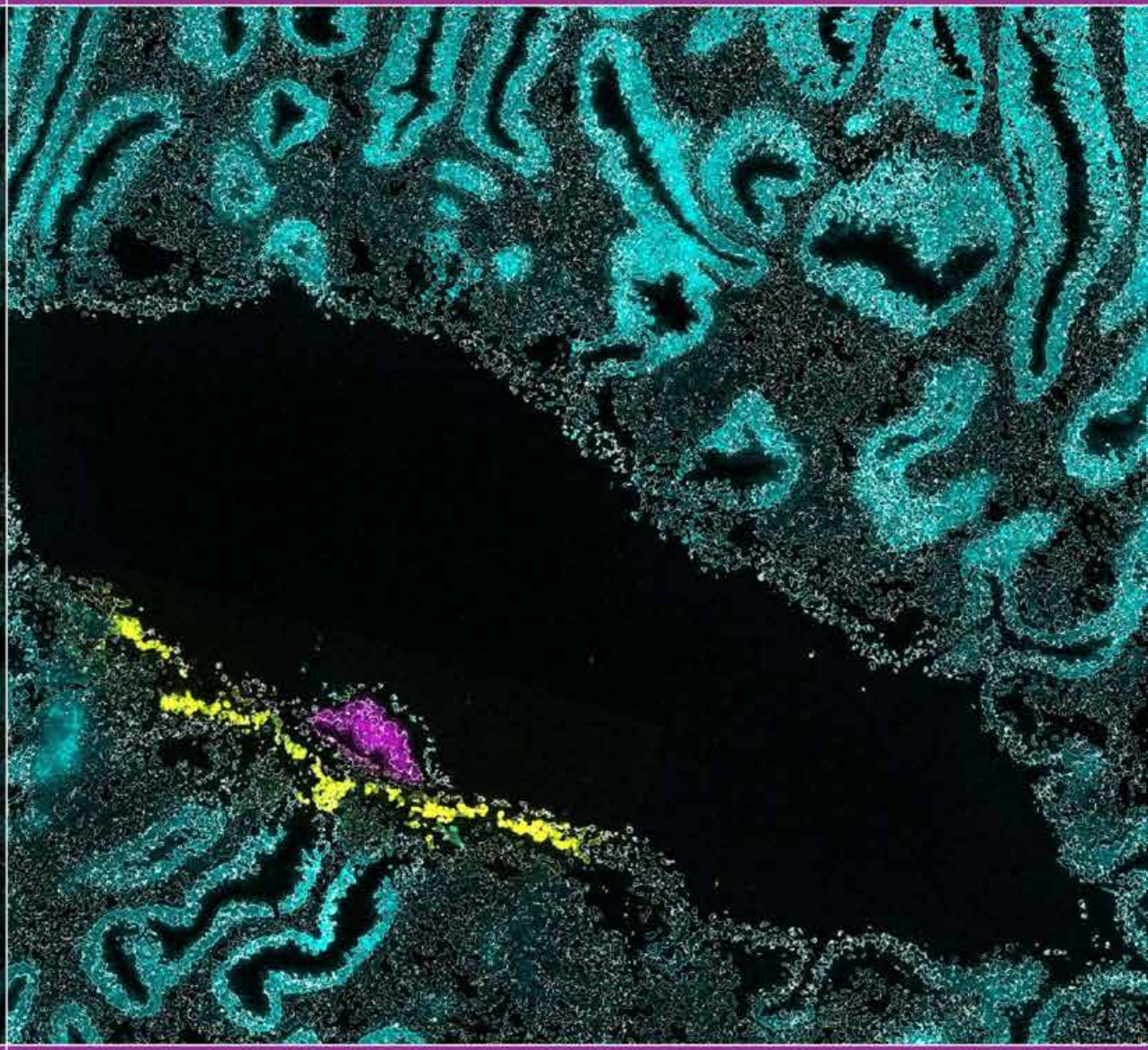
Centre for Trophoblast Resarch

Annual Report
2022/2023



UNIVERSITY OF CAMBRIDGE

CTR

Contents

A Message from the Director

Welcome to the CTR Annual Review of 2022 - 2023. Over the past year, CTR groups have made exceptional progress, securing over £27M in competitive grant funding, much of which is collaborative across groups. CTR investigators also published landmark studies and along the way developed and applied novel technologies.

