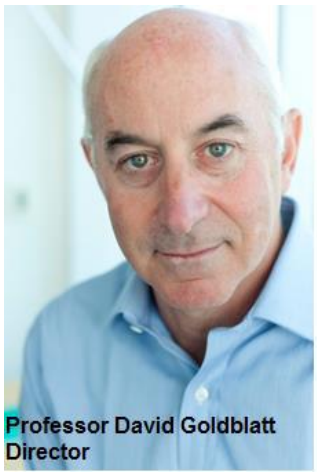
National Institute for Health Research

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

Director's introduction


Professor David Goldblatt
Director

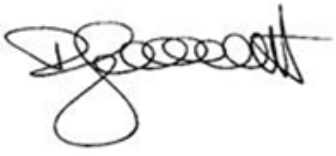
Welcome to the June 2016 edition of our newsletter, highlighting the activity and achievements of our National Institute for Health Research Biomedical Research Centre (BRC) at Great Ormond Street Hospital for Children NHS Trust and University College London.

I would like to congratulate Professors Francesco Muntoni, Jane Sowden and Helen Cross who have all been successfully appointed as new NIHR Senior Investigators. They join myself and Professors Phil Beales, Neil Sebire, Lyn Chitty and Catherine Law. NIHR Senior Investigators represent the country's most outstanding leaders of clinical and applied health and social care research and are fundamental to the formation of the NIHR faculty.

I would also like to take the opportunity to thank all those who contributed to the BRC annual report return. This report provides valuable data to the NIHR from which we are ranked against all other BRCs therefore, it is vital that the data we return is as accurate as possible, and so your help with this is greatly appreciated. The annual report is of even more importance this year due to the upcoming BRC renewal. We have now submitted the full application to apply for funding for a further five years from 1 April 2017 and representatives will be attending an interview on the 19 July.

This issue features the launch of ORCHARD Therapeutics, a clinical-stage biotechnology company formally partnered with UCL and GOSH. ORCHARD's founding scientists include BRC Deputy Director Professor Bobby Gaspar and the Theme Lead and Deputy of the Gene Stem and Cellular Therapy Theme, Professor Adrian Thrasher and Professor Waseem Qasim.

I hope you enjoy reading this newsletter and as always welcome any thoughts and contributions you would like to make. Please e-mail BRC Newsletter with any future contributions to the newsletter you would like to include.



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

BRC newsletter- June 2016

Visit our website

CONTENTS

SPECIAL FEATURE

Orchard therapeutics launched to treat rare diseases

Orchard Therapeutics, a clinical-stage biotechnology company, launched in May and announced formal partnerships with University College London (UCL), Great Ormond Street Hospital (GOSH), The University of Manchester, The University of California Los Angeles and Boston Children's Hospital.

Orchard Therapeutics has secured £21 million in their first round of financing from F-Prime Capital, a leading international venture capital firm with a focus on healthcare and life sciences and extensive experience in investing in rare diseases and gene and cell therapies. It's also received support from UCL Business PLC and additional participation from the UCL Technology fund.

Orchard Therapeutics' mission is to translate results from pre-clinical and early clinical research into commercially approved gene therapies for patients all over the world. The focus of Orchard Therapeutics' development programmes is on the restoration of normal gene functioning in primary immune deficiencies, metabolic diseases and haematological disorders, through the use of *ex vivo* autologous haematopoietic stem cell gene therapy. This pioneering technique makes use of the patient's own stem cells, which are taken and modified outside of the body, by replacing the faulty or missing gene with a functioning copy and then transplanted back into the patients. The use of the patient's own cells eliminates the need for a donor and minimises the risk of transplant rejection. Furthermore the correction of the patient's cells outside of the body allows each patient to be treated with a unique product.

Orchard Therapeutics' lead programme is for the treatment of severe combined immunodeficiency caused by adenosine deaminase deficiency (ADA-SCID) with ex-vivo autologous lentiviral stem cell gene therapy. ADA-SCID is a very rare genetic disorder which results in those affected having a highly fragile immune system causing them to be highly susceptible to life-threatening infections and untreated ADA-SCID is lethal. However, interim results from ORCHARD's programme show significant immune reconstitution in 32 patients with 100% survival.

