Paediatric Endocrinology research at the Royal London Children's Hospital, Barts Health NHS Trust and the Centre for Endocrinology, William Harvey Research Institute (WHRI), Barts and the London School of Medicine, Queen Mary University London (QMUL).

Paediatric Endocrinology research at the Royal London Children's Hospital is facilitated by the partnership between the Department of Paediatric Endocrinology and Diabetes at Barts Health NHS Trust and the Centre for Endocrinology at the WHRI, QMUL and is underpinned by a core ethos of outstanding translational research, knowledge dissemination and clinical excellence.

The Department of Paediatric Endocrinology and Diabetes at Barts Health is the second largest unit for Paediatric Endocrinology in London https://www.bartshealth.nhs.uk/royal-london-children and provides comprehensive multidisciplinary care for young patients with endocrine disorders. The diabetes department is consistently in the top 10 of units of England and Wales, and is frequently a positive outlier for outcome measures in the National Paediatric Diabetes Audit (https://www.bartshealth.nhs.uk/childrens-diabetes)(https://www.rcpch.ac.uk/work-we-do/quality-improvement-patient-safety/national-paediatric-diabetes-audit).

The Centre for Endocrinology at the WHRI http://www.whri.qmul.ac.uk/research/endocrinology comprises 80 researchers. It has an international reputation for basic and translational research, with research income over the last 5 years in excess of £13M, a major contribution to the School of Medicine's UOA1 REF submission and clinical researchers leading on and participating in numerous multi-centre national and international clinical trials.

The paediatric endocrinology team has consistently delivered ground-breaking discoveries and developed an international patient-referral base, providing access to unique patients and families. Our Discovery Science and Experimental Medicine successes include major advances in understanding the genetic causes of familial pituitary adenoma, familial glucocorticoid deficiency, the timing of Puberty and childhood growth disorders, providing new insights into the cellular processes/mechanisms regulating pituitary tumour development, steroidogenesis and human growth and puberty.

Adrenal/pituitary development, mitochondrial research, stem cell physiology and intracellular trafficking are complementary research interests within Endocrinology. We were early adopters of 'Omics technologies and these are integral to the research methodology of our department. The extensive expertise in cell and developmental biology is expanding to encompass newer themes which include the generation/phenotyping of *in vivo* models, reprogramming strategies and bioinformatics capability to add value and depth of knowledge to genomic information.

We remain committed to our ethos of harnessing the close collaboration of excellent basic science and outstanding clinical expertise to achieve world-leading bidirectional translational activity.

Team members

Dr Li Chan – Reader in Molecular Endocrinology and Metabolism/Honorary Consultant Paediatric Endocrinology https://www.qmul.ac.uk/whri/people/academic-staff/items/chanli.html (l.chan@qmul.ac.uk, li.chan1@nhs.net)
Professor Leo Dunkel - Professor of Paediatric Endocrinology https://www.qmul.ac.uk/whri/people/academic-staff/items/dunkelleo.html (l.dunkel@qmul.ac.uk)
Dr Evelien Gevers - Consultant in Paediatric Endocrinology and Diabetes and Honorary Reader in Paediatric Endocrinology https://www.qmul.ac.uk/whri/people/academic-staff/items/eveliengevers.html

(evelien.gevers@nhs.net, e.gevers@qmul.ac.uk)
Dr Sasha Howard – Senior Lecturer and Honorary Consultant in Paediatric Endocrinology
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Dr Rathi Prasad - Consultant in Paediatric Endocrinology and Diabetes and Honorary Senior Clinical Lecturer https://www.qmul.ac.uk/whri/people/academic-staff/items/prasadrathi.html
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Dr Pratik Shah - Consultant in Paediatric Endocrinology and Diabetes and Honorary Senior Clinical Lecturer https://www.researchgate.net/profile/Pratik-Shah-36
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Professor Helen Storr - Professor and Honorary Consultant in Paediatric Endocrinology
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Dr Ruben Willemsen (Diabetes Lead) Consultant in Paediatric Endocrinology and Diabetes
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Research Collaborators at the Centre for Endocrinology, QMUL

Dr Carles Gaston-Massuet – Senior Lecturer in Genetics and Endocrinology
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Dr Leo Guasti - Reader in Endocrinology
https://www.qmul.ac.uk/whri/people/academic-staff/items/guastileonardo.html
Professor Marta Korbonits - Professor in Endocrinology
https://www.qmul.ac.uk/whri/people/academic-staff/items/korbonitsmarta.html
Dr Peter McCormick - Reader in Molecular Pharmacology
https://www.qmul.ac.uk/whri/people/academic-staff/items/mccormickpeter.html
Professor Lou Metherell - Professor of Endocrine Genetics
https://www.qmul.ac.uk/whri/people/academic-staff/items/metherelllou.html

Research Themes

DIAGNOSIS AND TREATMENT OF ADRENAL DISEASE

We have a longstanding research portfolio on the investigation and management of primary adrenal insufficiency.

