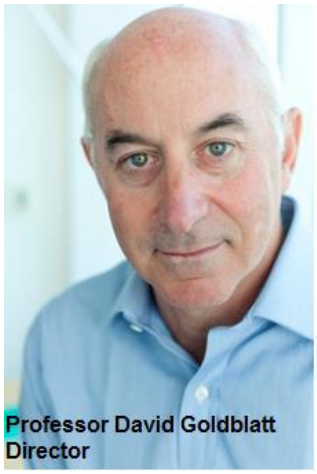
News from the
NIHR Biomedical Research Centre at
Great Ormond Street Hospital for Children NHS Foundation Trust
and University College London

SEPTEMBER 2015

Director's introduction


Professor David Goldblatt
Director

Welcome to the September 2015 edition of our newsletter, which is designed to highlight 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 welcome the appointment of Professor Thomas Voit as Director Designate of the NIHR Great Ormond Street BRC. Professor Voit is a leader in the field of genetics and neuromuscular disease and joins us from Pierre et Marie Curie Sorbonnes Universities, Paris. He joins the organisation on 1 October 2015 and will be responsible for developing our strategy for renewal of the BRC (the current BRC is funded until April 2017). In the event of a successful renewal, he will take over as the Director of the next BRC in 2017.

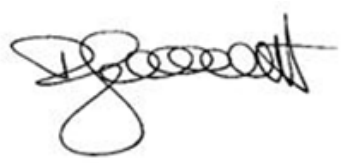
In this issue we focus on the role of UCLPartners (UCLP) Academic Health Sciences Network (AHSN) in improving outcomes for children and young people (CYP) with epilepsy. This initiative has been a successful collaboration between the UCLP-AHSN, Professor Helen Cross and Young Epilepsy, the national charity for CYP with epilepsy.

A number of BRC supported staff have recently been recognised and honoured. Professor Helen Cross received an OBE in the Queen's Birthday Honours for her services to Children with Epilepsy. Professor Waseem Qasim has been awarded a prestigious NIHR Research Professorship, one of only four awarded nationally this year. The posts are designed to support the country's most outstanding research leaders during the early part of their careers, to lead research, to promote effective translation of research and strengthen research leadership at the highest academic levels. Special

congratulations to Drs Paul Brogan, Patrizia Ferretti, Andreas Roposch, Lesley Rees, Juan-Pedro Martinez-Barbera, Paul Winyard and Waseem Qasim who have all been promoted to UCL Professors. Drs David Carmichael, Darren Hargrave, Thomas Jacques, Naomi Dale, Rukshana Shroff and Owen Williams have been promoted to Reader. Finally, Manju Kurian has been promoted to Principal Research Associate. Well done!

I would also like to congratulate Professor Nigel Klein and Ms Louise Paine (NIHR funded research nurse) for their hard work in recruiting the first global patient to the Valgan Toddler study, funded by the National Institute of Allergy and Infectious Diseases (NIAID) (National Institutes of Health (NIH)) and sponsored by UCL. This is a phase II, randomised study investigating the benefits of six weeks of Oral Valganciclovir Therapy in Infants and Children with Congenital Cytomegalovirus Infection and Hearing Loss.

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

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SPECIAL FEATURE

Improving epilepsy care for children and young people - the role of UCLPartners-AHSN

UCLPartners (UCLP) is one of fifteen accredited Academic Health Science Networks (AHSNs) in the UK. Over the past year, UCLP has been integral in improving outcomes for children and young people (CYP) with epilepsy (Programme Director, Professor Monica Lakhanpaul). To achieve this, UCLPartners has worked closely with Professor Helen Cross (UCL-ICH), who has provided a wealth of paediatric epilepsy expertise and significant strategic support to the project. Young Epilepsy, the national charity for CYP with epilepsy, has been central to the project's success, providing crucial third sector input.

The achievements of this collaboration include the creation of a pan-London Paediatric Epilepsy Steering Group, the hosting of a multi-professional stakeholder event and the publication of an influential policy report. The team's work has also been referenced in a Backbench Debate in

Parliament, and the partnership was subsequently invited to speak at the All-Party Parliamentary Group on epilepsy.

