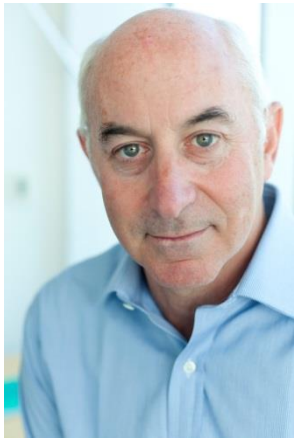
September 2016

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

Director's introduction



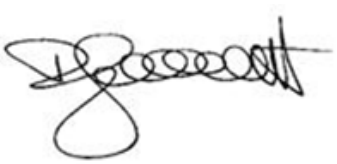
Welcome to the September 2016 edition of our newsletter, highlighting the activity and achievements of our National Institute for Health Research Biomedical Research Centre (BRC) at Great Ormond Street Hospital for Children NHS Trust and University College London.

I am sure you will have heard this week's news of the outcome of the Biomedical Research Centre (BRC) Competition funded by the National Institute for Health Research (NIHR). Leading NHS clinicians and universities will benefit from new world-class facilities and support services built by the 5-year funding package totaling £816 million – the largest ever investment into new health research. The GOSH BRC has been awarded £37 million for a further 5 years of support to drive forward translational research into rare disease in children. This builds on the legacy of NIHR funding for a BRC at GOSH and UCL which began in 2007, and has provided funding since then totalling £73 million over 10 years.

The renewed funding is focussed on 4 principal themes: Gene, Stem, and Cellular Therapies (theme leads Professors Adrian Thrasher and Waseem Qasim); Genomics and Systems Medicine (theme leads Professors Phil Beales and Maria Bitner-Glindzicz); Novel Therapies and their Translation into Childhood Diseases (theme leads Professors Francesco Muntoni and Paul Gissen) and Advanced Treatments for Structural Malformation and Tissue Damage (theme leads Professors Jane Sowden and Paolo De Coppi). These themes will be further strengthened by cross-cutting support from the Education, Innovation Accelerator, Rare Disease Cohorts, and Clinical Research Facility for Inpatients Cross-cutting themes.

I was particularly pleased to see the comments from the international panel who considered the applications, interviewed our team and advised the NIHR on the awards. There were many superlatives and they considered that the quality, volume and breadth of research across GOSH/UCL to be excellent. The partnership was acknowledged as being internationally excellent in paediatric health research, and in cell therapy translational research in particular. They also commented that the proposed research was highly relevant to the health of patients and the public and agreed that we had demonstrated a strong track record in translating advances into practice for the benefit of

patients. I'd like to congratulate the clinical academic team who worked so hard on the renewal and acknowledge the excellent support they received from the BRC management team including Katie Payne, Su Jayakody, Lottie Hyett and the rest of the R&D Office led by Emma Pendleton. Thomas Voit, Lucy Wedderburn and Bobby Gaspar will be taking over the leadership of the BRC from me as BRC Director and Deputy Directors respectively on the 1st April 2017 and I wish them and the BRC Team every success.



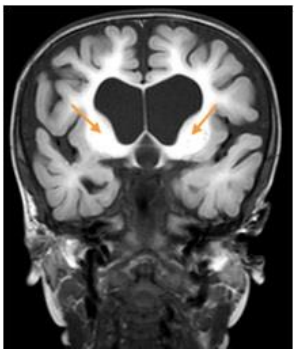
David Goldblatt Director, NIHR Biomedical Research Centre Director, Clinical Research and Development Professor of Vaccinology and Immunology NIHR Senior Investigator

Visit our website

News

Molecular basis of childhood diseases theme news

Identification of defective gene causing a form of childhood Parkinsonism



Researchers led by BRC-supported Dr Karin Tuschl in collaboration with Dr Esther Meyer have discovered that a form of childhood Parkinsonism is caused by a defective gene encoding a metal transporter called SLC39A14.