Professor Kathy Niakan
Mary Marshall & Arthur Walton Professor of Reproductive Physiology

The CTR coordinated a response to a national consultation on human embryo research in the UK and we anticipate this leading to changes in law over the coming year. CTR investigators have pioneered stem cell-based models of human development, including models of the embryo and placenta. To ensure governance keeps pace with the science, CTR groups are also leading and contributing to the development of national self-governance of these sophisticated models which have much to teach us about human biology.

The CTR continues to lead the way in training in fundamental and cutting-edge placental research across the basic and clinical science. This year, we have prioritised matched funding and supporting core activities through grant funding where possible. We are delighted that our two CTR PhD studentships this year were supported by matched funding, and we are thrilled to have appointed two exceptional candidates who will be integral in fostering collaborative links between CTR research groups.

We are very grateful to our outgoing SAB members, Theresa Powell and Hubert Schorle, for supporting the CTR and for all of their expert advice. We are delighted that Hongmei Wang and Miguel Branco will be joining the SAB and look forward to working with them to support the CTR.

We have also prioritised staff recruitment to align support functions with strategic and academic priorities of the CTR, allied Departments and School of Biological Sciences. We have been fortunate to recruit three outstanding individuals this year. Dr Erin Slatery, our Executive Manager, joins us after completing her PhD with Thorsten Boroviak in the CTR. Erin has been instrumental in coordinating strategic priorities, supporting networks and recruitment, and implementing mechanisms to ensure long-term financial sustainability of the CTR.

We were also fortunate to recruit Dr Laura Woods as the CTR Bioinformatics Manager. With a background in placental research as a PhD student with Myriam Hemberger and stem cell biology as a postdoc with Anna Philpott at the Cambridge Stem Cell Institute, Laura provides expert bioinformatics support and has been instrumental in establishing a cost recovery mechanisms. Additionally, we welcomed Goitseone Thamae as the CTR Technician, who has a background in placental immunology and pathogen research. Goitseone prioritises support for the CTR shared laboratory facilities and helps manage the CTR Biology of the Human Uterus in Pregnancy and Disease Tissue Bank, facilitating access to human placental and related tissues for research to groups across the CTR. Our new structure is therefore enhancing collaborative working and improving the scope and effectiveness of CTR support. In this next year, we are looking forward to prioritising long-term financial sustainability and ramping up support for collaborative research and grant applications.

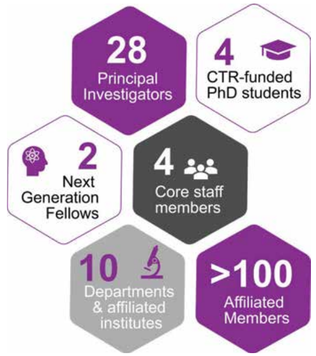
About the CTR

Each year, pregnancy and childbirth lead to millions of maternal, fetal, and neonatal deaths and countless suffering. A significant proportion of these devastating consequences are caused by a spectrum of common placenta-related disorders. These range from miscarriage (accounting for 10-12% of all pregnancies, with 90-95% occurring within the first 12 weeks), growth restriction (affecting 15% of live births), preeclampsia (occurring in 2-8% of pregnancies), and preterm birth (making up 10% of all live births) to stillbirth, which causes over 2 million perinatal deaths worldwide annually (Horton & Samarasekera, 2016; Magnus et al., 2019; Stock & Aiken, 2023). Despite these alarming statistics, our understanding of placental development and function remains inadequate. Until we understand the pathophysiology underlying these common disorders, we will not be able to offer effective interventions.

Recognizing the urgency and complexity of this challenge, the Centre for Trophoblast Research (CTR) was established in 2007 as the University of Cambridge's flagship cross-school initiative. The Centre serves as a nexus for interactions between basic and clinical sciences to unite the study of pregnancy complications that emerge at a late stage with the study of their developmental origins.

Over 16 years, the CTR has evolved into a world-leading centre of excellence in placental research and training. The CTR unites 28 group leaders across 10 departments and affiliated institutes and provides diverse opportunities for scientific interaction through events and shared state-of-the-art facilities. To support the next generation of trophoblast researchers, the CTR directly funds PhD students and early career researchers who benefit from close interactions in a vibrant, creative and diverse community of scientists. We seek to promote and sustain the field of placental and reproductive biology at Cambridge and beyond in order to prevent, treat and mitigate the effects of placental dysfunction on pregnancy.

