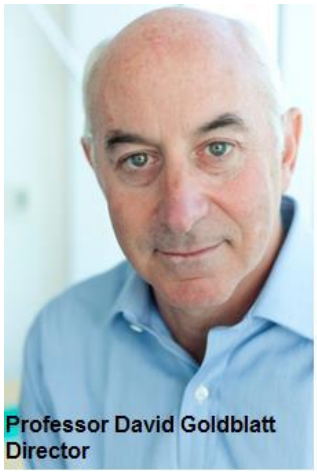
December 2016

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 December 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.

In this edition we have a focus on our new GOSH BRC and with that in mind I would like to take the opportunity to congratulate Dr William van't Hoff, Christy Rowley, Lorraine Hodsdon and the wider R&I team in successfully applying for NIHR funding for the Somers Clinical Research Facility (CRF). The NIHR funding is for a total of £3M over the next 5 years. The CRF was previously funded in part through the BRC and it is a great achievement to receive independent funding.

I would like to congratulate Professor Helen Cross (BRC Faculty) who has been awarded the 2017 Sidney Carter Award in Child Neurology by the American Academy of Neurology, in recognition of her outstanding achievements in the field of child neurology. Congratulations also to Dr Rukshana Shroff who has been awarded an NIHR Career Development Fellowship to study calcium balance and its effects on bones and cardiovascular disease in children with chronic kidney disease.

Congratulations to Polly Livermore who has been successful in her application for a HEE/NIHR Clinical Doctoral Research Fellowship. Polly was awarded a 6 month internship position by the GOSH BRC to help support her application, she will be the first nurse from the GOSH BRC to be successfully awarded an NIHR Doctoral Fellowship, Polly's project is entitled 'Understanding the lived experience and psychosocial needs of children and young people with Juvenile Dermatomyositis: a mixed methods study'.

Finally thank you to those who have added the GOSH BRC to their publication acknowledgments. Please can I remind all those who haven't already started doing so that this is essential for all researchers across ICH and GOSH, due to the vital support that the BRC provides to infrastructure across the Institute and the hospital. For information on the correct wording please visit our website.

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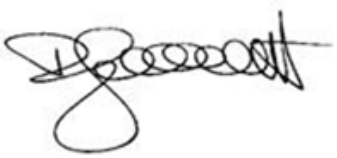


David Goldblatt Director, NIHR Biomedical Research Centre Director, Clinical Research and Development Professor of Vaccinology and Immunology NIHR Senior Investigator

Visit our website

SPECIAL FEATURE

Introduction to the new GOSH BRC

As announced in the September edition of the BRC newsletter, the GOSH BRC was successful in securing £37M to take the GOSH BRC forward into its third term, which will run from April 2017 to March 2022.

This was the outcome of a nationwide competition, with a total of £816M awarded across 20 BRCs. The panel acknowledged the partnership between ICH and the hospital as being internationally excellent in paediatric research with a particular emphasis on the strength of the Cell Therapy translational research. The panel feedback also highlighted the strong track record of the previous BRCs as well as the strong strategic partnerships.

The 2017-2022 GOSH BRC will be focused around four key research Themes:

Gene Stem and Cellular Therapies: This will build on the work of the previous BRC, aiming to refine, advance and expand our state-of-the art infrastructure to enable the delivery of new gene and cell therapies into the NHS. This will include investment in our manufacturing, regulatory and trials expertise to offer treatments to a wider range of diseases.

Genomics and Systems Medicine: This theme aims to exploit the established technologies, teams and infrastructure of the current BRC to further develop Personalised Medicine for the NHS. This theme will enable rapid translation of genomics for patient benefit. Development in this area will be underpinned by investments into bioinformatics, infrastructure and integration with large patient databases.

Novel Therapies and their Translation into Childhood Diseases: We aim to initiate and conduct high quality clinical trials in our rare disease population. We will ensure that our cohorts of rare disease patients are 'trial ready' through improving deep phenotyping of these patients. Through exploiting our advances in understanding the molecular basis of these rare diseases, we will identify novel therapeutic targets for diseases which currently are not accessible to experimental therapies.