Research was carried out in a cohort of children with excessive accumulation of manganese in the blood and the brain leading to rapidly progressive childhood-onset parkinsonism-dystonia. Findings showed that these patients carried a loss-of-function mutation in *SLC39A14*, which affects the body's ability to clear manganese. Promisingly, these elevated levels of manganese were found to be lessened by a manganese-binding drug called disodium calcium edetate, which acts to increase urinary manganese excretion.

These findings could help facilitate correct diagnosis of patients with this disease, as well as facilitating counselling for families for future pregnancies. Furthermore, these findings also provide a potential avenue for effective treatment and have been published in Nature Communications

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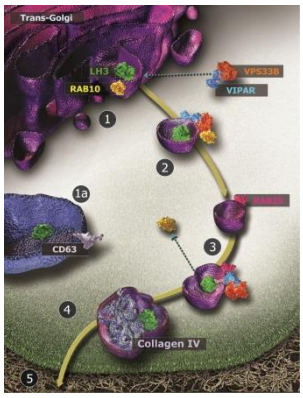
Research identifies novel intracellular pathway important for collagen homeostasis



A collaboration between researchers at UCL, led by BRC-funded Professor Paul Gissen, has identified a novel intracellular pathway important for generic collagen homeostasis. Furthermore, this pathway was found to be dependent on two proteins that are defective in Arthrogryposis Renal dysfunction and Cholestasis (ARC) syndrome.

Findings showed that regulation of post-Golgi LH3 trafficking is essential for collagen homeostasis and the development and function of multiple organs and tissues. This pathway was found to be dependent on the protein VIPAR and its partner proteins. These findings were confirmed in patients with ARC.

ARC syndrome is a multisystem disorder, characterised by defects of the musculoskeletal system and LH3-specific collagen modification levels are reduced in these patients. Findings showed functional collagen abnormalities in cells and tissues of these patients, which are caused by VIPAR and VPS33B deficiencies, suggesting that these deficiencies result in abnormal LH3-dependent post-translational modification of collagen in these patients. Furthermore, Kevin Mills' laboratory, funded by the BRC discovered urine biomarkers that will allow easy and early diagnosis in these patients which could help avoid unnecessary investigations.

Findings have been published in Nature Communications.

Novel therapies for translation in childhood disease theme news

NICE recommend drug trialled at GOSH for the treatment of Duchenne Muscular Dystrophy

NICE have published final guidance recommending ataluren for the treatment of Duchenne Muscular Dystrophy (DMD) caused by a nonsense mutation, in children aged 5 years and over who are able to walk.

DMD is a severe, muscle-wasting condition caused by a fault in a gene, resulting in a failure to produce functional dystrophin; currently DMD has few treatment options.

Ataluren is a novel drug, aimed at the root cause of the disease, allowing the body to continue to produce dystrophin by reading over the mutation in the DNA. Ataluren targets a specific change in the DNA called a nonsense mutation, which affects approximately 13% of Duchenne sufferers. Research in which GOSH recruited a substantial number of patients, has suggested that ataluren could delay the loss of walking in these patients by up to 7 years.

A 5-year managed access agreement for ataluren has been arranged, permitting patients with this disorder to access the drug whilst allowing more data to be collected on the drug's efficacy.

Read full article here.

The importance of prognostic biomarkers in improving risk stratification in Wilms' Tumour

Research led by BRC funded Professor Kathy Pritchard-Jones has demonstrated the importance of prognostic biomarkers in improving risk stratification in Wilms' Tumour (WT).

85% of children diagnosed with WT are classified as having low or intermediate risk tumours. These children have a 90% chance of survival but because they make up the majority of patients, they also have the largest number of relapses. Survival after relapse is less good in WT, with 50% of relapses being fatal. Novel biomarkers may provide data which could improve risk assessment of tumours and maximise the chance of first line therapy being successful (this is measured as event-free survival (EFS)).

Kathy Pritchard-Jones' group was the first to show that a specific change in the genetic material of the tumour (additional material from chromosome 1, known as 1q gain) is associated with poorer outcomes. She has now led a new international study to analyse genomic copy number changes at several chromosomal regions in nearly 600 WT patients from 7 countries in Europe.