- Genetics of Primary adrenal Insufficiency led by **Professor Lou Metherell** with clinical input from **Dr Li Chan, Dr Rathi Prasad** and **Prof Helen Storr**. To date the cohort of referrals stands at >400 patients from over 30 different countries, in which we have a genetic diagnosis for 2/3 and climbing.

For more information visit:
https://www.qmul.ac.uk/adrenal/

- Management and development of new therapies led by **Dr Li Chan** seeks to establish novel ways of biochemical monitoring in conditions such as CAH as well as developing new therapies to treat primary adrenal insufficiency.

- Disordered sphingolipid metabolism in adrenal disease led by **Dr Rathi Prasad,** who first identified SGPL1 deficiency as a cause of adrenal insufficiency, exploring the role of sphingolipids in endocrine disease and physiology.

Investigators:
Dr Li Chan (Group Lead)
Dr Lou Metherell (Group Lead)
Dr Rathi Prasad (Group Lead)
Professor Helen Storr (Group Lead)

CHILDHOOD GROWTH

Professor Helen Storr leads an active programme of clinical and laboratory research and directs an international genetic diagnostic service for patients with undiagnosed short stature. Current research focuses on the recognition and diagnosis of growth disorders in children with particular emphasis on identifying novel conditions, enhancing understanding of the genetic and molecular mechanisms underlying short stature and to identify new therapeutic targets.

The main research areas include:

- A unique whole genome next generation targeted sequencing gene panel developed to facilitate rapid and accurate genetic testing of patients with short stature. Whole exome sequencing (WES) and copy number variant analyses to identify defects in genes not currently implicated in pathological short stature.

- Established methodology and bioinformatic pipelines to prioritise genetic variants. 'In house' functional pipelines to allow comprehensive validation of genetic variants. To date the group have received >250 International and national referrals of undiagnosed short stature for genetic testing with >60% achieving a genetic diagnosis.

- Screening and early identification of growth disorders:
  - Collaboration with researchers from the Centre for Genomics and Child Health and the Centre of Primary care at QMUL and Institute of Population Health Research at St. Georges University, London to develop an evidence-based screening and diagnostic algorithm, to be piloted in East London.
  - Interdisciplinary collaboration to develop and validate a novel growth monitoring smartphone app to enable the early detection of growth disorders and provide timely and individualised advice to parents/carers.

For more information visit:
https://www.bsped.org.uk/research/active-clinical-studies/growth/
http://www.qmul.ac.uk/grasp/
https://www.qmul.ac.uk/growth-monitor/

Investigators:
Professor Helen Storr (Group lead)
Dr Avinaash Maharaj (PDRA)
Dr Miho Ishida (PDRA Bioinformatician)
Dr Afiya Andrews (Clinical Fellow)
Dr Thilipan Thaventhiran (Research Nurse)

PUBERTAL DISORDERS

Puberty research, led by **Dr Sasha Howard**, is focused on optimising the diagnosis and management of patients with pubertal disorders. *Genetics of Disordered Puberty Project:* our aim is to identify genetic mutations that cause Central Precocious Puberty and Delayed Puberty. To achieve this, we utilise next generation sequencing methods with downstream functional characterisation to diagnose patients that have been referred to us. To date, our cohort of referrals stands at >200 patients in whom we have found a genetic diagnosis in 28%. *Mini-Puberty Induction with Gonadotropins (Mini-PInG) Study:* our aim is to address whether gonadotropins are superior to testosterone for male infants with absent mini-puberty for gonadal development.