CTR at a glance 2022-23



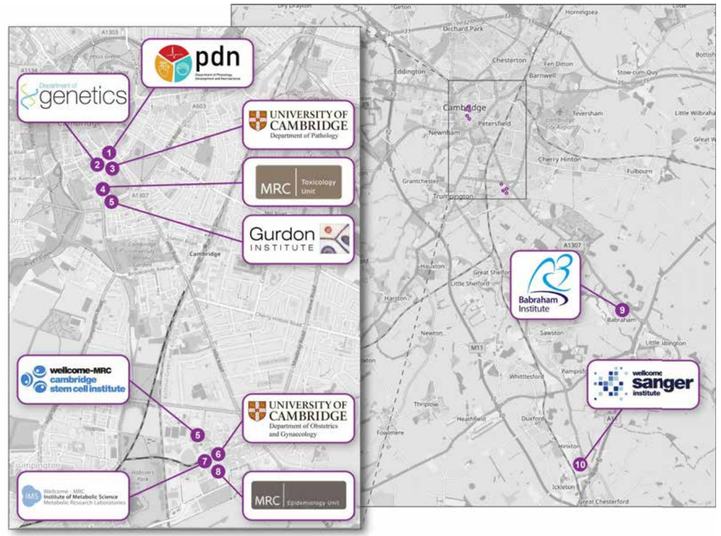
A Network of Expertise

The CTR connects world leading trophoblast-related research across Cambridge in the **School of Biological Sciences** (Departments of Pathology, Genetics, and Physiology, Development and Neuroscience), **School of Clinical Medicine** (Institute of Metabolic Science, Medical Research Council Epidemiology Unit and Department of Obstetrics & Gynaecology) and **affiliated institutes** (Gurdon, Sanger, Babraham and the Cambridge Stem Cell Institutes). The CTR administrative base and shared laboratory facilities are housed in the Department of Physiology, Development and Neuroscience.

We have particular expertise in reproductive immunology, clinical research, epigenetics and genomic imprinting, single-cell and spatial multi-omics analysis, developmental and stem cell biology, metabolism, organoid models, trophoblast stem cell biology, and placental and fetal physiology.