Findings published in The Journal of Clinical Oncology show that 1q gain is one of the most common copy number changes in WT and demonstrate that 1q gain is significantly associated with poorer EFS. Other notable genomic changes associated with poorer EFS, included MYCN gain and TP53, genes that are also abnormal in some other high risk childhood cancers. However, when all of the other tumour and patient characteristics are taken into account, gain of 1q is not significantly associated with poorer survival, suggesting that further molecular features of the tumours need to be studied before patient treatment can be altered. Prof Pritchard-Jones' group is now using next generation DNA sequencing approaches to do this.

Gene, stem and cellular therapies theme news

Launch of H2020 project- SCIDNET

SCIDNET is a European Commission Horizon 2020 -funded project which launched in January 2016. It aims to take gene therapy from current clinical trials to a medicinal product that can be delivered to any child in the EU. It follows on from previous EU collaborations that UCL have been involved in.

SCID refers to a group of rare disorders that cause severe abnormalities of the immune system, resulting in the inability to fight infections, and death in the first year of life if no effective treatment is given. The team at UCL ICH/GOSH have developed gene therapy for two specific forms of SCID, and BRC infrastructure has been essential to the implementation of these gene therapy clinical trials. Over the next 4 years, SCIDNET proposes to offer gene therapy as a curative option for over 80% of all forms of SCID in Europe.

SCIDNET is a collaboration between 12 different partners across Europe and is coordinated by BRC Deputy Director Professor Bobby Gaspar. In 2015 a total of 49 Health-related projects across Europe were awarded H2020 grants, 5 of which were given to UCL.

Construction underway of Zayed Centre featuring new 'cleanrooms' for the production of gene and cell therapy medicinal products

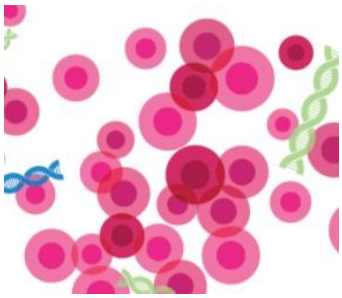
The Zayed Centre for Research into Rare Disease in Children (ZCR) is currently under construction in Guildford Street. Importantly this will include a dedicated facility comprising seven 'cleanrooms' where gene and cell therapy medicinal products can be made to treat children compassionately or on a clinical trial.

Currently GOSH has two 'cleanrooms' which are licensed by the Medicines and Healthcare products Regulatory Agency (MHRA) as compliant with "Good Manufacturing Practice (GMP)" and one 'cleanroom' for routine bone marrow manipulations licensed by the Human Tissue Authority (HTA). However, these rooms are close to maximum capacity at present.

As so many new advanced therapy products are being developed to treat an ever wider range of diseases, the new ZCR GMP will provide essential new capacity by 2018, when the facility opens. It is not easy to predict exactly what new treatments will become available, but so far these include: severe combined immunodeficiencies, different types of leukaemia, whole tumours, skin disorders and viral infection post bone marrow transplant.

Diagnostics and Imaging in Childhood Diseases theme news

Research demonstrates clinical and economic benefits of implementing NIPT into NHS care pathway



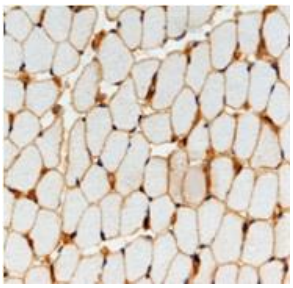
The UK National Screening Committee, based on a research programme led by BRC-funded Professor Lynn Chitty, has recommended to the Government that NIPT for Down's Syndrome be implemented into the NHS maternity care pathway and is currently awaiting ministerial decision.

A prospective cohort study, led by BRC-funded Professor Lyn Chitty, was carried out at eight maternity units across the UK, to investigate the costs and benefits of implementing non-invasive prenatal testing (NIPT) for Down's Syndrome into the NHS maternity care pathway.

