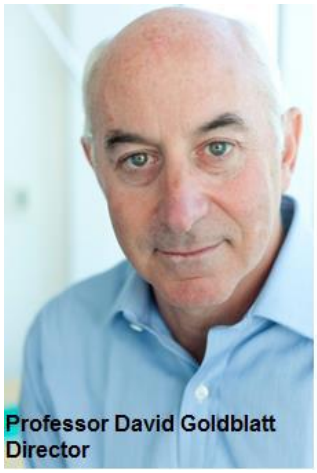
March 2017

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 March 2017 edition of our newsletter, the final issue for the 2012-2017 National Institute for Health Research Biomedical Research Centre (BRC) at Great Ormond Street Hospital for Children NHS Foundation Trust and University College London.

It has been my privilege to lead the BRC for the last 10 years, a period that has seen a transformation in our capacity to undertake high quality experimental medicine. In 2007 when the first BRC was awarded there was relatively little infrastructure support for research, we had no dedicated research space in the Trust, our Research Nurses were scattered throughout the organisations and there was little patient and public involvement in our research. Pre-NIHR NHS research income to the organisation was provided via a block grant and transparency linked to this funding was sub-optimal. Excellent research was undertaken, driven by the curiosity of the staff attracted to work here with the rare and complex patients and conditions we see. Today, with a similarly dedicated cohort of research active staff we have a bespoke Clinical Research Facility (CRF), recently awarded its own direct NIHR funding. The CRF hosts complex clinical trials and runs these to the highest standards of research and clinical practice. The CRF also acts as the focal point for our cadre of Clinical Research Nurses now organised professionally under the umbrella of the lead nurse for Research. We also have a mature program of patient and public involvement designed to improve the research we do.

The BRC has been able to fund dedicated research linked to our major themes and many of the highlights of our research have been celebrated in this bulletin over the last 5 years; below we focus on some of the major scientific successes for the current BRC, there are many more! The success of the BRC and the foundation it laid for the recent renewal and a further 5 years of funding would not have occurred were it not for the dedication of the staff who have supported the BRC directly and indirectly. The huge support from UCL, the GOSH Chief Executive and the BRC Strategy Board members over the last 10 years has been invaluable. The dedication of the current (and previous)

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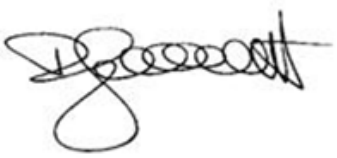
R&D Office staff and BRC administrative staff helped keep the BRC on track while the contribution of the BRC Theme leads and BRC faculty has played a major part in securing further BRC funding for our organisations. I wish the new BRC leadership team the best of luck over the next five years.



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

As we are now coming to the end of the current BRC term we would like to take the opportunity to look back on some of our top achievements over the past five years and acknowledge some of the world-leading research carried out by the GOSH BRC faculty.

The establishment of GOSgene

In 2010, NIHR BRC funding created the opportunity for the development of GOSgene, a facility dedicated to accelerating rapid gene identification in uncharacterised genetic diseases in children. GOSgene has since identified 110 disease genes; 66 known and 45 novel and contributed to the resolution of countless undiagnosed cases of rare diseases worldwide; These discoveries have been rapidly translated into new diagnostic NHS services in our Regional Genetics Lab.

Moving forward, GOSgene's flagship project will be the Rapid Paediatric Sequencing (RaPs) project, which aims to provide a rapid genetic evaluation of acutely sick children from the Paediatric Intensive Care Unit (PICU) at GOSH. This can then be used by the treating clinicians, to better inform clinical management of the patient. To date, we have fully analysed and interpreted the results from 20 trios; of these we have identified clinically pathogenic variants in 8 patients with potentially pathogenic variants being identified in a further 3 patients. Within the next two years we will validate this protocol in the NHS lab to take it into clinical service, offering it to PICU's across the UK.