Advanced Treatments for Structural Malformation and Tissue Damage: This is a new theme for the 2017-2022 GOSH BRC. It aims to pioneer advanced treatments such as regenerative medicine and development of new devices to provide therapeutic options for children with congenital malformations and tissue damage. This theme will invest in translational platforms including stem cell bioengineering and an iPSC core platform to build capacity and to initiate first-in-child UK trials.

Examples of work in this theme include stem cell engineered organs for trachea, oesophagus, small intestine and bladder, stem cell repair of the retina, and novel devices to transform craniofacial surgery.

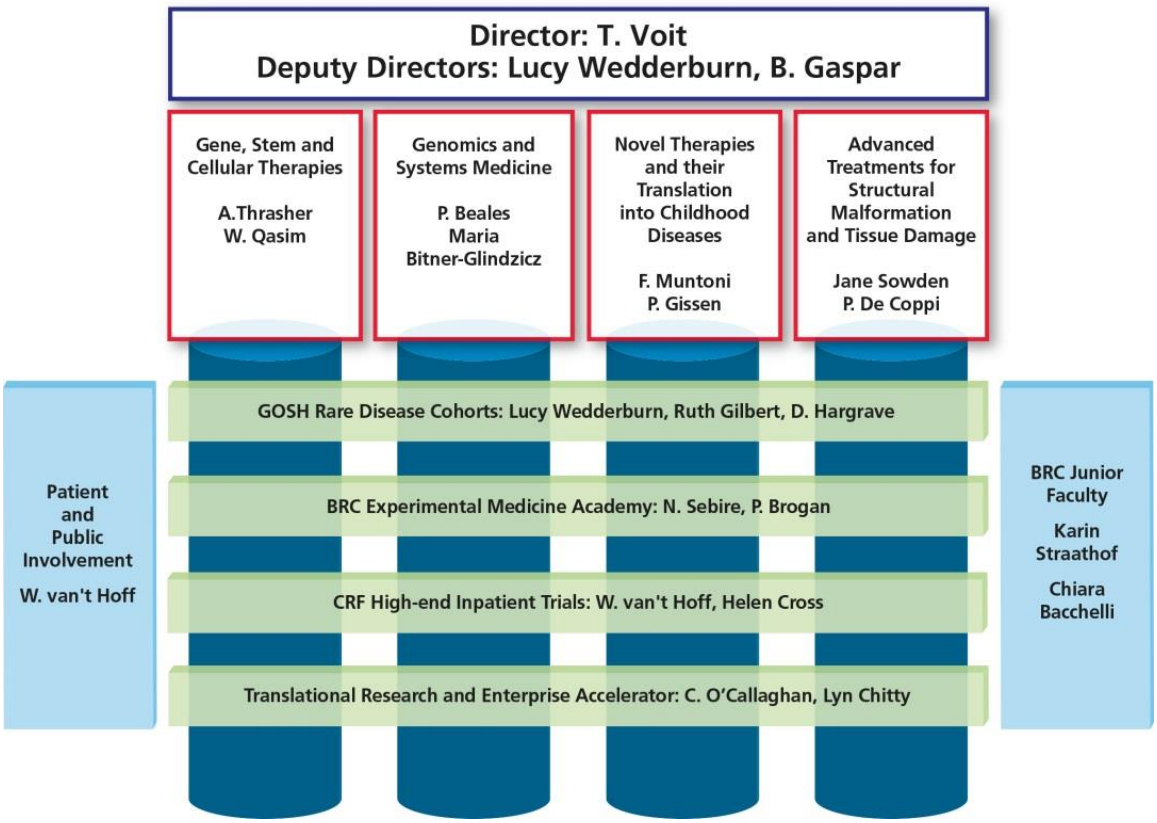
Work across these four Themes will be supported and underpinned by four Cross-Cutting Themes:

GOSH Rare Disease Cohorts: This theme recognises the unique nature of our patient population and aims to carefully define these cohorts to maximise health informatics data and sample collection to better inform novel diagnostics and therapeutic interventions.

