Paediatric Endocrinology research at the Royal Manchester Children's Hospital

Research in paediatric endocrinology has high priority and the specialty is considered a Top Seven speciality in Research and Innovation across children's services in Manchester. The team has focus on three main areas within paediatric endocrinology, namely Growth, Congenital Hyperinsulinism and Metabolic Bone Disorders while also continuing to build on clinical research in other areas relevant to children and young people.

Childhood Growth
The Manchester team has an international reputation in defining mechanisms of human growth, contributing to a deeper understanding of growth disorders, unravelling genetic factors and gene networks that modulate growth in the natural state, in disease and with pharmacological intervention.

Our main areas of research are:
i) the pharmacogenomics and genetics of disordered growth,
ii) the prediction of the response to growth hormone,
iii) development of novel diagnostic techniques for endocrine assessment
iv) the multi-omic modelling of human growth trajectories using population data and
v) the use of knock down/out models in Zebrafish to model human growth.

The group has expertise in:
i) characterising the role of specific genes in growth disorders, e.g. ubiquitination in 3M syndrome, intracellular adapter molecules such as GRB10 in a Zebrafish model
ii) identifying sets of genes with co-ordinated transcriptomic responses that predict the clinical response to growth hormone treatment in multiple growth disorders,
iii) using the transcriptome as a novel tool in endocrine diagnosis (recent MRC CARP award)
iv) using available datasets such as the Avon longitudinal study of parents and children (ALSPAC) to model growth trajectories and 'omic data to predict cardiovascular health in later life,
v) modelling growth trajectories that link early embryology and in utero development with child growth and later life health risks in both Fetal Growth Restriction (BabyGro study) and Assisted Reproductive technologies.

The group also has experience at managing large observational studies such as the Manchester Growth & Vascular Health Study, as part of the International Hyperglycaemia & Adverse Pregnancy Outcomes study (**HAPO**), the Ibadan Growth & Vascular Health study in Nigeria, and the European Safety & Appropriateness of Growth Hormone treatments in Europe [**SAGhE**]), and most recently the Manchester **BabyGro** study (antenatal exposures in fetal growth restriction that lead to adverse cardio-metabolic disease risk).

Researchers within the group are:
* Professor Peter Clayton
* Dr Philip Murray
* Dr Adam Stevens
* Dr Andrew Whatmore
* Dr Reena Perchard

BSPED Office
Starling House, 1600 Bristol Parkway North,
Bristol, BS34 8YU, UK
Tel: +44 (0)1454 642258 Fax: +44 (0)1454 642222
Email: bsped@endocrinology.org Web: www.bsped.org.uk
Charity No: 1135319

* Mr Terry Garner

Internal collaborations are with Obstetrics, Reproductive Health, Cardiovascular, Diabetes, Genetics, Data Science & Artificial Intelligence.

External Collaborations are with Endocrinology in Goteborg; Child Health in Shanghai Jiao Tong University School of Medicine (including birth cohorts); NovoNordisk (prediction of growth response to long-acting GH in GH deficiency and SGA; Lumos Pharma (US) (trial of an oral GH secretagogue)

5-year Vision for child growth research in Manchester:

We will continue our overall ambition of defining Normal & Disordered Human Pre- and Post-natal Growth & Development at clinical and molecular levels in patients & populations. We will build on our recent MRC award to develop new tools for endocrine diagnosis extending from growth hormone deficiency into assessment of the hypothalamo-pituitary-gonadal axis and well as the hypothalamo-pituitary adrenal axis.

As poor intra-uterine growth, stillbirth and postpartum maternal and child health are major issues in the UK, particularly GM, research will focus on:
i) discovering and translating biomarkers, mechanisms, modifiable risk factors and novel therapies for perturbed embryonic, fetal, placental and child growth,
ii) explore the effects of maternal comorbidities on child health,
iii) obtain a better understanding of early embryo development, particularly following ART and how this influences growth and development in later pregnancy.

We will continue to deliver a consistent high output in growth research of an international standing and be recognised as national/international leaders in the field. This will be achieved through a combination of high value grant awards, strengthening collaborations in growth research, emphasis on and further development of the science of computational biology and translation to clinical practice through innovation and pharma partnerships.

Congenital Hyperinsulinism

Congenital Hyperinsulinism (CHI) is a rare and complex disease, causing hypoglycaemia in infants and young children with significant deleterious impact on the brain. Manchester is a national centre for the treatment of the rare disease of Congenital Hyperinsulinism (CHI) and partners Alder Hey Children's Hospital through the Northern Congenital Hyperinsulinism (NORCHI) service. Alongside the development of a strong and effective clinical service, NORCHI has extensive collaboration with the University of Manchester to investigate pathobiology of beta cell dysfunction and derive a deep phenotype of CHI. The department has contributed to both the science and therapy of CHI through clinical studies, genomic and post-genomic investigations and undertaking and participating in clinical trials. The team has combined computational biology with clinical datasets and natural history information to rearrange and redesign standards of care. As a consequence of research efforts from the wider multidisciplinary clinical and research teams, NORCHI has emerged as a national and international leader working with parent groups, international charities, regulatory agencies and pharmaceutical companies to improve therapeutic options.