Professor Bobby Gaspar, Deputy Director of the NIHR GOSH BRC is Orchard Therapeutics' Chief Scientific Officer and sits alongside Professors Adrian Thrasher and Waseem Qasim, Gene Stem and Cellular Theme Lead and deputy, on ORCHARD Therapeutics' Scientific Advisory Board. Orchard Therapeutics' founding scientists include Professors Bobby, Adrian and Waseem and the work at UCL ICH was developed through their laboratories which received funding support from the NIHR GOSH BRC.

Orchard therapeutics

GENERAL NEWS

Parents fight for approval of drug originally developed at GOSH to treat Duchenne Muscular Dystrophy

Parents of children with Duchenne Muscular Dystrophy (DMD) are fighting for approval of drug developed at GOSH by Novel Therapies Theme Lead, Professor Francesco Muntoni.

DMD is a rare X-linked degenerative neuromuscular disorder that causes severe progressive muscle loss resulting in death, usually before the age of 30.

Trials of the drug, Eteplirsen, have shown that it enables patients to continue to walk. The US Food and Drug administration (FDA) is considering whether to grant accelerated approval for a trial drug. The FDA evidence session in Washington in April had an unprecedented attendance by hundreds of affected boys and families, including 40 families from the UK. All DMD boys in the trial and their parents gave their perspective to the FDA panel. The outcome of the FDA panel on the accelerated approval of Eteplirsen is expected imminently.

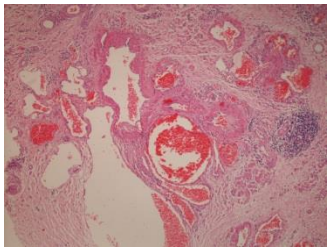
Read the full article in the London Evening Standard.

MedCity have launched an online guide to clinical trials in London

MedCity is a collaboration between the Mayor of London and the capital's three Academic Health Science Centres - Imperial College Academic Health Science Centre, King's Health Partners, and UCL Partners, with the aim of promoting and growing the world-leading life sciences cluster of England's greater south-east.

MedCity have now launched an online guide to clinical trials in London. This features three multi-centre studies hosted at GOSH, which all successfully recruited first global patients. These were headed by Professor Francesco Muntoni (Phase 1, open-label, single and multiple oral dose, safety, tolerability and pharmacokinetic study in paediatric patients with Duchenne Muscular Dystrophy), Professor Ri Liesner (haemophilia study designed to evaluate the safety and efficacy of a recombinant fusion protein- Coagulation Factor VIII Fc Fusion Protein) and Dr Anna Martinez (Phase 3 multi-centre, randomised, double-blind, placebo controlled trial investigating the efficacy and safety of SD-101 cream in patients with Epidermolysis Bullosa).

Collaboration between 3 NIHR BRCs leads to discovery of genetic mutation thought to cause Venous Malformations



A collaboration between three NIHR BRCs including GOSH BRC, UCLH BRC and Cambridge BRC has led to the discovery of a genetic mutation linked to Venous Malformation's (VM's) and the possible treatment of VM's using a drug currently being trialled to treat cancer patients.

VM's are present at birth and can result in painful lumps on the skin, currently the primary intervention for VM's is Sclerotherapy, however this is not fully efficient and can cause a number of side effects.

Researchers aiming to investigate cancer genetically engineered mice to have a mutation in PIK3CA. However, this mutation unexpectedly led to the development of VM's. Subsequent genetic tests carried out on VM patient samples confirmed the presence of this genetic mutation in around a quarter of these patients. Researchers then tested a drug on the mice that directly inhibits PIK3CA and is currently being trialled for cancer treatment.

Findings showed that the drug significantly reduced the size of the malformations, results which were seen when the drug was administered either through the blood stream or when applied as a cream to the skin. These findings could provide guidance for advanced diagnosis and a possible targeted therapy and have been published in Science Translational Medicine

Read the full press release here.

Molecular basis of childhood diseases theme news

Positive preliminary results from the Rapid Paediatric Sequencing Project

The Rapid Paediatric Sequencing project (RaPs) is a pilot project aimed at evaluating the use of rapid Whole Genome Sequencing (WGS) for rare diseases in a clinical setting. Successful results have been received back from the first patients to have taken part. The project is being led by BRC supported Dr Hywel Williams.