BRC Experimental Medicine Academy: The BRC will continue to invest in training and education for both non-clinical and clinical professionals including medics and allied health professionals. This will include specific experimental training posts as well as the formation of an interdisciplinary Junior Faculty group who will work with the Senior Management team.

CRF High-end Inpatient Trials: BRC funding for the CRF will move to focusing support on high intensity early-phase clinical trials which require inpatient and/or intensive care accommodation. Support will be in the form of a team consisting of an Advanced Nurse Practitioner and research nurses.

Translation Research and Enterprise Accelerator: We aim to accelerate partnerships through initiatives such as support in IP protection, trial design, 'match making' with industrial partners and facilitating licencing agreements.



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THEME NEWS

Molecular basis of childhood diseases

North Thames recruitment to 100,000 genome project exceptionally strong for rare diseases

The North Thames Genomic Medicine Centre's (GMC) recruitment to the 100,000 Genomes project for rare diseases is excellent, exceeding 5,200 genomes across the GMC, making up around 28% of these genomes recruited nationally.

The North Thames GMC has recruited more than twice the number of rare disease patients compared to the next most active GMC. At GOSH we have now recruited roughly 1,800 participants, and are on course to meet our contracted target of 2,640 by Spring 2017. However, as national recruitment is slow, the programme is being extended until the end of 2018 and so we may be asked to continue recruiting.

Furthermore, many results from the pilot project are now being returned to the regional labs and validation and feedback to patients is currently underway. Sequencing of patient samples from the main programme is also continuing, however interpretation of the sequencing results requires us to enter the phenotypic data and so we are now focussed on this to expedite return of these results too. We would encourage all referring clinicians to help us with this. Please contact the 100,000 Genomes team for help with this if you have any queries (Jay Wataranan).

Unfortunately, recruitment to the cancer programme remains challenging, however we are opening new pathways at GOSH, Homerton, Royal Free and the Royal National Orthopaedic Hospital, which we hope will improve our performance.

Please see the training section below for information on funding for training in Genomic Medicine.

Investigation into the effectiveness of an extended gene panel for the diagnosis of complex neurometabolic phenotypes

BRC supported Dr Philippa Mills, Professor Peter Clayton and Professor Paul Gissen have led an investigation into the effectiveness of a gene panel, targeting 614 genes, in establishing a diagnosis for patients presenting with a wide array of neurometabolic phenotypes.

Patients with suspected neurometabolic disease can undergo extensive and often invasive diagnostic testing however, diagnostic delays or

difficulties establishing a definitive diagnosis are commonly encountered. Extended gene panels have gained popularity for the diagnosis of genetically heterogeneous conditions providing a rapid method for identifying mutations in genes. This would be of particular benefit for neurometabolic disorders, as early diagnosis is crucial due to early initiation of treatment resulting in more positive outcomes.

This study looked at the effectiveness of an Inborn Errors of Metabolism gene panel at establishing a diagnosis in patients presenting with a range of neurological features, all of whom had undergone extensive previous investigations but lacked a definitive molecular diagnosis. Despite the large number of genes included, coverage of targeted areas was similar or indeed superior to that for other gene panels. Findings showed that genetic defects that could, at least partially, explain the observed phenotype could be identified in 53% of patients and when biochemical abnormalities were present this rose to 89%. The panel was shown to be a powerful tool which improved diagnostic ability in the clinical setting.

The findings suggest that gene panel approaches provide a cost-effective method for testing patients with neurometabolic disorders, enabling a more timely diagnosis and therefore more prompt treatment initiation in these patients.

The findings of this study have been published in Brain

Novel therapies for translation in childhood disease

Accelerated approval granted for drug developed at GOSH

The United States Food and Drug Administration (FDA) granted accelerated approval for a new medication to treat Duchenne Muscular Dystrophy (DMD). The drug, Eteplirsen, was developed by a UK consortium led by Novel Therapies theme lead, Professor Francesco Muntoni.