Findings showed that implementation of the test for individuals with a risk greater than 1/150 significantly decreased the false positive rate with a subsequent significant decrease in invasive tests needed and procedure-related miscarriages. There was no significant effect on costs and an increase in the number of Down's Syndrome cases detected. Furthermore, some women used NIPT for information only; therefore implementation of NIPT may not significantly affect the Down's Syndrome live birth rate.

These findings have also been published in the BMJ.

Identification of biomarker which could aid risk stratification in Juvenile Dermatomyositis



Research led by BRC-funded Professor Lucy Wedderburn has shown that muscle pathology and myositis-specific antibodies (MSA) predict the risk of remaining on treatment in Juvenile Dermatomyositis (JDM). These findings could aid risk stratification.

JDM is a rare disease characterised by proximal muscle weakness, rashes and elevated levels of muscle enzymes. Although some JDM patients achieve remission following standard disease management, others fail to respond.

In this study, muscle biopsies from JDM patients were analysed and autoantibodies were measured. Findings showed that MSA was linked to muscle pathology and that MSA influenced the relationship between muscle pathology and long-term treatment status in JDM. This suggests that muscle pathology and MSA could be used to identify patients who may require a more aggressive form of treatment. Furthermore, understanding the link between these biomarkers and long-term outcomes may allow sub-phenotypes of JDM to be classified with the potential to provide more tailored therapies.

These findings have been published in Arthritis Rheumatology and are also highlighted in a recent editorial of Nature Reviews Rheumatology.

PATIENTS AND THE PUBLIC

Parent carer research advisory group

Our BRC-funded Parent/Carer research advisory group provides important parental insight for research teams on the design of their studies. Following our most recent meeting on the 4th of July, one researcher provided feedback saying:

"The nature of the questions made us understand better what matters to parents who would have their child participating in a clinical study… we appreciated the candid questions and comments on different aspects of the study we are planning".

The group will next meet in the autumn and in the meantime, can provide consultation to researchers via email, for more information please contact research.ppi@gosh.nhs.uk.

Young Persons Advisory Group

Our Generation R Young Persons Advisory Group (YPAG) met in early September and provided advice to researchers on a range of projects including improving treatments for children/young

people with rare auto inflammatory diseases, and information provision around genomic sequencing. For more information about Generation R and YPAG, visit the link.

Any researcher at GOSH/ICH looking for PPI can consult with either of these groups. If you would like any information or advice about PPI/E, please get in touch with Ruth Nightingale, Lead for PPI/E in Research via research.ppi@gosh.nhs.uk

PPI training for researchers

In collaboration with UCLH BRC and colleagues across North Thames, we are hosting a series of PPI in Research training sessions for researchers with a range of experience. Workshops take place until December this year, see the link for details.

Development of a new animation at GOSH to inform young people about whole genome sequencing

Researchers from the Genetics Service at GOSH have received funding to develop an innovative animation on the topic of whole genome sequencing.

Patients with rare conditions are currently accessing whole genome sequencing at GOSH as part of the 100,000 Genomes Project. This is a Government initiative to sequence 100,000 genomes with the aim to transform NHS genetic services by speeding up the diagnosis of rare diseases and to develop new therapies.

Many of the patients offered genome sequencing are unfamiliar with what it is. To try and address this issue, researchers at GOSH are developing an animation which will be hosted on the GOSH website. Researchers have been working with students aged between 10 and 16 from schools across London, exploring their opinions as to how best to explain whole genome sequencing. They have also consulted a number of young people who have taken part in the 100,000 Genomes Project.

The animation will be tested out with the YPAG group at GOSH and with students in schools in the autumn, with the final version being ready in the New Year. It is hoped it will be a useful resource both for young people and their parents being recruited to the 100,000 Genomes Project, for those undergoing sequencing in the future as it becomes more readily available in clinical practice, and also as a potential educational tool.

Launch of Beyond My Brain Exhibition

The Beyond My Brain exhibition is now open in the link corridor of ICH and will run from 8 September to 8 December.