For more information visit:
https://www.bsped.org.uk/research/active-clinical-studies/dsd-adrenal-and-puberty/
https://www.qmul.ac.uk/pituitary

Investigators:
Dr Sasha Howard (Group Lead)
Professor Leo Dunkel (Co-PI)
Dr Leo Guasti (Co-PI)

PITUITARY DISORDERS

Barts Pituitary Centre focuses on pituitary research to understand genetic causes of pituitary conditions including pituitary tumours. The pituitary research programme comprises of:

- Establishing the genetic bases of hypopituitarism, either isolated pituitary hormone deficiency, multiple pituitary hormone deficiency or syndromic pituitary dysfunction, using clinical data and mouse models (PI Gevers, Co-PI Gaston-Massuet). Special interest in ARID1B deficiency, SOX9 mutations.
- Craniopharyngioma. We have established a large international database of samples of craniopharyngiomas accompanied with clinical phenotypic data. Research is focused on predicting outcome at several stages of the disease, using clinical and genetic data and mouse models. (PI Gaston-Massuet, Gevers)
- Prolactinoma and other pituitary tumours. We have a large database of isolated and familial cases. Research focuses on rapid diagnosis, genetic mechanisms and therapeutic interventions. (PI Korbonits)
- Pubertal disorders – pubertal delay, gonadotropin deficiency and precocious puberty (see above, PI Howard, Dunkel)

The principal investigators (**Dr Evelien Gevers, Professor Marta Korbonits, Dr Carles Gaston-Massuet, Dr Sasha Howard, Professor Leo Dunkel**) have some of the largest cohorts of patient data and samples from UK and international collaborators with pituitary conditions, including familial delayed and disordered puberty, pituitary adenomas, craniopharyngiomas and congenital isolated and syndromic hypopituitarism, allowing for comprehensive and high impact genetic studies.
https://www.qmul.ac.uk/pituitary

Investigators:
Professor Marta Korbonits
Dr Carles Gaston-Massuet
Dr Sasha Howard
Dr Evelien Gevers

Professor Leo Dunkel

OBESITY AND METABOLISM RESEARCH

Basic and Translational Metabolism research group

We are establishing the Tier 3 Complications of Excess Weight (CEW) service at the Royal London Hospital headed by general paediatric lead Dr Gin Peh along with Dr Li Chan as research lead. The Royal London Children's Hospital are building capacity for the treatment of severe childhood obesity offering bariatric surgery as a treatment modality (Mr Desai lead, Drs Peh, Shah, Chan). This work complements the basic and translational metabolism research group headed by Dr Li Chan at the Centre for Endocrinology who is leading a programme of work on elucidating central and peripheral mechanisms of energy homeostasis. She is also leading a study on co-morbidities in Down Syndrome.

Investigator:
Dr Li Chan (obesity and metabolism)

Prader Willi Syndrome

Dr Evelien Gevers runs a MDT clinic for children with Prader Willi Syndrome (PWS), including a Respiratory Physician with interest in sleep apnoea, a dietitian, a psychologist, and a CNS for Paediatric Endocrinology. She is interested in new treatments for PWS and is National Coordinating Investigator and PI for several clinical trials for PWS (see list below). She is interested in optimising care for patient with PWS and is part of an interest group for PWS.

Investigator:
Dr Evelien Gevers (PWS)

FAMILIAL ENDOCRINE TUMOUR SYNDROMES

The paediatric and the adult endocrine teams work closely together to manage rare endocrine tumours in clinics of familial complex endocrine diseases such as:

- Multiple Endocrine Neoplasia
- Von Hippel Lindau syndrome
- Diseases related to succinate dehydrogenase (*SDHx*) mutations (service designated a Centre of Excellence by the Phaeochromocytoma and Paraganglioma Alliance, largest international patient advocacy group for these conditions).

Management including surgical decision-making is within the framework of a multi-disciplinary setting and the vast majority of patients consent to surplus tissue being used for NIHR-approved translational research programmes. These research programmes seek to further understand molecular mechanisms of disease, identify new biomarkers and therapeutic targets for pituitary tumours (Professor Marta Korbonits, Dr Carles Gaston-Massuet), SDH-related paragangliomas (Professor Paul Chapple, Dr Scott Akker), VHL (Professor Paul Chapple, Professor Will Drake) and adrenocortical carcinoma (Dr Leo Guasti, Dr Rathi Prasad).

BONE AND CALCIUM

Dr Evelien Gevers has a long-standing interest in regulation of growth from the hypothalamus to the pituitary to the growth plate and bone in both rodent models and humans, focusing both on abnormalities of the GH secretion and signalling (STAT5B) and abnormalities of chondrocytes and

bone as a cause for short stature. She collaborates with radiologists and geneticists at GOSH and the GECIP as well as orthopaedic surgeons, with the main aim to increase genetic diagnoses in short stature. She has a large cohort of patients (>150) with short stature with and without confirmed diagnoses, including patients with IGF1R mutations and deletions, 3M syndrome, KGB syndrome, rasopathies, pseudorheumatoid arthritis, pseudohypoparathyroidism, hypophosphataemic rickets, pseudoachondroplasia, SRS, Temple syndrome, Bloom syndrome, Cockayne syndrome, Myhre syndrome, Meier-Gorlin syndrome, Coffin Siris syndrome, Desanto-Shiwani syndrome, SHOX variants, MMP9 mutations, DYRKA mutations, NPR2 mutations.