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.

Eteplirsen was filed by Sarepta Therapeutics for accelerated approval by the FDA and is planned for immediate clinical use in the US. The approval for use in the EU is still underway. The drug will be used to treat patients with a specific subset of mutations of the dystrophin gene that affects around 13% of boys with DMD. The drug 'skips' a part of the gene that makes dystrophin, which results in a shortened form of the dystrophin protein being produced, alleviating some of the symptoms of DMD and potentially extending their mobility for a longer period of time.

Click here to read the full press release.

Positive interim analysis of Phase 3 studies in Spinal Muscular Atrophy

Biogen and Ionis Pharmaceuticals announce positive results at interim analysis of two Phase 3 studies both trialling the drug nusinersen in patients with Spinal Muscular Atrophy (SMA).

SMA is a rare, genetically inherited neuromuscular condition, affecting the lower motor neurones. It is caused by a fault in the *SMN1* gene which results in a reduction in the production of SMN protein, causing the lower motor neurons in the spinal cord to deteriorate. Currently there is no cure for SMA.

Nusinersen is a drug which corrects this faulty gene expression. Two Phase 3 studies have been carried out by Biogen and Ionis Pharmaceuticals to investigate the safety and efficacy of nusinersen in patients with SMA.

The first study, ENDEAR, for which GOSH was the highest UK recruiter, studied nusinersen in the most severe form of SMA (SMA type 1), known as infantile-onset SMA. The findings at a pre-specified interim analysis showed that patients who received nusinersen displayed a statistically significant improvement in the achievement of motor milestones compared to those who did not receive treatment. These findings were replicated in the CHERISH trial which investigated nusinersen in patients with later-onset SMA (consistent with Type 2).

Based on the results of the interim analysis, all participants from both trials can now elect to receive nusinersen by transitioning to the open label extension study, SHINE. SHINE is intended to evaluate the long-term safety and tolerability of nusinersen.

In addition to GOSH's involvement in ENDEAR, GOSH will be involved in the expanded program in 2017.

Click here to read the full press release on the ENDEAR trial.
Click here to read the full press release on the CHERISH trial.

Gene, stem and cellular therapies

Genetic mutation identified causing a novel form of Severe Combined Immunodeficiency

Research led by BRC Deputy Director Professor Bobby Gaspar and supported by the BRC funded GOSgene facility, has found that a mutation in the linker for activation of T-cells (LAT) gene leads to a specific form of Severe Combined Immunodeficiency (SCID).

SCIDs are a group of immunological disorders characterised by a lack of lymphocyte development and function, and more specifically, a low number of autologous T-cells. Untreated patients with SCID do not survive past the first year of life.

T-cell receptor (TCR) signalling is an essential process for the development of T-cells and currently a number of genetic defects in the TCR signalling pathway have been shown to lead to a SCID. LAT performs a critical function in TCR signal transduction and LAT has been considered a strong candidate for SCID.

In this study, genetic, molecular and functional analyses were used to identify and characterise the LAT defect in 5 patients with a well-defined SCID immunophenotype (patients demonstrated a significant lack of T-cells) caused by a frameshift mutation in LAT. Findings showed that in these patients there was a mutation in the *LAT* gene which led to a complete loss of LAT expression and function, suggesting that inherited LAT deficiency should be considered in patients with combined immunodeficiency with T-cell abnormalities.

These findings were published in Journal of Allergy and Clinical Immunology.

What does BREXIT mean for UK Gene and Cell Therapy?

In a new editorial published in Human Gene Therapy, leading researchers, including BRC Gene, Stem and Cellular Therapies theme lead, Professor Adrian Thrasher call for urgent action to ensure continued access to critical funding and on-going collaborative opportunities within the broader scientific community in the European Union (EU).