UNIVERSITY OF CAMBRIDGE
School of Biological Sciences

UNIVERSITY OF CAMBRIDGE
School of Clinical Medicine

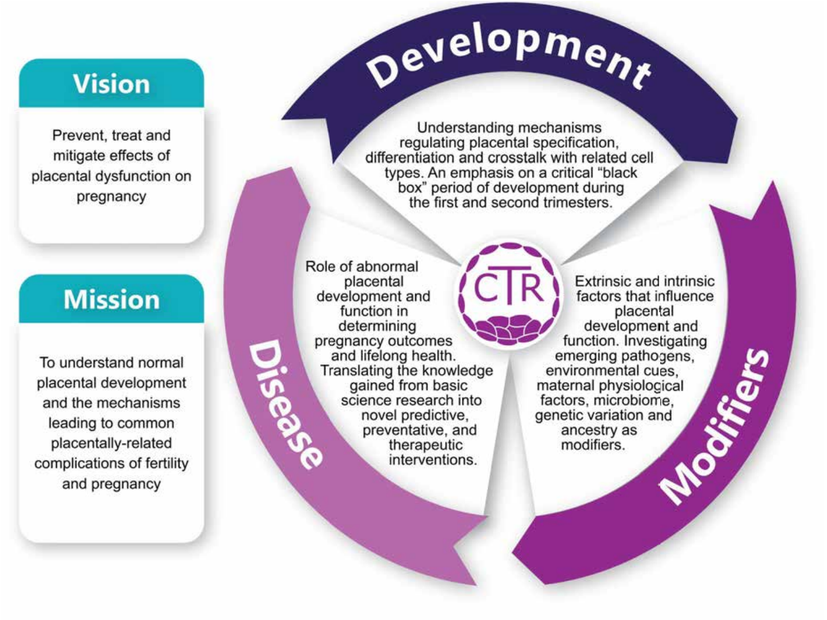


Our vision

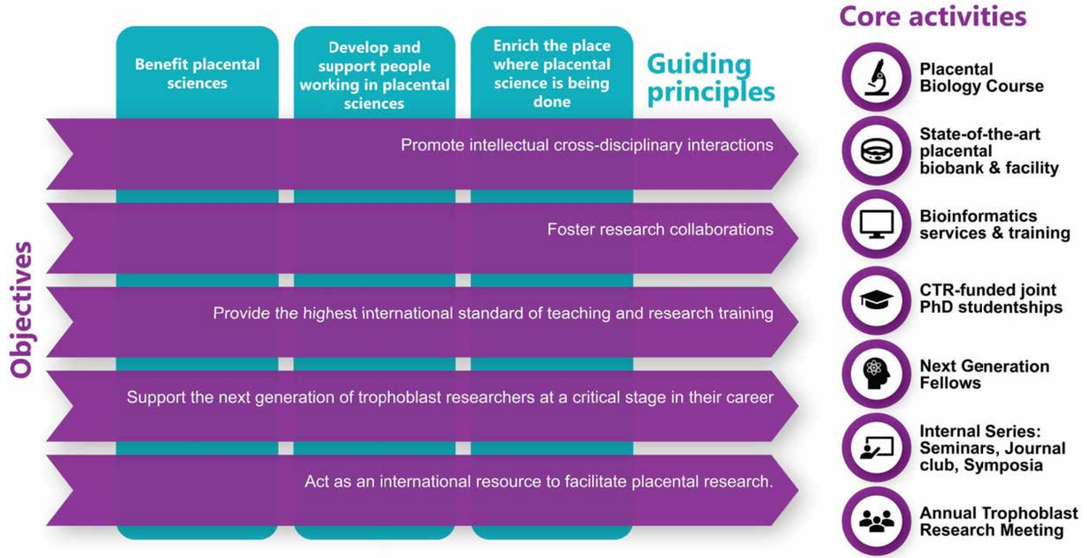
In May 2023, CTR group leaders came together to revisit the vision, mission and remit of the CTR.

CTR members are brought together around a mission to understand normal placental development and the mechanisms leading to common placentally-related complications of fertility and pregnancy. Interdisciplinary research aligned to our mission is split into three cross-cutting themes: Development, Modifiers, and Disease. Specific challenges within these themes will guide priority setting for funding over the next 5 years.

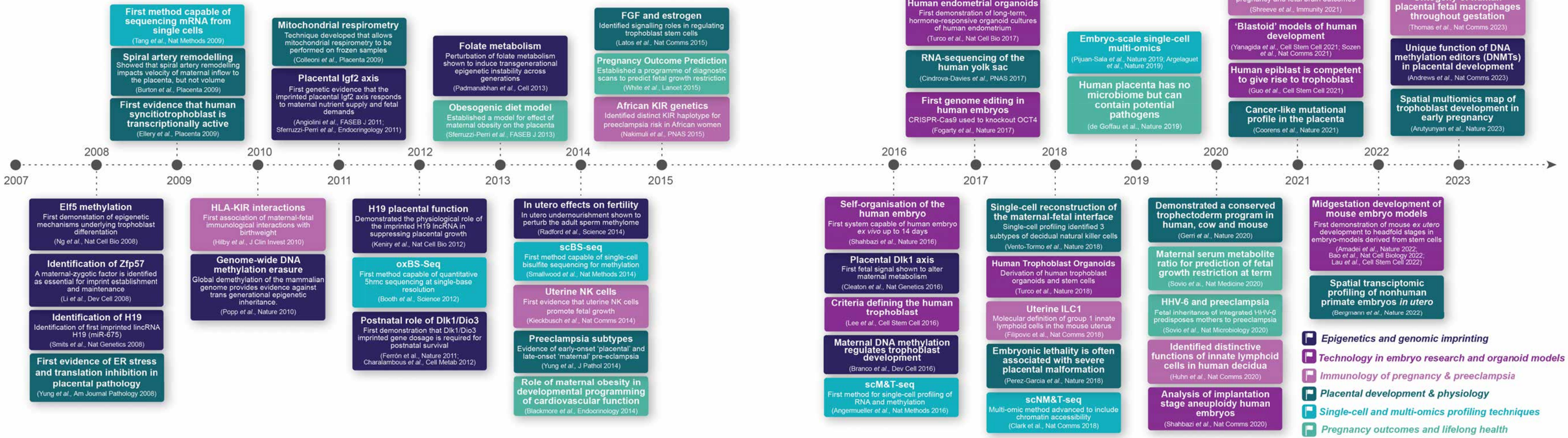
A set of three principles guides the Centre's approach to achieving this vision. Each of the core activities underlying our virtual network are informed by objectives aligned to these principles.