The pilot phase of this project aims to identify 10 patients (run as family trios e.g. patient plus their two parents) from the Paediatric Intensive Care Unit (PICU) at GOSH and to date 8 patients have been successfully enrolled. These patients were identified as having immediate clinical need, presented with a phenotype of genetic aetiology and for whom the rapid identification of a causative gene could have a positive impact on their clinical management.

The Rapid Paediatric Sequencing pipeline begins with patients being identified by a senior clinician on PICU. Blood samples are then collected from the patients which then undergo DNA extraction and sequencing.

Preliminary results show that actionable findings could be returned to the PICU clinicians within five days of the initial consent. Of the patients processed so far, they have identified three genes known

to cause the underlying disease present in the patient and two genes that are candidates for the disease. This project is run by GOSgene, which is wholly funded by the BRC.

Dr Wendy Heywood awarded Investigator initiated research proposal from Shire Pharmaceuticals

Following BRC support, which led to the creation of a high-throughput targeted proteomic urine test, Dr Wendy Heywood has been awarded an industry Investigator initiated award from Shire Pharmaceuticals.

This award is for a GOSH research nurse to facilitate the clinical sample collection pipeline and manage a database of patient samples/clinical information. This Rare Disease Sample Collection will allow researchers at ICH and Clinicians from the GOSH Metabolic disease clinic, to find new biomarkers, new disease mechanisms, design new treatments and test patients.

This streamlined UCL-GOSH collaboration will enable translation of current and future new metabolic disease biomarkers to clinical laboratories for use in future clinical trials of existing and novel therapies.

Novel therapies for translation in childhood disease theme news

Biomarin release results from CLN2 trial being carried out at GOSH

Biomarin have released positive 48-week results from a clinical trial of cerliponase alfa treatment for CLN2 disease. GOSH's involvement in the trial was led by Novel Therapies Deputy Theme Lead, Professor Paul Gissen.

CLN2 disease is a form of Battens Disease, a fatal neurodegenerative disease. It is the result of mutations in the TPP1/CLN2 gene causing deficient activity of the tripeptidyl peptidase 1 enzyme (TPP1). Cerliponase alfa treatment is a recombinant form of TPP1 and is designed to restore TPP1 enzyme activity.

In this phase 1/2 trial, cerliponase alfa treatment was administered directly into the brain ventricles via intracerebroventricular infusions. At one year the results have shown an 80% reduction in the progression of the disease relating to decline in motor and language functioning, when compared to the natural progression of the disease. Furthermore, treatment was also found to reduce cortical grey matter loss.

Biomarin plans to submit marketing applications and is planning to implement an early access programme to enable additional CLN2 patients to have access to this treatment.

Read the full press release here.

Reduced risk of pulmonary embolism in children treated with long term parenteral nutrition.

Researchers at GOSH have shown a reduction in the incidence of Pulmonary Embolism (PE) in patients receiving parenteral nutrition (PN) after the introduction of a new mixed Intravenous Lipid Emulsion (ILE).

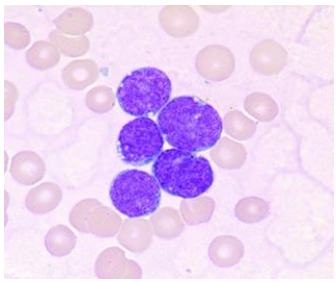
The prevalence of PE occurring in patients receiving PN is 35%, however since the introduction of a new ILE in 2003 there has been a reduction. The ILE given prior to 2003 contained Ω-6 fatty acids and has been shown to generate a pro-inflammatory response and impair immune system function. New ILE's have the beneficial effect of reducing Ω-6 fatty acids, with a shift towards a less inflammatory state.

The aim of the study was to compare the incidence and severity of PE before and after the change in PN lipids in 2003, through retrospectively reviewing surveillance ventilation-perfusion (V/Q) scintigraphies.

The findings showed that with the change in ILE after 2003 the number of patients who had an episode of PE at some point during PN significantly dropped from 45% to 11%. However, patients receiving the new mixed ILE's were still at risk of PE, therefore regular surveillance on an annual basis with V/Q scintigraphy was recommended. Findings have been published in Clinical Nutrition, March 2016.