Breakthrough in the treatment of Duchenne Muscular Dystrophy

BRC funding has been instrumental in achieving FDA approval for the first drug to treat Duchenne Muscular Dystrophy (DMD). DMD is a severe, muscle-wasting condition caused by a fault in a gene, resulting in a failure to produce functional dystrophin. Researchers led by GOSH BRC Theme lead and NIHR Senior Investigator Francesco Muntoni, designed an early clinical study to obtain proof-of-concept data for an antisense oligonucleotide for DMD. This was used to induce exon-skipping of exon 51 in the DMD gene in children with specific dystrophin gene mutations, which can lead to the production of functional dystrophin. A phase I-II clinical trial of the novel drug, Eteplirsen, was conducted in DMD boys with eligible mutations. Results of this dose escalation study showed that Eteplirsen restored missing dystrophin protein in seven of the 19 children treated, who received the highest dose of the drug. Eteplirsen has now received accelerated approval from the United States Food and Drug Administration and the EU approval process is underway. It is believed that similar approaches, targeting other DMD exons, could work for at least 70% of DMD patients. An

on-going study, coordinated by Muntoni and funded by the EU and Sarepta, is now using a new antisense oligonucleotide to target exon 53, a strategy that could benefit another group of DMD boys.

Development and roll out of NIPD/NIPT

Supported by the GOSH BRC and an NIHR Programme Grant for Applied Research, Professor Lyn Chitty has developed Non-invasive prenatal diagnosis (NIPD), which detects genetic conditions by analysing fetal DNA in maternal blood samples. This approach avoids the 1 in 200 risk of miscarriage associated with invasive testing. Professor Chitty led the development of NIPD for autosomal dominant disorders including the more common skeletal dysplasia's and, more recently, autosomal recessive conditions such as cystic fibrosis. These are now commissioned in the NHS and are available in the UK for families at increased genetic risk. More than 30% of molecular prenatal diagnosis in our regional laboratory is now done by NIPD and we have performed testing for approximately 300 families and 27 different conditions.

Leading on from this, a collaboration between the GOSH BRC, Illumina and UCL Genomics led to the development of Non-invasive prenatal testing (NIPT) for aneuploidy in our Regional Genetics Laboratory. Professor Chitty has since carried out a comprehensive evaluation of the implementation of NIPT in the NHS, the results of which informed the National Screening Committee's decision to introduce NIPT into the NHS in 2018 and offer it to women who are at increased risk of having a child with Down's syndrome, Edward's syndrome or Patau's syndrome.

Pioneering gene therapy

We are the leading centre for implementation of gene and cell therapies, with the largest number of gene therapy trials open in Europe. This has been made possible through GOSH BRC funding which has established infrastructure to support complex cell and gene therapy clinical trials in a joined-up academic and NHS environment. Successful application of gene therapies in inherited immunodeficiency and metabolic disease has demonstrated remarkable clinical efficacy with little toxicity.

In November 2015, GOSH reported the world's first use of gene-edited immune cells to treat drug resistant leukaemia. The new treatment uses the highly sophisticated TALEN technology to edit genes and create designer immune cells from human cells, which are programmed to hunt and kill drug resistant leukaemia. Previously only tested in the laboratory, these modified cells were used to treat a one-year-old patient, who had relapsed acute lymphoblastic leukaemia (ALL). She is now cancer free. This provides early proof of concept evidence for a ready-made T-cell strategy that is now being tested in clinical trials. For an update on the progress of this work please see the Gene and Cell Therapy theme news.

Success in this field has led to the launch of Orchard Therapeutics, which aims to develop and commercialise therapies for primary immunodeficiencies and metabolic diseases. This spin-off was the result of work led by BRC researchers Professors Bobby Gaspar, Adrian Thrasher and Waseem Qasim.

Success of the epilepsy research programme

GOSH BRC research has led to a significant impact in the treatment of children with drug resistant epilepsy. Successes include:

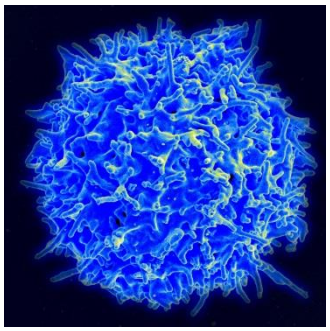
- Epilepsy surgery is now an accepted management option in young children, with the demonstration of long term benefits both in terms of seizure freedom and neurodevelopmental achievement.
- GOSH BRC researchers performed the first randomised controlled trial of the ketogenic diet in the treatment of drug resistant epilepsy, demonstrating efficacy in children 2-16 years of age. These findings have contributed to the 2012 pharmacological update of the NICE guidelines for the diagnosis and management of epilepsies.