As a NIHR-BioResource centre, NORCHI is engaged in steps to develop biomarkers for disease and international clinical trials of novel therapies such as soluble glucagon and insulin receptor antibodies for which Manchester remains the chief UK site. Its recent research programme is centred around mathematical modelling of glycaemic profiles in hypoglycaemia. As a further step, NORCHI is engaged in technologies to develop predictive algorithms/machine learning devices for sophisticated individualised therapy choices and contributing to digital research strategies outlined in Children's Research 2025.

Researchers:
Prof Mark Dunne
Dr Karen Cosgrove
Prof Indi Banerjee
Dr Maria Salomon Estebanez
Dr Christopher Worth
Sister Elaine O'Shea

Supporting consultants:
Professor Leena Patel
Professor Peter Clayton
Dr Mars Skae
Dr Raja Padidela
Dr Amish Chinoy
Dr Phil Murray

5 year vision: To strengthen CHI research through high impact publications, investigator led high value grants, participation in international clinical trials and shifting treatment choices and boundaries through continuous innovation. NORCHI has well established links with Patient Advocacy groups; it aims to develop this partnership to improve and prioritise research focus. NORCHI will aims to develop and support talented individuals and trainees to continue research aspirations, thereby sealing its reputation as a beacon for research excellence and translational medicine in CHI.

Metabolic Bone disease

Our ambition for research:

To continue world class research and enhance our reputation as a leading research centre for metabolic bone disorder nationally and internationally. We aim to achieve this by continuing industry funded research, judicial use of charitable funds and applying for funding through national and international research funding agencies. In addition, we aim to expand our research into genetics and molecular fields. Building on our current research project on musculoskeletal health on Neurofibromatosis-1, our aim is to become a centre for research into musculoskeletal health in NF1 and other genetic disorders.

Our service:

Metabolic Bone Disorder service at Royal Manchester Children's Hospital is a research active unit. We have initiated and led on many research projects and have also been collaborating locally,

nationally and internationally in performing high quality research which has generated novel data, improved patient care and have been published in high impact peer review journals. Our involvement in pharmaceutical funded research has led to licensing and national commissioning of life saving medications for rare metabolic bone disorders. Our track record in successfully recruiting and completing clinical trials have attracted multiple industry led studies and we are currently engaging with them in many early and late phase clinical trials.

The following is a summary of our industry led clinical trials:

Completed Studies:

1. Asfosate alfa for HPP- phase 3 trial. One international patient recruited. National commissioning obtained at RMCH
2. Burosumab for XLH- Phase 2 and Phase 3. Eight patients recruited. Drug licensed and approved by NICE for NHS funding.

Studies in early phases:

1. Phase 1 study for use of recombinant 1-84 PTH in hypoparathyroidism in children and adolescents. Ethics approval granted. Awaiting setup of study
2. Phase 2/3 study of Burosumab in XLH- Ethics meeting on 28th of September
3. Natural history study of paediatric and adolescents with Generalised arterial calcifications in infancy: Centre selected for UK. Study pending ethics approval.
4. Achondroplasia- PROPEL study.

In addition to above industry led studies, our team has been actively involved in clinical research which has generated novel data and contributed towards changing clinical practice.

Completed studies which have been published or awaiting publishing in peer review journals:

1. Cost-effectiveness of vitamin D supplementation in children- published in Frontiers. Industry funded
2. Resource utilization in HPP- Published in orphanet journal of rare diseases- Industry funded
3. National survey of Metabolic Bone Disease of prematurity in UK- Published in Acta Paediatrica
4. Characterisation of neurodevelopment in children with FHH type 3: No funding

Ongoing studies

1. Preliminary interventional trial investigating the effect of whole-body vibration therapy on muscle strength in children with NF1 - in addition, this trial will also establish baseline data of muscle function in children with NF1, and highlight whether muscle-strengthening exercises have a role. Funded through charity funds.
2. QOL in children with rickets- awaiting industry funding
3. XLH- registry study: CI for UK and first and one of the largest recruiters of patients in UK.
4. Raman Spectroscopy assessment of Bone protein and mineral content: MRC funded collaborative research study with Lancaster university. Ethics approved obtained. Recruitment in progress

Researchers:
Dr Amish Shenoy,
Dr Mars Skae,

Dr Raja Padidela
Prof Zulf Mughal.

5 year vision :

1. To continue research on mineral metabolism in neonates.
2. To investigate muscle and bone function in metabolic bone disorders and other endocrine conditions
3. To explore benefits of whole-body vibration in endocrine disorders
4. To unravel genetics of rare Metabolic Bone Disorders
5. To continue on industry sponsored trials on medications for metabolic bone disorders
6. To increase publication in high impact journals

BSPED Office
Starling House, 1600 Bristol Parkway North,
Bristol, BS34 8YU, UK
Tel: +44 (0)1454 642258 Fax: +44 (0)1454 642222
Email: bsped@endocrinology.org Web: www.bsped.org.uk
Charity No: 1135319