Gene, stem and cellular therapies theme news

Clinical trial to investigate treatment of Acute Lymphoblastic Leukemia has opened at GOSH



A Phase 1 clinical trial (CARPALL) has opened at GOSH to investigate the use of immunotherapy with genetically modified T-cells for Acute Lymphoblastic Leukemia (ALL), the trial is led by BRC supported Professor Persis Amrolia.

Relapse is the primary cause of treatment failure for paediatric ALL with 25 children in the UK dying a year from untreatable leukemia relapse. Emerging data shows unprecedented responses to immunotherapy, with genetically redirected T-cells expressing 2nd generation chimeric antigen receptors (CARs) enabling them to recognise and kill ALL cells. However currently it is unclear how sustained these remissions are, as most responding patients have been consolidated with stem cell transplant (SCT).

The trial will take place at GOSH, UCLH and Manchester Children's hospital. It aims to treat 15 children and young adults with high risk relapsed ALL to investigate the durability of responses to CD19CAR T-cells and whether this strategy could obviate the need for SCT. If successful, it could mean that the short term mortality and late toxicities of SCT could be avoided.

Phase 1 clinical trial utilising CAR T cells to treat refractory neuroblastoma has opened at GOSH

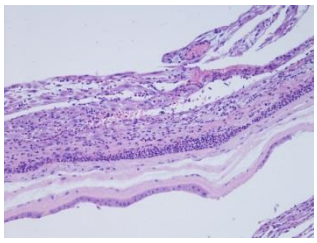
A Phase 1 clinical trial of T cell immunotherapy for relapsed or refractory neuroblastoma has opened at GOSH. The trial is led by BRC funded Professor John Anderson, Dr Karin Straathof, Dr Barry Flutter and Dr Martin Pule, and is funded by Cancer Research UK who will manage sponsorship through the Cancer Research UK Centre for Drug Development.

Neuroblastoma is the most common paediatric solid cancer outside of the brain and remains a significant cause of child mortality. Emerging data in the leukaemia and lymphoma field has shown the capacity of immunotherapy using CAR gene modified T cells to induce sustained clinical remissions in patients with chemotherapy refractory disease.

The current trial tests whether applying the same second generation CAR technology to solid tumours can induce similar clinical responses in a group of patients with no prospect of cure with conventional therapies. The trial will open at GOSH as a single site but with the prospect of expansion into phase 2 and opening at other centres, initially UCLH. The trial has been made possible by the unique infrastructure in gene and cell therapy at Great Ormond Street Hospital.

Diagnostics and Imaging in Childhood Diseases theme news

Trial suggests no adverse effects of vaginal progesterone prophylaxis for the prevention of preterm birth on child at age 2



Diagnostics and Imaging Theme Lead, Professor Neil Sebire has teamed up with researchers from nine other establishments to carry out the largest randomised trial to investigate the long-term safety of vaginal progesterone prophylaxis for preterm births.

Research has shown reduced risk of preterm births in high risk women when progesterone is administered, however, there remains uncertainty over the long term effects on the child.

A randomised control trial was carried out in 1228 women who were at increased risk of preterm birth. Women were randomly assigned to either progesterone capsules or placebos. Results showed that administration of progesterone did not significantly affect the risk of obstetric (fetal death or birth before 34 weeks), neonatal (including death, brain injury, or bronchopulmonary dysplasia) or childhood outcomes (standardised cognitive score at 2 years of age). Results showed progesterone use was not associated with preterm birth or adverse neonatal outcomes, as well as having no longer term effects at age of 2. Findings have been published in the Lancet.

Identification of new technique to aid diagnosis of Congenital Disorders of Glycosylation

Congenital disorders of glycosylation (CDG) are a group of rare genetic, metabolic disorders caused by an error in glycosylation. There are over 60 different CDG identified, resulting in a broad range of clinical symptoms, making initial clinical assessment challenging. Screening of CDG is currently based on the investigation of the glycoproteins transferrin and apolipoprotein CIII. However, this cannot diagnose all potential defects in the glycosylation pathway and overlooks new inborn errors of metabolism, resulting in more subtle defects being missed.