Our approach

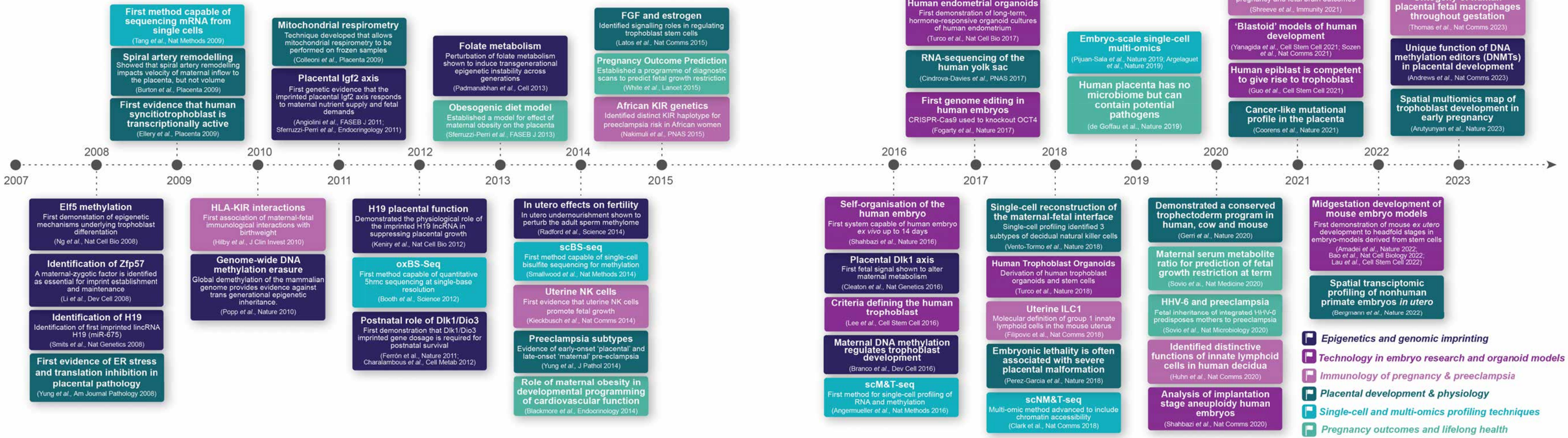


History of Scientific Achievements



Centre for Trophoblast Research annual report 2022/23

History of Scientific Achievements



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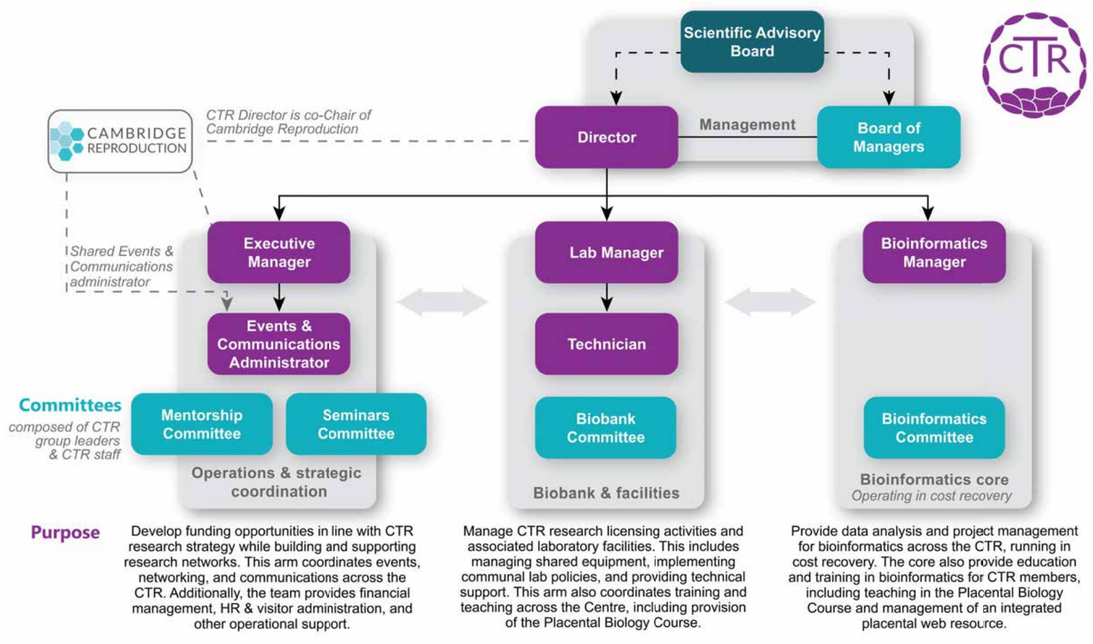
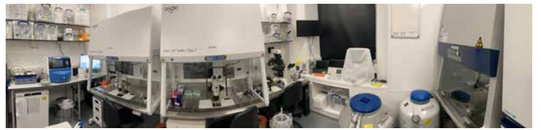
Structure