This exhibition, which includes a number of different pieces of work, aims to raise awareness of the impact of brain injury in the context of childhood through challenging stigmas and informing the public. The artwork on display was created by a collaborative effort between artists, scientists, and children with various different types of brain injury and their families.

The Beyond My Brain exhibition is part of The London Brain Project which has been funded by the GOSH BRC.

TRAINING

GOSH BRC trainees win awards for best presentations at the NIHR research training camp

Three GOSH BRC trainees attended the NIHR research training camp from the 6-8th of July. Julianne Brown, a GOSH BRC trainee won an award for the best oral presentation at the camp and both Julianne and Hanna Sakki were members of groups who won the prize for best presentation at the event.

The weekend consisted of a number of talks and workshops but it was centred around a team exercise which required individuals to work together to develop a research idea and grant proposal. The GOSH BRC trainees reported that:

"The NIHR training camp was a whirlwind of networking, inspiration and expert advice, which I shan't forget in a hurry."

"I would highly recommend this to any doctoral researcher who is thinking ahead of a future career in clinical academia."

Please visit our website to read the trainees full write up of the day.

NIHR BRC summer studentship 2016

Each year the GOSH BRC funds two Child Health Research Summer Vacation studentships. This year's students, Charlotte Cook and Sarah Leathem, supervised by Lucy Wedderburn and Frederique Liegeois respectively, have now completed their placements. Charlotte Cook was awarded a studentship to 'investigate the link between the presence of inflammatory infiltrates and type 1 interferon induced genes in Juvenile Dermatomyositis' and Sarah Leathem was awarded a studentship to investigate 'Neural correlates of fine motor abilities in children with developmental coordination disorder' under the supervision of Frederique Liegeois. One of the students reported that:

"I found this studentship to be incredibly valuable; being around actual scientists and experiencing the real day to day life of a scientist, both the busy moments and the quiet ones, was great and very useful to me as a future scientist."

EVENTS

Upcoming Events

The 2nd NIHR GOSH BRC National Residential Training weekend 1-2 October

The 2nd National Residential Training weekend, organised by the NIHR GOSH BRC, 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 Michael Levin, Dr Shelley Dolan, Professor Jonathan Grigg, Professor Peter Callery, Professor Clare Lloyd and Dr Jack Kreindler.

Registration for this event has now closed.

BRC Open Day: 15 October

Following the success of our 2015 BRC Open Day, which was attended by over 200 children and parents, we have started planning for this year's Open Day. The free event will take place on Saturday 15 October and will provide an opportunity for the public to find out more about research happening at GOSH and ICH, through interactive activities, microscope presentations, lab tours and much more!

To register for the event please click here
If you are interested in volunteering at the open day please contact Lottie Hyett

Past Events

Juvenile Dermatomyositis Family day

On Saturday 9 July, the first Juvenile Dermatomyositis (JDM) Family Day was run with the aim to bring families together to share experiences and gain support from one another.

JDM is a childhood onset illness which affects the skin (dermato) and muscles (myositis) as well as other parts. It is a rare condition meaning research is harder to carry out and patients and families often never meet another person with this illness. To help tackle this the GOSH Paediatric Rheumatology Team,

in collaboration with the Juvenile Dermatomyositis Research Group and the Centre for Adolescent Rheumatology, held a family day, which was a great success!

Nine young people aged 5-23 and 16 family/friends attended and heard clinicians and researchers from GOSH speak about the condition and ongoing cutting-edge research. Three young people also spoke to share their experiences of living with JDM. The parents and young people had the chance to play, chat and get to know each other and know that they are not alone in this.

Please visit corresponding websites for more information on the Juvenile Dermatomyositis Research Group and the Centre for Adolescent Rheumatology both supported by the GOSH and UCLH BRCs.

Health and Care Innovation expo 2016

The Health and Care Innovation expo returned to Manchester on 7 and 8 September 2016.
It is one of the NHS' biggest events, celebrating world leaders in science, research and innovation.
The NIHR had a stand at the expo and the GOSH BRC was asked to represent the BRC scheme on the stand, which also featured research from the GOSH BRC.