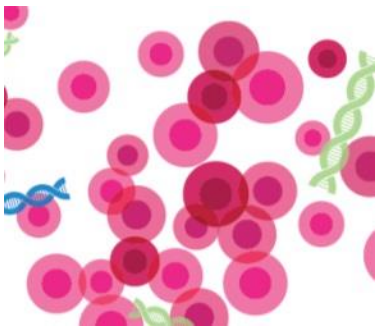
Following the referendum vote on Europe, researchers have publicly outlined the threat to crucial scientific progress and clinical advances in the development of innovative gene and cell therapies.

In the article, Professor Adrian Thrasher, along with co-authors Professor Andrew Baker, University of Edinburgh, Professor Robin Ali, UCL Institute of Ophthalmology, London – emphasise the need for a rapid response to alleviate the current uncertainty, which is "potentially harmful, for both building and maintaining scientific interactions," and "to avoid loss of momentum in a rapidly developing field."

The UK is a leading force in both the basic science and clinical translation of gene and cell therapies, with GOSH having the largest numbers of gene therapy trials open in Europe. Historically the EU has invested substantially to drive scientific advances which depend on on-going collaboration and mobility across national borders for research, training and clinical studies.

Diagnostics and Imaging in Childhood Diseases

NHS to offer Non-Invasive Prenatal Testing to pregnant women



A Non-Invasive Prenatal Test (NIPT) evaluated by a team led by BRC supported Professor Lyn Chitty is to be introduced into the NHS for the screening of Down's Syndrome, Edwards' syndrome and Patau's Syndrome.

NIPT is a maternal blood test which checks the amount of cell-free DNA present in the mother's blood to screen for chromosomal abnormalities in the baby. The introduction of NIPT will mean a reduction in the number of women who need to have the current invasive procedure carried out, therefore reducing the number of associated miscarriages.

NIPT will be launched in 2018 and will be offered to around 10,000 women a year who are at increased risk of having a child with Down's Syndrome, Edwards' syndrome or Patau's syndrome.

This announcement comes after a positive recommendation from the government's expert UK national screening committee. For more information please read the full press release in the Guardian.

Wendy Heywood-awarded an MRC UCL confidence in concept award

GOSH BRC funded, Senior research associate, Dr Wendy Heywood has been awarded £98,000 from the UCL Confidence in Concept fund to develop newly discovered biomarkers for disease stratification of Mucopolysaccharidoses (MPS) into a clinical translatable assay for validation.

Earlier in the year we reported the publication of new urine markers for downstream disease pathology features of patients with MPS that could be used for early disease phenotyping and treatment monitoring. This work has now led to further funding for these markers to be developed to clinical translation.

Study calls for further research to improve post mortem techniques for stillbirths

Research led by Diagnostics and Imaging Theme Lead, Professor Neil Sebire aimed to investigate which aspects of post-mortem examinations in stillbirths are most effective at providing a cause of death.

After extensive analysis of findings from a large number of post-mortem examinations, results showed that separately clinical review and placental examination both identified a cause of death in around 20% of cases. Invasive post-mortem examinations only provided a cause of death in a small percentage of cases. This suggests that non-invasive techniques have the potential to be just as effective at providing a cause of death in stillbirths as invasive techniques. However, it also highlights the need to develop more refined techniques.

Furthermore, results also suggested that the risk of stillbirth associated with low foetal body weight may have been overestimated. These findings could impact on current health policy, which focuses on the detection and elective birth of small foetuses to reduce the risk of stillbirth.

Findings from this research have been published in a series of articles in Ultrasound in Obstetrics and Gynaecology, click here to read the full press release.

PATIENTS AND THE PUBLIC

December 2016

PPI training for researchers

In collaboration with UCLH/UCL BRC and colleagues across North Thames, we are hosting a series of PPI in research training sessions for researchers with a range of experience. Sessions are free and any level of researcher at GOSH/ICH can attend. Workshops take place until January 2017, see the link for details.

For further information on the Young Persons Advisory Group and Parent / Carer Research Advisory Group, please visit our website.

Listening Event

At our research stall at GOSH's space-themed Listening Event in November, hospital patients and their parents told us their research priorities. Thank you to patients in the Somers Clinical Research Facility for their help in creating the starry night sky and rocket, they made our stall look out of this world!