- GOSH BRC researchers have also determined decanoic acid as a possible active component of the ketogenic diet, and in collaboration with the nutritional company Vitaflo, have produced a decanoic acid rich product to supplement patients' diets. This product is now being taken forward into tolerability trials in children and adults with drug resistant epilepsy.
- The development of a gene discovery programme for the early onset epileptic encephalopathies has resulted in the gene panel being clinically available within and outside GOSH, with a yield in previously unknown diagnosis determined in 20% of patients (40% in children with onset under 2 months of age).
- GOSH was recently announced as the lead for a Europe-wide epilepsy network, ERN EpiCARE, led by BRC funded Professor Helen Cross. Read more under Diagnostic and Imaging in childhood diseases theme news.

THEME NEWS

Gene, Stem and Cellular Therapies

World first use of gene-edited immune cells to treat leukaemia: One year on



GOSH reported a breakthrough application of gene-editing late in 2015 after a team led by NIHR funded Professor Waseem Qasim and Professor Paul Veys treated an infant with an otherwise incurable form of leukaemia. That experience, and success in a second infant, has now been published in Science Translational Medicine. The cells had been manufactured in the highly specialised BRC supported clean room facility, in collaboration with Dr Martin Pule at UCLH and French Biotech company, Cellectis. This is the most sophisticated version of gene-edited cells made to date using TALEN technology.

These gene-edited cells, called CAR-T cells, can effectively induce remission of acute lymphoblastic leukaemia (ALL) however in some patients, especially infants, it can be hard to manufacture and modify cells directly from the patient. Alternatively, in some cases it may be possible to use donor cells from matched allogeneic hematopoietic stem cell donors. In 2015, the team at GOSH used modified T cells from donors, called UCART19 cells, for the first time in humans to treat two infants with extremely aggressive forms of ALL. This treatment led to successful induction of remission which then allowed an allogeneic stem cell transplantation to go ahead.

Over 12 months later both patients are doing well, and the successful application of this technology provides a demonstration of the potential of gene-editing strategies for engineered cell therapies. However, the investigators remain mindful of residual risks of graft-versus-host disease (GVHD) and the likelihood that in some patients the leukemia will inevitably 'escape' immune effects. Phase I trials are underway and aim to treat ten further infants in combination with bone marrow transplantation as part of a company sponsored trial at GOSH. Meanwhile, Professor Qasim's group,

again with BRC support, are moving rapidly to produce the next generation of universal T cells using the next form of gene-editing technology, CRISPR/Cas9.

This work was also highlighted in the Independent.

Identification of a new genetic cause of complex early-onset dystonia

BRC supported researcher, Dr Manju Kurian has collaborated with researchers at the University of Cambridge and the NIHR Rare Disease Bioresource, to identify a new genetic cause of complex early-onset dystonia.

Dystonia is a movement disorder, affecting around 70,000 people in Britain and is characterised by abnormal body movements and postures. Currently for a large proportion of children with childhood-onset dystonia, the underlying cause remains unknown.

This paper defines a new genetic movement disorder, reporting 27 patients with early-onset complex progressive dystonia, associated with variations in the gene, *KMT2B*. The research suggests that this newly defined disorder could be effectively treated with deep brain stimulation (DBS); 10 of the 27 patients reported were treated with bilateral globus palidus interna DBS, all 10 patients showed clinical benefit with some patients re-gaining the ability to walk, with marked improvement of dystonic symptoms. For 5 of the patients it has now been 3 years since DBS insertion and all 5 have shown sustained reduction in dystonia, restoration of function and prevention of progressive disability.

This research has identified a clinically recognizable form of genetic dystonia, which has shown to be treatable through DBS, findings which have been published in Nature Genetics and highlighted in The Telegraph, The Guardian and The Daily Mail.

Molecular basis of childhood diseases theme news

GOSH BRC researchers have identified a novel genetic mutation causing a rare form of epilepsy

GOSH BRC supported researchers Dr Philippa Mills and Professor Peter Clayton, have identified a fault in the gene proline synthetase co-transcribed homolog (bacterial) (*PROSC*) in children with a rare strain of vitamin-B6 dependent epilepsy who are un-responsive to standard anti-epilepsy drugs.

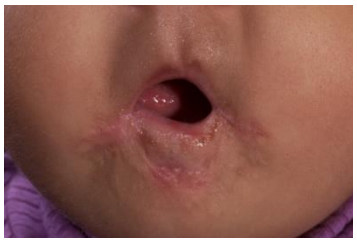
This research carried out homozygosity mapping and exome sequencing of a family in which there were 3 children with vitamin-B6 dependent epilepsy. The results showed a variation in both copies of the patient's *PROSC*

gene, a gene whose function was previously unknown. Subsequent sequencing of 29 children with B6 responsive epilepsy, which wasn't explained by any known causes, identified 4 children with biallelic PROSC mutations.

