability.

2 October 2014, 12:00– 13.30, Kennedy Lecture theatre, UCL Institute of Child Health

GOSH BRC Seminar

Chair: Professor Phil Beales.
Dr Kate Oulton: Nurses and AHPs as researchers.
Dr Kate Khair: Living with haemophilia – what children tell us.
Ms Victoria Selby, Ms Danielle Ramsey: Recent Developments in Outcome Measures for Children with Neuromuscular Disorders.
Ms Sonja Soskic: Advanced imaging in cerebral palsy.
Dr Claire Booth: Gene therapies for rare diseases: translation to clinical benefit.
Followed by lunch in Winter Garden after 13:30