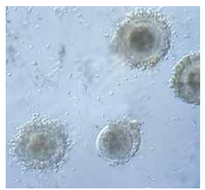


Facilities

CTR placental, endometrial and human embryo shared facility



The CTR placental, endometrial and human embryo shared facility opened in January 2023 following refurbishment of the space in the Physiology Building. It is outfitted with state-of-the-art, IVF clinic grade equipment, including a an Embryoscope live embryo incubation and imaging system, a microinjection suite, 3 laminar flow hoods, incubators, and liquid nitrogen storage which were funded by a Wellcome Investigator Award and matched funding from the School of Biological Sciences. Refurbishment of the facility was supported by the PDN Department. Operation of the facility is supported by the CTR Technician, Goitseone Thamae, *pictured above*.



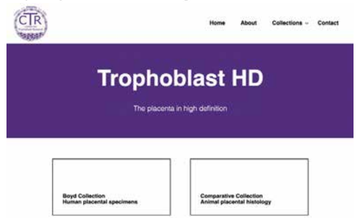
Bovine IVF conducted in the facility

The shared facility will support basic and clinical scientists to gain access to and training in placental, endometrial organoids and human embryo culture.

CTR Bioinformatics Facility

The CTR bioinformatics facility reopened in November 2022, run by the newly-appointed CTR Bioinformatics Manager, Dr Laura Woods, and supported by the Bioinformatics Committee. The facility has taken off at full speed and has made significant progress in its first 9 months of operation. Laura said: "We already have a number of exciting collaborative projects underway, and are working to support the bioinformatic needs of CTR groups and provide learning opportunities for CTR students."

The Bioinformatics facility has also spearheaded development of Trophoblast HD. The CTR holds an array of precious placental specimens that have been scanned to produce high-quality images. Trophoblast HD is a web-based resource in development at the CTR, which aims to provide access to these high-quality, detailed, and expertly annotated image collections to an international community of researchers, funded by a discretionary award made from the Wellcome Trust in 2019 to digitise the Boyd collection of placenta-in-situ slides and to make these freely available for researchers online.

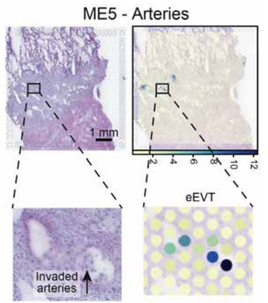


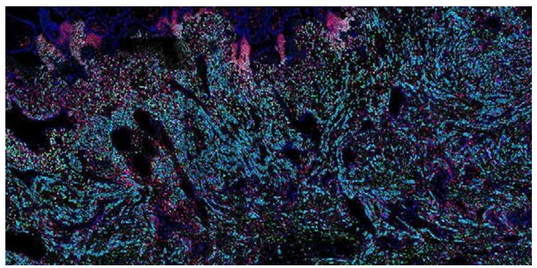
Scientific Highlights

Highlight: Spatial transcriptomics

A collaborative project led by Roser Vento-Tormo and Ashley Moffett mapped the complete trajectory of placental development in unprecedented detail using spatial transcriptomic analysis of rare historical samples.