Research topics:

- Growth – genetic causes of short and tall stature.
  We run a bone and growth clinic and uses a combination of diagnostic modalities (skeletal imaging, dynamic function tests of the GH-IGF1 axis including 3 step IGF generation tests, MDTs with radiologists and geneticists and GeCIP, including WGS) with the aim to improve the diagnostic pathway, shorten time to diagnosis and find new gene variants as a cause for short stature. Dr Gevers has an interest in rasopathies including Noonan syndrome and cardiofaciocutaneous (CFC) syndrome) working with Carles Gaston-Massuet on a mouse with a BRAF mutation as a model for CFC syndrome. She also has an interest in tall stature with the aim to improve time to a correct diagnosis.

- Treatment for short stature
  We collaborate with Dr Ajay Thankamony (Cambridge University) on an NIHR trial to improve response to GH with metformin in patients with SGA and short stature, with Professor Mehul Dattani for IGF1 treatment in treatment in STAT5B deficiency, and in commercial studies for new GH treatments and databases, and has interest in developing new treatments for growth and bone disorders.

- Calcium sensing receptor (CaSR) disorders, especially autosomal dominant hypocalcaemia and its features and treatment, such as continuous PTH infusion with insulin pumps for treatment in the most severe patients. The department is a designated centre for treatment for X linked hypophosphataemic rickets and is part of the British Paediatric and Adolescent Bone Group.

Investigators:
Dr Evelien Gevers
Dr Carles Gaston-Massuet

NON-DIABETIC HYPOGLYCAEMIA DISORDERS AND SYNDROMIC FORMS OF HYPOGLYCAEMIA (KETOTIC AND NON-KETOTIC HYPOGLYCAEMIA)

Dr Pratik Shah is a clinician and researcher in Paediatric hypoglycaemia disorders, working in collaboration with colleagues nationally as well as internationally. His main research includes understanding the molecular basis of various forms of non-diabetic hypoglycaemia in children and identifying novel therapies in ketotic and non-ketotic forms of hypoglycaemia.
He also initiated “Transition Clinics in rare disorders like unusual forms of hypoglycaemia (and hyperinsulinism) and diabetes” in London. He has been primary investigator for various investigational studies and clinical trials and has been part of the Betacure study, establishing novel isotopes for recognising pancreatic focal lesions in Hyperinsulinism. Dr Shah works with various international parent/rare disease organisations and has joined as a Patron for the Hyperinsulinism UK charity. He is also Senior Advisory Member for Ketotic Hypoglycemia International and Scientific Advisory Board Member in Congenital Hyperinsulinism International (CHI).

His current research projects include:
1. Understanding the molecular basis of hypoglycaemia in Syndromic conditions
2. Unravelling the genetic aetiology and understanding the molecular basis of ketotic hypoglycaemia
3. Genotype-Phenotype analysis of Children with Hyperinsulinemic Hypoglycaemia in India
4. Understanding the molecular basis of Hypoglycaemia in Children with Downs Syndrome

Investigator:
Dr Pratik Shah

TYPE 1 DIABETES

We have one of the largest cohorts of patients with type 1 and other forms of diabetes nationally (approximately 700 patients). We are a designated centre, recruiting to studies from the European INNODIA consortium (www.innodia.eu) and have a longstanding collaboration with Cambridge, recruiting patients into various closed loop insulin pump studies. We are also part of the Type 1 Diabetes Immunotherapy Consortium (T1DUK – Type 1 Diabetes UK Immunotherapy Consortium; type1diabetesresearch.org.uk) and have been very successful in including patients into immunotherapy studies from our own centre as well as out of area. We are well supported by the Children's Clinical Research Facility to facilitate these and other trials. We are a Centre of Reference for the SWEET initiative (SWEET initiative; sweet-project.org), which is an international collaboration of certified diabetes centres utilising bi-annual data collection and benchmarking to improve care, publishing regularly in peer-reviewed international journals. We have also been actively involved in their international peer review program.