These findings are extremely important as they open up new therapeutic options for these patients. *PROSC* will now be added to the list of currently identified genes known to cause vitamin B6-dependent epilepsy, providing a test which can now confirm a diagnosis of epilepsy that will be improved by treatment with vitamin-B6.

These findings have been published in The American Journal of Human Genetics

GOSH BRC team define a new autoinflammatory disease caused by a mutation in *WDR1*



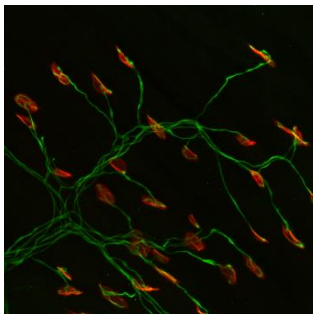
Research carried out by BRC funded Professor Paul Brogan and his team has defined a new autoinflammatory disease (AID) in humans with periodic fevers, immunodeficiency and intermittent thrombocytopenia (PFIT).

AIDs are a group of diseases that cause systemic inflammation caused by abnormalities in the innate immune system. Recently a new AID, which is caused by a recessive mutation in the *WDR1* gene, has been described in an animal model. This study identified a family with severe AID displaying similar features to those displayed in the *WDR1* deficient mice. The 2 patients described, exhibited severe oral inflammation with scars (figure), periodic fevers with immunodeficiency and thrombocytopenia (low blood platelet count) and findings revealed both patients to have a homozygous missense mutation in *WDR1*, resembling that exhibited in the *WDR1* mutated mice. These findings extend the findings from the animal model and highlight the importance of *WDR1* in the activation of the inflammasome and in human autoinflammation.

These findings have been published in The Journal of Experimental Medicine

Novel therapies for translation in childhood disease theme news

Spinraza: the first treatment for SMA to receive FDA approval



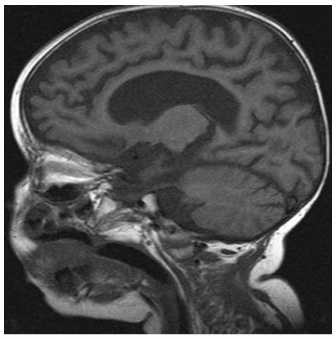
At the end of 2016, the American Food & Drug Administration (FDA) granted approval for the use of SPINRAZA (Nusinersen) for the treatment of Spinal Muscular Atrophy (SMA) in paediatric and adult patients. This is unprecedented for the SMA community witnessing the first approved drug for this disease.

The FDA approval was based on positive results from multiple clinical studies in more than 170 patients. GOSH was the highest UK recruiter for the first study, ENDEAR, a Phase 3 controlled study evaluating SPINRAZA in infantile-onset, which took place in the BRC supported Somers Clinical Research Facility. The interim analysis of the data from ENDEAR, (previously reported in the December BRC newsletter)

was considered throughout the approval process. In particular, patients with infantile-onset SMA recruited to the ENDEAR study and treated with SPINRAZA, achieved and sustained clinically meaningful improvement in motor function compared to untreated study participants. Furthermore, a greater percentage of patients on SPINRAZA survived compared to untreated patients. In open-label studies, some patients also achieved unexpected milestones such as ability to sit unassisted, stand or walk. To read the full press release click here.

Diagnostics and Imaging in Childhood Diseases theme news

Researchers awarded grant to set up new diagnostic service for encephalitis



BRC funded researchers have been awarded a two year grant to set up a new diagnostic service for encephalitis.

Encephalitis is inflammation of the brain, it is a rare condition which can be fatal. In a number of cases the causative agent is unknown due to the current diagnostic test (Polymerase chain reaction, PCR) used to identify infectious causes of encephalitis being highly targeted and specific.

Research carried out by BRC funded staff at GOSH and ICH, has investigated RNAseq as a new technique to identify causes of encephalitis. This technique sequences all of the genetic material in a patient's sample allowing any microorganisms to be identified. This technique has led to several unexpected causes of infection being identified.

Julianne Brown and Professor Judy Breuer have now been awarded a two year grant from GOSH Children's Charity to translate this research technique into a fully accredited diagnostic service. This will make GOSH one of the only laboratories in the world offering this service and will allow patients to access this new diagnostic test.