The group continue to build on their successes, including establishing an epilepsy registry, developing a standardised template for individualised education health and care plans for CYP with epilepsy and helping create a network for young people with epilepsy. The team also plans to commission a whole-system health care economics analysis to map the advantages of an integrated approach to treatment.

UCLP harnesses world-class academic and clinical specialty expertise to speed up the development of new treatments, diagnostics and prevention strategies. In doing so, the AHSN plays a pivotal role in fulfilling the mission of UCLP to transform the health of our population and drive economic growth. Following a successful first-term, the Department of Health confirmed UCLP to continue as an AHSN for a further five years from 1 April 2014.

GENERAL NEWS

100,000 Genomes Project opens at GOSH

The North Thames NHS Genomic Medicine Centre, led by Great Ormond Street Hospital, is a collaboration between Great Ormond Street Hospital and Bart's Health, Moorfields Eye Hospital, London North West Healthcare, The Royal Free London and UCLH. We recruited our first patient to the government's 100,000 Genomes Project in June. This project aims to sequence 100,000 whole genomes from people across England, which could lead to more effective treatments for cancer and rare conditions, as well as speedier and more comprehensive diagnosis for patients with rare diseases. The North Thames NHS Genomic Medicine Centre hopes to provide 15,000 of the 100,000 genomes to be sequenced. Many blood samples are being donated by parents and children at GOSH and by patients at Moorfields Hospital and we will soon be recruiting patients and their relatives across the partnership. For more information about eligibility criteria and how to refer patients to the project, please go to: 100,000 Genomes Project.

Professor Bobby Gasper participates in Live Twitter Q&A

Professor Bobby Gaspar, Deputy Director of the NIHR Great Ormond Street BRC and expert in paediatrics and immunology at GOSH, appeared in the first episode of the new series of *Great Ormond Street*, entitled *Fix my Genes.* Following the programme, he sat down with GOSH Children's Charity to take part in a live Twitter Q&A.

Did he always want to be a doctor? What's the most important aspect of gene therapy to research further? Why GOSH? Here are just a few highlights…

To access this, please follow the link.

Clinical Academic Programme Lead: Nursing and Allied Health Research awarded NIHR grant

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 awarded a NIHR Health Services and Delivery Research Programme grant to study 'Pay More Attention: A national mixed methods study to identify the barriers and facilitators to ensuring equal access to high quality hospital care and services for children and young people with learning disability and their families'. The award of £582,227.07 will help facilitate the evaluation of how the NHS might improve delivery of services for children and young people with learning disability and their families.

BRC Health Research Trainee features in the NIHR's Faculty World e-Magazine

The most recent edition of the NIHR's Faculty World features one of our NIHR Great Ormond Street BRC trainees, William Mifsud. William is a pathologist, who with the support of the NIHR Great Ormond Street Hospital BRC is able to undertake some research work alongside his clinical activity.

Read the full feature here.

Editorial report describes the development of the minimally invasive autopsy

Diagnostics and Imaging Theme Lead, Professor Neil Sebire, along with NIHR Clinician Scientist Dr Owen Arthurs, have recently published an editorial in the British Medical Journal describing the development of the minimally invasive autopsy and how this may allow investigation after death for families for whom traditional post-mortem examination is not acceptable. This work has been supported by the Great Ormond Street BRC and this editorial was also written in conjunction with a bereaved parent and stillbirth support group. To read the full article, please click here.

Our NIHR Great Ormond Street BRC exhibited at this year's Health and Care Innovation Expo2015

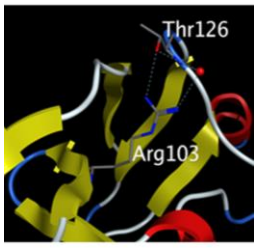
Health and Care Innovation EXPO 2015

Our NIHR Great Ormond Street BRC attended and represented the NIHR, the research arm of the NHS, at this year's Health and Care Innovation Expo 2015 on the 2 and 3 September 2015 in Manchester. The Expo is one of the NHS' biggest events and celebrates world leaders in science, research and innovation. Around 5000 people a day from health and care, the voluntary sector, local government, and industry joined together at Manchester Central Convention Centre for two packed days of speakers, workshops, exhibitions and professional development.