This study investigated the use of a 2D-Differential Gel Electrophoresis (DIGE) method that provides a global analysis of the serum glycoproteome (glycomic profiling). 2D-DIGE allows multiple samples to be run simultaneously, eliminating gel-to-gel variations, and allowing direct overlay comparisons.

The results showed that for some CDG patients not all glycoproteins were consistently affected. The results identified several new and specific markers of N- and O-linked glycoproteins, never before described. These proteins were shown to be changed in patients, something that conventional tests failed to identify. The findings showed that 2D DIGE is an ideal method for investigation of the global glycoproteome and it could aid diagnosis and sub classification of complex CDG cases, with the potential to identify new diseases. This work was supported by the NIHR GOSH BRC and findings have been published in Molecular Genetics and Metabolism reports.

PATIENTS AND THE PUBLIC

Parent/Carer Research Advisory Group

The group, which formed in June 2015, has their next meeting on 4 July. Researchers will be attending to consult with the group and hear parents' perspectives on their projects. The group has 18 members, with a range of experiences; about 90% have experience of parenting a child with a health condition and/or have had a premature baby, some have research experience and some have been involved in PPI previously. Any researcher at GOSH/ICH looking for PPI can consult with the group, it's a free resource and consultation can take place through attendance at a meeting and/or virtually.

Young Persons Advisory Group

Our Generation R Young Persons Advisory Group (YPAG) has seen a flurry of activity since our last update in the March newsletter. The group was involved in the launch of Sofie Layton's Under the Microscope exhibit on 3 March, and led tours of the installation on 12 March.

YPAG had a stand at the local AWARE for All health research engagement event at the Camden Centre on 7 March, where two of our young members presented in a panel session as, 'Medical Heroes'.

Another one of our members spoke at a meeting at the Nuffield Council on Bioethics about young person engagement with industry, and her presentation was extremely well received. She also participated in a panel session at the recent NIHR at 10 Conference on the value of young people getting involved in research, again to much acclaim.

Part of the role of the group is to advocate for children and young people's involvement in research and our members are excellent examples of how young people can meaningfully contribute to child health research. Similar to the Parent/Carer Research Advisory Group, YPAG advise on specific research projects, as well as local research engagement activities. The group will next meet in August and anyone interested in attending the meeting or accessing YPAG should contact Ruth Nightingale

PPI training for researchers

In collaboration with NIHR UCLH BRC and colleagues across North Thames, we will be hosting a series of PPI in research training sessions for researchers with a range of experience (from 'beginner' to 'experienced'). Workshops will take place from June to December this year, for more information please visit their website.

If you would like any information or advice about PPI/E, please get in touch with Erin Walker and Ruth Nightingale, Joint Leads for PPI/E via research.ppi@gosh.nhs.uk

TRAINING

Recipients of the NIHR Great Ormond Street BRC 2016 Doctoral Training Support Funds

Congratulations to the seven trainees who have been awarded Doctoral Training Support Funding to support their PhD research. The NIHR GOSH BRC Doctoral Training Support Fund provides consumables funding for translational clinical research/experimental medicine projects being undertaken by PhD students within GOSH and ICH. It is anticipated that another call for funding will be advertised early next year.

To view the abstracts of the seven successful applicants please visit our website.

EVENTS

Upcoming Events

NIHR GOSH BRC trainees selected to attend NIHR Infrastructural Doctoral training camp

Congratulations to Hanna Sakki and Hoong-Gan Wei who have been selected to represent the NIHR GOSH BRC at the seventh NIHR Infrastructural Doctoral training camp. The event is due to take place at Ashridge Business School on 6-8 July 2016. The training camp is an intense three day annual event for NIHR trainees offering workshops, guest speakers and opportunities for networking and mentoring. The focus of this year's camp will be on 'A call for proposals'.

UCL small molecule dragons' den event 7th July

The Translational Research Office (TRO) in collaboration with UCL School of Pharmacy Drug discovery cluster, are holding a small molecule dragons' den event at UCL school of Pharmacy on 7 July 1pm-5pm.