GOSH announced as lead for new Europe-wide epilepsy network

GOSH has been announced as the lead in a new Europe-wide epilepsy network, aiming to increase collaborations across Europe and improve access to innovative and highly-specialised diagnostics.

EpiCARE is a European Reference Network funded by the European Commission and led by BRC funded Professor Helen Cross. The network will enable collaborative working across Europe to develop and deliver highly-specialised diagnostics, such as advanced structural brain imaging and molecular and metabolic diagnostics, to improve treatments and outcomes in patients with rare or complex epilepsy. The network will be made up of 28 care providers across Europe and will run from 2017 to 2021.

To read the full press release click here.

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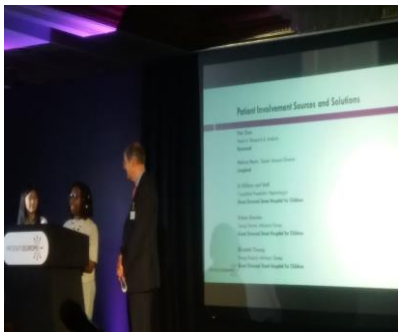
PATIENTS AND THE PUBLIC

Young Persons Advisory Group

Our Generation R Young Persons Advisory Group (YPAG) have been very busy, meeting with researchers to provide advice on a range of issues, including feedback on materials for an industry study on a rare neuromuscular condition, and methodology advice for a service evaluation project on a surgical intervention for children and young people with Cerebral Palsy.

In addition the group were part of The Patients as Partners Europe conference in February; out of the five members who attended the event, two YPAG members spoke at the conference about young people and their involvement in paediatric health research, while the additional three members manned an information stall.



Our YPAG group were also invited to present as part of International Rare Disease day at a large Biotech Company in Switzerland. One member of YPAG attended and presented along with a Birmingham YPAG member.

The Film *GenerationR News: Myth Buster - Research in the Hospital*, is now available to view online. The video shows YPAG members, Esme, Nicke and Freya exploring research at GOSH and interviewing various GOSH members of staff involved in research.

For more information about Generation R and YPAG, please visit their websites.

Rare Disease Day on 28th February 2017

The 10th anniversary of Rare Disease Day was on Tuesday 28 February, which was celebrated by over 90 countries. With a special focus on research this year, GOSH hosted a range of interactive activities around rare disease and rare disease research; activities included a 'how rare is your name' activity, an interactive muscle research activity and exhibition of the new 100,000 genome animation.

The event was run by ICH researchers, CRF and BRC staff with representatives from the North Thames Genomic Medicine Centre education programme and Syndromes Without a Name (SWAN UK). The day was a great success with lots of patients and families getting involved, so a big thanks to all those who helped!

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If you would like any information or advice about PPI/E, please get in touch Linda von Neree, PPI/E Lead in Research at research.ppi@gosh.nhs.uk

TRAINING

BRC funded trainee shortlisted for Advancing Healthcare awards

Congratulations to Dr Elaine Cloutman-Green, an Infection, Prevention and Control Practitioner who has been shortlisted for the Advancing Healthcare awards in the Research Champions category. Elaine was a recipient of an allied health professional internship funded by the BRC she then went on to be awarded a NIHR Clinical Lectureship.

The advancing healthcare awards programme acknowledges and rewards allied health professionals, healthcare scientists and those who work alongside them. The awards are very competitive and are UK-wide so we wish Elaine all the best in the rest of this competition.

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UPCOMING EVENTS

2017-2022 GOSH BRC Celebration symposium: 17 May

The GOSH BRC will be holding a symposium on May 17 16:00-17:30 in the Kennedy Lecture Theatre in ICH to celebrate the start of the GOSH BRC's third term of funding. This will be followed by a drinks reception held in the Winter Garden. We would like to encourage all individuals to attend to learn further about the future visions of the 2017-2022 GOSH BRC.

ORCHID conference: Keeping Patients and Parents at the Centre of Research

The centre for Outcomes and Experience Research in children's health, illness and disease (ORCHID) will be holding a conference on 15 June 10:00-17:30 in the Leolin Price Lecture Theatre focusing on putting patients and parents at the centre of research. The conference will showcase Nursing and Allied Health Professions research with guest speakers including Dr Abi Masterson (Deputy Chief Executive of Florence Nightingale Foundation) and Dr Tracy Long-Sutehall (Associate Professor from Southampton University).

Free to attend, contact Kate Oulton to book your place.