To learn more about the Expo, please click here.

Molecular basis of childhood diseases theme news

Novel mutation in *LHX4* leads to a severe form of hypopituitarism



Researchers at GOSH and ICH have been the first team to identify a novel recessive mutation in the transcriptional regulator *LHX4* in a family with severe hypopituitarism – a condition that describes the loss of all pituitary hormones.

In this study, 97 unrelated patients with the loss of more than one pituitary hormone were screened for mutations in the *LHX4* gene. From this screening, two brothers were identified with a missense mutation on both copies of this gene, termed 'homozygous' mutations. Sequencing of the unaffected parents' DNA showed that they both only carried one copy of the mutation, suggesting that one copy of the mutation was inherited from each parent. Despite early intervention with hormone therapy, both boys died within one week of birth.

LHX4 encodes a member of the LIM-homeodomain family of transcription factors that is required for normal development of the pituitary gland. To date, mutations in *LHX4* have only been described in patients carrying a mutation on one allele, resulting in varying loss of pituitary hormones. This is the first report describing a homozygous *LHX4* variant in a patient. The authors propose that impaired protein formation, such as decreased binding of LHX4 to its protein partners, may be a possible mechanism that leads to this lethal condition.

These findings were published by Professor Mehul Dattani in the Journal of Clinical Endocrinology and Metabolism. Professor Dattani is a BRC-supported investigator and Louise Gregory (the lead author on the publication) is a recipient of the 2015 BRC Doctoral Support Fund.

Protein responsible for rare childhood disorder gives clues to common neurodegenerative conditions

A new mutation in the protein STAT2 has been identified in patients with mitochondrial disease. These findings could also be beneficial for more common neurodegenerative diseases, including Alzheimer's, Huntington's and Parkinson's diseases.

Mitochondria are dynamic organelles that constantly go through elongation (fission), and shortening (fusion) in order to share their genetic material and contents. There is a delicate balance between these fission and fusion events, which are very important for normal cell function. Modulation of this dynamic can lead to mitochondrial disorders.

The team, led by Professor Shamima Rahman, identified a novel mutation in a gene called *STAT2*, which codes for a protein involved in the innate immune system, in two children presenting with severe neurological deterioration following viral infection. The researchers also observed that the mitochondria of these two patients and a third unrelated STAT2-deficient patient, appeared abnormally elongated in shape. Through studying the function of these organelles in the lab, the researchers were able to show that one of the proteins involved in mitochondrial fission is inactive in cells that lack the STAT2 protein.

These findings imply that STAT2 is a novel regulator of mitochondrial fission. It is also the first study to link the innate immune system to mitochondrial function. It is hoped that new therapeutic targets for mitochondrial diseases can be developed from these findings, for which currently there are no effective cure.

This study was led by BRC-supported Professor Shamima Rahman and is published in Brain.

Read the full press release here.

Diagnostics and Imaging in Childhood Diseases theme news

The development of new diagnostics techniques for a group of lysosomal disorders

BRC-supported researchers have teamed up with BioMarin, a company that develops and commercialises innovative biopharmaceuticals for serious diseases and medical conditions, to develop a new and more efficient method to identify patients with a particular type of lysosomal storage disorders.

The particular group of disorders are known as the mucopolysaccharidoses (MPS). Essentially in these disorders there is a failure of the cell's ability to recycle large molecules. These then accumulate and can appear in the urine as a group of chemicals collectively known as GAGs. Identification of GAGs is important in achieving a MPS diagnosis and monitoring the effectiveness of treatment. Currently the methods employed are relatively complicated and not fully quantitative.