The event is an opportunity to learn about a wider range of drug discovery activities at UCL and the available support. The event will feature researchers from across UCL pitching their small molecule discovery ideas to a panel of industry experts; this will be followed by a poster session and networking event.

The event is open to all researchers at UCL, for more information please click here.

Registration now open for NIHR GOSH BRC National Residential Training weekend

Registration is now open for the 2nd National Residential Training weekend organised by the NIHR GOSH BRC. The event will be held on the 1-2 October at Ashridge Business School. The weekend is open to clinical academic trainees working in child health including medical, nursing and allied health professionals. The event offers an opportunity to network with fellow clinical trainees and academic leaders in paediatrics, providing a unique opportunity to develop research skills and gain career advice. The event focuses on developing skills in undertaking research with children and young adults and explores different research methodologies. Confirmed guest speakers include Professor Terrence Stephenson, Dr Shelley Dolan, Professor Jonathan Grigg, Professor Peter Callery, Professor Clare Lloyd and Dr Jack Kreindler.

To register please visit the NIHR GOSH BRC website.

Health and Care Innovation Expo 2016

The NHS Health and Care Innovation Expo is one of the NHS' biggest events, celebrating world leaders in science, research and innovation. The event will be returning to Manchester on 7 and 8 September 2016.

To register for the event please visit their website.

Past Events

Celebration of ICH/GOSH translation event

Following the successful ICH Rare Diseases Elevator Pitch event, ICH, in collaboration with UCL's TRO and UCL Business (UCLB), held an event on 8 April to showcase the exceptional translational science taking place at ICH/GOSH with the aim of highlighting the available support within UCL required to perform it.

The event featured a series of talks from ICH scientists on how they have tackled moving their research along a development path, into the clinic and on to commercial readiness. This was followed by a panel debate on the challenges of translation, with representatives from UCLB, R&D and the TRO. Attendees included PIs, Post Docs and PhD students who were invited to meet with representatives from the TRO, R&D and UCLB at a networking event in the afternoon, held in the Winter Garden.

This marks the second in a series of events aimed at fostering a translational culture within ICH/GOSH. For further information and to request a follow-up meeting to discuss translational projects please contact Dr Pamela Tranter from the TRO.

Spotlight on Research fortnight success

To celebrate International Clinical Trials Day, staff from the BRC and ORCHID organised a series of research awareness events to put the 'Spotlight on Research'. Various activities for patients, families and staff took place during the fortnight to raise the profile of research at GOSH, showcase examples of the work we do and encourage engagement with research.

Highlights for patients included a research trail around GOSH where at least 70 children and their families met with researchers, participated in interactive activities to learn more about research and win prizes. All those who took part enjoyed the experience and reported learning something, one parent commented: 'Very educational, great idea and research teams very friendly and child friendly. My daughter is only three and a half, but she found it really interesting'. Families were also invited to record photo-messages about research at GOSH and what they think it means for GOSH to be a research hospital. Everyone seemed to value the opportunity to share their views and some parents found it emotional reflecting on how important research was to their child's life.

'Spotlight on Research' events for staff included a pub quiz, attended by over 50 GOSH/ICH members of staff. The nine quiz teams demonstrated their knowledge in various areas, including a specially developed research round. Congratulations to the winning team from R & D!

Staff also attended a workshop led by artist Sofie Layton and bioengineers from the cardiovascular imaging team to find out about the research behind 3D heart models and create their own embossed heart. The well-attended

ORCHID research conference included a range of presentations and posters showcasing nursing/AHP led research in GOSH/ICH. An inspiring keynote lecture was given by Professor Bernie Carter, Professor of Children's Nursing at Edge Hill University and Director of the Children's Nursing Research Unit Alder Hey Children's NHS Foundation Trust.

NIHR's 10th anniversary conference

Representatives of the NIHR GOSH BRC attended the NIHR's conference to celebrate our 10th anniversary. The conference showcased some of the world-class research funded and supported by the NIHR and featured guest speakers including The Rt Hon Jeremy Hunt MP and Professor Dame Sally Davies. Those who attended also heard from a patient with a diagnosis of Alzheimer's disease. The conference concluded with a panel debate where attendees had the opportunity to ask questions about future challenges and possible directions for the NIHR in the future.