TYPE 2 DIABETES

We have possibly the largest cohort of paediatric type 2 diabetes patients in the UK (approximately 60-70 patients at Barts Health) and solid experience in managing these patients, using the latest technology and drug treatment in combination with a strong MDT team in specialised Type 2 Diabetes clinics. We have successfully recruited patients into various commercial randomised clinical trials in the NIHR portfolio (see below). We are active members of the National Type 2 Diabetes Work Group

Investigators:
Dr Ruben Willemsen
Dr Evelien Gevers
Dr Rathi Prasad
Dr Claire Hughes
Dr Pratik Shah

CURRENT SUPPORTED CLINICAL TRIALS

GROWTH, GH/IGF-I DEFICIENCY AND hGH/rhIGF-I TREATMENT

- Genetics of Primary IGF-I deficiency (PIGFD) (IRAS 226277, 2012 ongoing) PI Storr
- Test the feasibility of a novel smartphone growth monitoring app (IRAS 286683, 2021) PI Storr
- Global Patient Registry to Monitor Long-term Safety and Effectiveness of Increlex® in Children and Adolescents with Severe Primary Insulin-like Growth Factor-1 Deficiency (SPIGFD) (IRAS 3057645, 2021 in set up). PI Storr

- Effect of insulin sensitization on insulin like growth factor-1 responses to growth hormone treatment in children born small for gestational age (NIHR, IRAS 197289) Multicentre, collaboration with Dr Ajay Thankamony, local PI Gevers

- The GHD Reversal Trial: Effect on final height of discontinuation vs continuation of growth hormone treatment in pubertal children with isolated growth hormone deficiency (2022, in set up) Multicentre study, local PI Gevers

- Pfizer Registry of Outcomes in Growth hormone RESearch (PROGRES): A multi country, non-interventional prospective cohort study among patients with human growth hormone (hGH) treatments under routine clinical care (IRAS 301829, in set up) Multicenter, local PI Gevers

PUBERTY

- Genetic Factors Affecting the Timing of Puberty (IRAS 95781) PI Howard

- Mini-PInG Study - Mini-Puberty Induction with Gonadotropin Treatment in Infants with Hypogonadotropic Hypogonadism (IRAS 274645, 2022 in set up) PI Howard

HYPOPITUITARISM, PITUITARY TUMOURS, CRANIOPHARYNGIOMA

- Genetics of Endocrine Tumours (REC Reference 06/Q0104/133), PI Marta Korbonits, Sub-PI Carles Gaston

- Genetics in Pituitary, bone and growth disorders (IRAS 275668, in set up 2022) PI Gevers

PWS

- An Open-Label, Long-Term Safety Evaluation of Diazoxide Choline Controlled-Release Tablet in Patients with Prader Willi Syndrome (C602, DESTINY, 2020-2023, IRAS 268966) PI and National Investigator Gevers

CUSHING SYNDROME

- A phase II, multicenter, open-label, non-comparative study to evaluate the pharmacokinetics, pharmacodynamics, and tolerability of osilodrostat in children and adolescent patients with Cushing's disease. (Recordati AG, IRAS 253366, 2018 ongoing) PI Storr

DSD/CAH

- The International Registry of Disorders of Sex Development and Congenital Adrenal Hyperplasia (i-DSD and i-CAH) (IRAS 153634; new IRAS number after recent review 269776) PI Gevers

DIABETES

- A phase III multicentre double blind, randomized, placebo-controlled, clinical study to evaluate the safety and efficacy of Ertugliflozin (MK8835/PF-04971729) in paediatric

participants (age 10-17 years) with Type 2 diabetes (Merck, 2019-2024, IRAS 261870) PI Gevers

- An innovative approach towards understanding and arresting Type 1 diabetes (INNODIA). Collaboration with Cambridge University and Addenbrooke's Hospital (IRAS 210497, 2017 ongoing) PI Willemsen

- A randomised crossover study comparing hybrid closed-loop insulin delivery using ultra-rapid acting insulin to hybrid closed-loop insulin delivery using standard rapid-acting insulin in children with type 1 diabetes in the home setting (FAST-Kids). Collaboration with Cambridge University and Addenbrooke's Hospital. Patient Identification Centre for this Multi Center Trial (2021, in set up). (IRAS 287595) PI Willemsen

- Phase II, dose ranging, efficacy study of anti-thymocyte globulin (ATG) within 6 weeks of diagnosis of type 1 diabetes (T1D) (MELD-ATG, INNODIA consortium) (2021, in set up). (IRAS 273083) PI Willemsen

- An incident and High-Risk Type 1 Diabetes Research Cohort – After Diabetes Diagnosis Research Support System-2 (ADDRESS-2) (IRAS 55225, 2019 ongoing)