In this project, the GOSH enzyme lab is working with the BRC-supported infrastructure GOSomics, which is run by Drs Wendy Heywood and Kevin Mills, to develop a new quantitative mass spectrometry based assay that will enable the rapid identification of patients with MPS disorders and permit more accurately the biochemical response to novel treatments. The BRC has also provided funds to support the work of a post-doc, Dr Nina Patel on this project. It is hoped that once developed, the new methodology will be translated into clinical use at GOSH.

Research suggests need for long-term follow-up for patients with Kawasaki Disease

Kawasaki disease is a rare condition that causes blood vessels to become inflamed and swollen. It predominantly occurs in children under the age of five. If left untreated, it results in balloon-like swellings (aneurysms) in the coronary vessels of approximately 25% of cases. To date, the cause of this disease remains unknown.

A group of researchers led by Dr Paul Brogan recently conducted a study aiming to shed light on how the disease develops. Ninety-two children with KD were examined at the Somers Clinical Research Facility (CRF) at GOSH. Levels of circulating endothelial cells (CECs), which are mature cells that have become detached from the vessel wall and are often associated with vascular injury, were measured years after patients developed KD. The researchers found CECs were elevated in KD patients, usually highest in patients with coronary artery aneurysms. Elevated levels of CECs were also seen in some KD patients that had not had coronary artery aneurysms.

While the relevance of elevated CECs are not yet known, this study provides rationale for long-term follow up of these patients.

This study has been accepted for publication in the journal, Heart. It was conducted at the BRC-supported Somers CRF at GOSH. Dr Brogan is a BRC-supported researcher.

Gene, stem and cellular therapies theme news

Clinical trial for a new stem-cell based therapy for a rare skin condition proves promising

Promising findings from a trial for a new stem-cell based therapy for a rare skin condition have been published in the Journal of Investigative Dermatology. The study, which involved intravenous injections of stem-cells, has led to an improvement in the quality of life for the subjects and their carers.

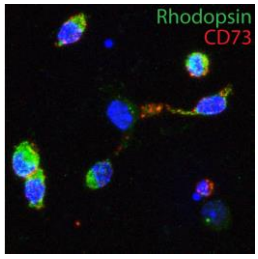
Recessive dystrophic epidermolysis bullosa (RDEB) is an inherited skin disease which results in the severe blistering of the skin. It is caused by a mutation in the protein, COL7A1, which leads to reduced anchoring of the upper skin layers to deeper tissue. Currently there is no effective cure for this condition.

The clinical trial, which recruited 10 patients with RDEB, was led by Professor John McGrath at Kings College London and BRC-supported Principal Investigator Dr Anna Martinez at GOSH. The patients were followed up for one year following the stem cell infusions, which took place three times over a six month period. Questionnaires revealed an improvement in skin healing following blistering and a reduced pain score after therapy. The severity of the condition has also reported to be lessened.

Overall, the results from this study appear promising. While the patients in this study were not blinded, which the researchers' state could lead to a positive bias towards the new treatment, patient benefits such as better sleep and reduced caring needs remains a positive from this study.

Read the full press release here.

How to purify photoreceptors from retina grown in a dish



Work recently published in Stem Cells has shown that photoreceptor cells can be grown and purified in the lab before being transplanted into a mature host retina. This research, led by BRC-supported Professor Jane Sowden, suggests that cell replacement therapy involving the transplantation of new photoreceptor cells, isolated from retina grown in a dish, may be a possible treatment for blindness.

Retinal diseases causing loss of the light-sensing photoreceptor cells in the retina are a major cause of blindness worldwide. These conditions are largely untreatable. Current research is aiming to develop photoreceptor cell therapy as a future treatment for blindness due to photoreceptor cell death.

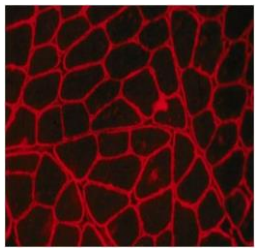
Stem cell cultures offer an inexhaustible source of new photoreceptor cells for cell therapy. Stem cells grown under certain conditions have the ability to form three dimensional eye cups containing layers of retinal cells resembling the embryonic eye.