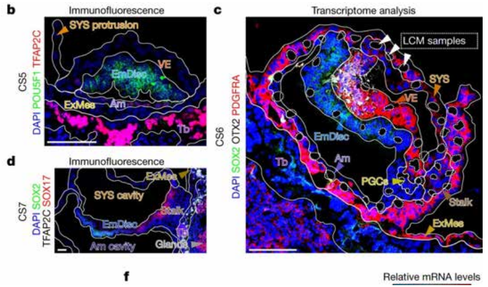
Roser brought together the laboratories of Prof Ashley Moffett and CTR Alumni Margherita Turco, *pictured below right*, to reconstruct the full human trophoblast trajectory of all populations of trophoblast cells by integrating transcriptomic and spatial information. Historical samples stored by Ashley Moffett and the CTR gave the team access to samples that encompassed all the stages of placentation occurring deep inside the uterus, including the spatial microenvironments of cells involved in spiral artery remodelling. Using this comprehensive atlas, the team benchmarked current trophoblast stem cell and organoid models, pinpointing that trophoblast organoids recapitulate early and mid-invasion, but do not exhibit terminal differentiation into all relevant cell types. The work provides an important placental contribution to the Human Cell Atlas, shedding light both on the intricacies of placental development and the strengths and limitations of existing models.
Arutyunyan et al., 2023, PMID: 34857954

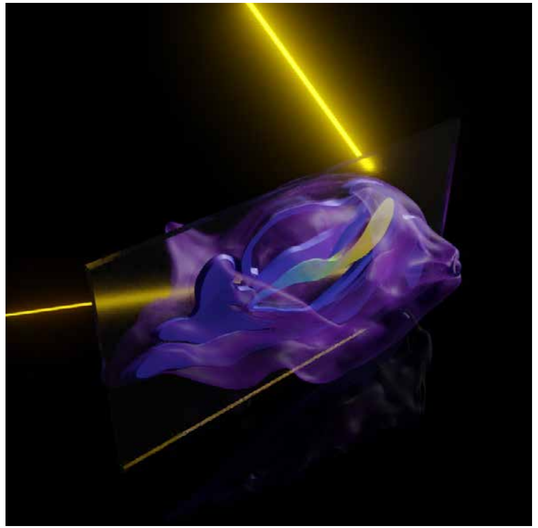




Dr Thorsten Boroviak, together with colleagues at the Babraham Institute and abroad, conducted spatial embryo profiling of the implanting primate embryo.

Human embryos of early postimplantation stages are inaccessible due to ethical considerations, which has limited our understanding of molecular mechanisms controlling embryo patterning and the diversification of extraembryonic lineages. The Boroviak lab has now opened the black box of primate development by developing spatial transcriptomic profiling approaches to decode the molecular framework of non-human primate embryos in the uterus. Their work reveals the cross talk between embryonic and extraembryonic lineages of the early embryo. They identify the earliest hallmarks of head and tail regions of the in utero primate embryo and determine the essential signalling cues controlling embryogenesis in stem cell-based embryo models.
Bergmann et al., 2023, PMID: 35709828

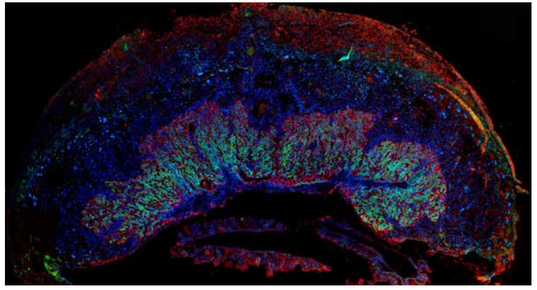




Highlight: Epigenetic regulation of placental development

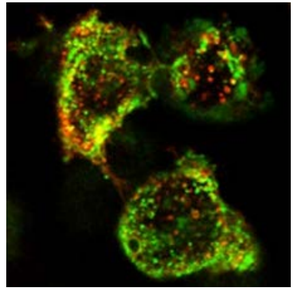
Dr Courtney Hanna's group revealed unique functions of DNA methylation editors (DNMTs) in placental development, in collaboration with Next Generation Fellow alumnus Vicente Perez-Garcia.

The study investigated the role of DNA methylation, a repressive epigenetic modification, in placental development and uncovered two surprising findings. Firstly, DNMT3L, a co-factor for de novo DNA methylation, has to date been shown to be important for DNA methylation in germ cells. The work revealed an undescribed role for DNMT3L in establishing DNA methylation in placental cells. Secondly, the team find that DNMT3B is essential for the correct formation of the placenta and when knocked out, compromises not only development of the placenta, but also growth and survival of the embryo.
Andrews et al., 2023, PMID: 36690623

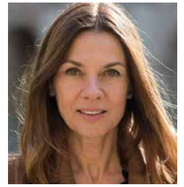


Dr Naomi McGovern together with CTR colleague Dr Courtney Hanna has uncovered the ontogeny of human placental fetal macrophages (Hofbauer cells) throughout gestation.