If you would like any information or advice about PPI/E, please get in touch with Ruth Nightingale and Linda von Neree, Joint Leads for PPI/E in Research at research.ppi@gosh.nhs.uk

GOSH BRC Open day 2016

The annual GOSH BRC Open day was held on Saturday 15 October 2016 in the Great Ormond Street Institute of Child Health. This was a free public event, which was aimed at raising awareness of child health research.

Over 80 members of staff and students from across ICH and GOSH were involved in the planning and running of the event and on the day the event was attended by over 300 members of the public, making it our most successful year yet!

Activities at the Open day included, tours of 2 different laboratories in the hospital, exhibition of the Sensory Installation 'In Isolation', a chocolate 'clinical trial' and the opportunity to explore human specimens under the microscope. There were also a series of short talks and films which ran throughout the day and these included an overview of the 100,000 Genomes project and the screening of the 2017-2022 GOSH BRC DVD.

Comments left by attendees included:

Best thing ever!!

Very informative and child friendly ☺

It's brilliant! Really weird things!

Do it again next year!! Well done!!

Just super great! I will definitely suggest to families with kids. Great job!

Really appreciate being welcomed by such enthusiastic staff

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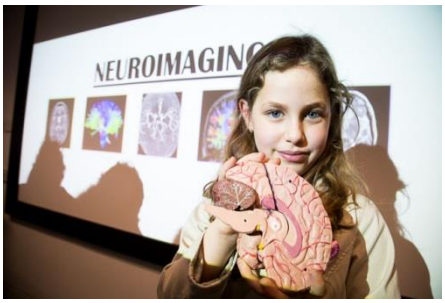
With the Open day going from strength to strength and with such positive feedback from both members of the public and staff, the team look forward to planning next year's event!



TRAINING

GOSH BRC hosts its 2nd National Residential Training Weekend

On 1-2 October 2016, the GOSH BRC held their 2nd National Residential Training Weekend for Paediatric Clinical Academics at Ashridge Business School.

The event was attended by 46 academic trainees from throughout the UK, including medics, nurses and Allied Health Professionals. The weekend provided a great opportunity for trainees to take part in facilitated workshops around developing and undertaking research with children and young people as well as the opportunity for trainees to network with peers and senior academics.

Members from the two research advisory groups shared their experience of being involved in research, feedback was really positive, 'it was a great way to demonstrate the importance of PPI'.

Ashridge Business School provided a great setting for the weekend which was a great success. Feedback from attendees included:

'Inspired. Increased awareness of opportunities available'

'Group work was a great opportunity to meet people and helped me gain confidence that I am not the only one to find project planning difficult. Great way to demonstrate importance of PPI and MDT working.'

'Excellent inspirational talk. Great networking lots of food for thought'

Funding for training in Genomic Medicine

Health Education England are offering to fund NHS staff to undertake either their whole Masters in Genomic Medicine or to take modules as Continuing Professional Development (CPD). These include an introduction to genomic medicine, counselling and genomics of rare and common diseases amongst others. Details can be found here.

In addition the Northern Thames Genomic Medicine education team can offer short teaching sessions, ranging from 30 minutes to 2 hours. If you would like a member of the education team to come and speak to your team or contribute to teaching schedules for any health professionals, please email Masuma Harrison to discuss how they can help.

UPCOMING EVENTS

MedTech industry to connect with BRCs at MedCity pan-London event

MedCity are holding a pan-London industry event on 8 February 2017 at the Wellcome Collection. The event is a first of its kind, enabling the MedTech industry to connect with the BRCs under one roof. To find out more about the event, please visit their website.

Third Adolescents Rheumatology symposium

The Arthritis Research UK Centre for Adolescent Rheumatology will be hosting its third one day National Symposium on Adolescent Rheumatology. The event will be held on 26 January 2017 in the Great Ormond Street Institute of Child Health. Speakers will be presenting on a wide range of novel and exciting topics related to adolescent rheumatology. For more information and to register for the event please click here.