In this study, the team showed for the first time that photoreceptor cells suitable for transplantation can be isolated from stem cell-derived retina using specific tags, termed biomarkers, which are located on the surface of the cells.

The next step following these proof-of-concept studies is to develop similar strategies for the purification of human photoreceptor cells from stem cell cultures for clinical photoreceptor cell therapy.

Novel therapies for translation in childhood disease theme news

Accelerated approval request for a new drug for a rare childhood muscle disorder



A drug for Duchenne Muscular Dystrophy (DMD), originally developed by BRC Theme Lead Professor Francesco Muntoni's Consortium in the UK, has been filed by Sarepta Therapeutics for accelerated approval by the United States Food and Drug Adminstration (FDA).

The drug Eteplirsen is an antisense oligonucleotide that is designed to enable the production of a functional truncated dystrophin protein to alleviate some of the symptoms of DMD.

DMD is an X-linked rare degenerative neuromuscular disorder that causes severe progressive muscle loss and premature death. It is one of the most common fatal genetic disorders, affecting approximately one in every 3,500 boys born worldwide. A devastating and incurable muscle-wasting disease, DMD is associated with specific errors in the gene that codes for dystrophin, a protein that plays a key structural role in muscle fibre function. The condition is universally fatal, and death usually occurs before the age of 30.

The findings from the original study were reported in the Lancet in 2011. The first patient to receive the systemic injection of this novel compound was performed in the BRC-supported Somers Clinical Research Facility at GOSH.

Read the full press release here.

Funding provided to develop new therapy for Acute Liver Failure

BRC-supported researcher Dr Kevin Mills has been awarded funding from the NIHR to investigate the regenerative ability of the liver following acute liver failure (ALF). If successful, the team hope that their research will lead to a novel therapy that could buy patients enough time to allow their livers to regenerate naturally, avoiding the need for liver transplants.

This research will be led by Professor Anil Dhawan at Kings College London in collaboration with Dr Mills at UCL Institute of Child Health. Specifically, the team aim to develop a novel technique where human liver cells grown in the lab are encapsulated in a material called alginate and delivered to a patient to help their ailing liver regenerate. Encasing the liver cells in alginate is particularly important as it reduces the need for immunosuppression.

Studies in the lab will focus on the feasibility of this novel therapy under lab conditions.

PATIENTS AND THE PUBLIC

Our PPI team have been busy in the last few months with both involvement and engagement activities including:

Young Person's Advisory Group (YPAG)

YPAG consists of young people, aged between 8-21 years old, who are interested in advising on research. At our most recent meeting in June, a researcher visited the group to get young people's opinions on a study looking at reporting adverse drug reactions. The group also completed metal embossing with artist Sofie Layton who has Wellcome Trust funding to work collaboratively with NIRH Great Ormond Street BRC to explore how young people view their disease. For more information about YPAG visit GenerationR

Parent/Carer Research Advisory Group

We have recently set up a group with parents/carers to advise on research into child health. At the group's first meeting in June, members discussed the role and remit of the group, and gave their views on publicity material being developed to promote research awareness at GOSH. Researchers looking for PPI can consult with the group, either by attending a meeting and/or virtually. Contact Erin Walker or Ruth Nightingale for further information.

The Big Bang London - Wednesday 1 July 2015

Over forty school students, their teachers and some parents attended our workshops at the Big Bang London Science Fair held at Westminster Kingsway College. We ran a series of mock clinical trials – using chocolate for pills –to help young people learn about clinical research and how we make sure medicine and other health treatments are safe and effective. 100% of participants said they enjoyed the workshops and reported learning more about research, so we plan to repeat the workshops at next year's Big Bang!

TRAINING

Improving healthcare through clinical research

Interested in finding out how the role of research improves healthcare? The National Institute for Health Research (NIHR) has a FREE online learning module starting 2 November 2015. For more details go to www.futurelearn.com/courses/clinical-research or contact Cassie Brady, Clinical Research Practice Educator.

NIHR BRC researchers win prizes for their poster presentations at the International American Society of Gene and Cell Therapy meeting

From a total of 700 posters entries, two poster prizes were won by our delegates:

- Christos Georgiadis, Anastasia Petrova, John A. McGrath, Adrian J. Thrasher, Wei-Li Di, Waseem Qasim 'Site-Specific Gene Editing of COL7A1 Restores Type VII Collagen in RDEB iPSCs'
- Farhatullah Syed, Wei-Li Di, Anastasia Petrova, Alya Abdul-Wahab, Christos Georgiadis, Su M. Lwin, Adrian Thrasher, John McGrath, Waseem Qasim 'A Phase-I Safety Study Protocol for Lentiviral-Mediated COL7A1 Gene-Modified Autologous Fibroblasts in Recessive Dystrophic Epidermolysis Bullosa'.

Christos Georgiadis was a recipient of the Great Ormond Street BRC 2014 Doctoral Training Support Fund and Dr Anastasia Petrova is a BRC-supported Springboard Fellow. Professor Waseem Qasim and Dr Wei-Li Di are both BRC-supported investigators. Professor Adrian Thrasher is the BRC 'Genes, Stem and Cellular Therapies for Childhood Diseases' Theme Lead.

6th NIHR Infrastructure Doctoral Research Training Camp

The sixth NIHR training camp took place at Ashridge Business School in Hertfordshire on 8-10 July 2015. Workshops were held over the course of the two days, focussing on the art of communicating science to a range of audiences.

Two delegates from NIHR Great Ormond Street BRC attended; Mary O'Sullivan was awarded the overall Patient and Public Involvement (PPI) Strategy award and Laween Mehan was awarded a Best Poster prize. Well done to them both!

Read our delegates experiences on our website shortly.

EVENTS

Upcoming Events

AHSN Children and Young Person (CYP) Event: Transforming Research Into Practice For Improved Child Health - 10 November 2015 13.00-18.30

Registration is now open for the second UCLP AHSN CYP Event. This event is intended to bring together a broad range of health professionals working in child health in London as well as leading child health charities. It will enable participants to learn about key discoveries to improve child health service design and delivery as well as providing a welcome networking forum.

To book tickets, please click here.

2015 NIHR Great Ormond Street BRC Open Day - 24 October 2015

In conjunction with the Bloomsbury Festival, the NIHR Great Ormond Street BRC will host its annual Open Day on Saturday 24th October 2015. 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 and to register, please visit our NIHR Great Ormond Street BRC events page.

'Introduction to PPI in Paediatric Research' training - 24 September 2015 9.00-13.00

In collaboration with the NIHR BRC at Guy's & St Thomas' NHS Foundation Trust and King's College London, we are running a half day training session for child health researchers interested in finding out about PPI. The session will involve: discussions about values, principles, and resources in PPI; case study examples of successful PPI as well as provide the opportunity for attendees to develop PPI for their own research projects. If you are interested in attending this event, please email research.ppi@gosh.nhs.uk.

Past Events

Translation of Research into Practice Conference - 19 June 2015

This was a well-attended event, with over 40 nurses and allied health professionals from GOSH, London South Bank University and City University. There were a wide range of presentations by nurses/Allied Health Professionals (AHPs) leading on research as well as a mini oral session with

eight award-based professional presenting clinical based research projects conducted in their own time or as part of a Masters/PhD. The day was well received.

NIHR Great Ormond Street BRC Annual Symposium on Rare Disease – 22 May 2015

The second NIHR Great Ormond Street BRC symposium, chaired by Professor Bobby Gaspar, the Deputy Director of the BRC, was held on the afternoon of the 22 May in the Kennedy Lecture Theatre at ICH. The aim of this series of talks was to highlight the recent advances in experimental medicine achieved at the NIHR Great Ormond Street BRC. Speakers and attendees had the opportunity to network during the poster session and drinks reception, about future potential collaborations. Audience feedback from the event was positive with 100% of responses saying that they had learnt something about the research activity supported by our BRC.

All presentations were recorded and are be uploaded to our website. Watch them here.

Our mailing address is:
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