Hofbauer cells arise from erythro-myeloid progenitors that are only found up to 9 weeks of gestation. It has long been asked whether first trimester Hofbauer cells are replaced by fetal blood monocyte-derived macrophages. Using the unique epigenetic profile of erythro-myeloid progenitor-derived cells, this studies demonstrates that first trimester Hofbauer cells proliferate to fill the expanding placental niche and self-maintain until term. This shows that the Hofbauer cells that initially seed the placenta are not replaced by fetal blood monocyte derived macrophages during healthy pregnancy.
Thomas et al, 2023, PMID: 33075123

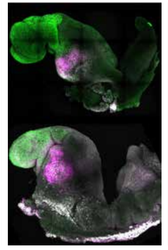


Highlight: Stem cell models of early development



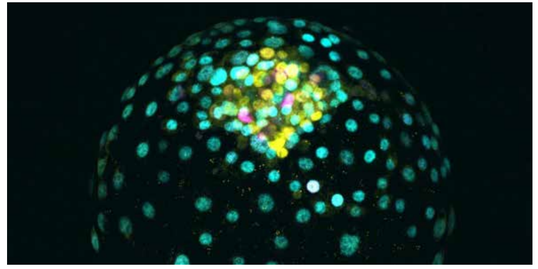
Professor Magdalena Zernicka-Goetz reported mouse stem cell-based embryo models that undergo neurulation and heart development ex utero.

In three studies published in 2022, the Zernicka-Goetz lab report the development of advanced stem cell-based embryo models of mouse development that progressed to remarkably late stages *in vitro*. They found that using inducible trophoblast stem cells improved the correspondence to the embryo, demonstrating the importance of capturing interactions between embryonic and extraembryonic lineages. They also reveal that lineage-specific cadherin codes and cortical tension drive the self-organisation of embryo models in vitro. This advance provides a powerful model of post-implantation embryogenesis that facilitates studies of embryonic and extraembryonic development.
Amadei et al., 2022; Bao et al., 2022; Lau et al., 2022 (PMIDs: 3600754, 36100738, 36084657)



Dr Peter Rugg-Gunn, in collaboration with groups in Austria and Belgium, used blastoid models to showed human-specific mechanisms in specification of the trophoblast lineage

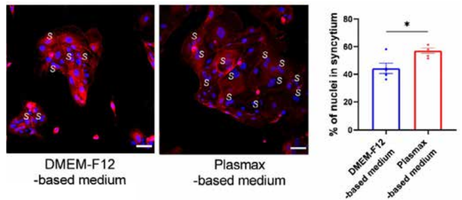
The team found that naïve-state human pluripotent stem cells are not epigenetically unrestricted as previously thought, but instead possess chromatin-based mechanisms that oppose the induction of alternative cell fates including trophoblast. Functional studies in stem cells and integrated stem cell-based embryo models led the group to propose that these chromatin regulators are pivotal mediators of the earliest lineage specification events and may underpin the extended period of cellular plasticity in human development.
Zijlmans et al., 2022, PMID: 35697783



Highlight: CTR PhD students

Giulia Avellino, a CTR-funded PhD student working in the laboratory of Dr Irving Aye, and colleagues show that the physiological medium (Plasmax) with nutrient and metabolite concentrations recapitulating human plasma improves human trophoblast stem cell proliferation and differentiation.

The group used human trophoblast cultures to model key processes of placental development. In vitro trophoblast studies to date have relied on commercial media that contains non physiological levels of nutrients, and the impact of these conditions on trophoblast metabolism and function was unknown. The team showed that commonly used culture media contain supraphysiological concentrations of nutrients and metabolites which alter trophoblast behaviour, and that the use of physiological media provides a further refined experimental system.
Avellino et al., 2023, PMID: 36878843

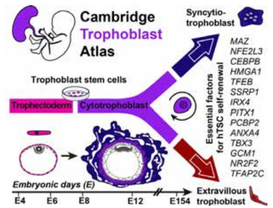


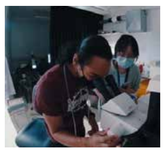
Giulia Avellino
Current CTR PhD student training in the lab of Dr Irving Aye from 2020-2024. Giulia's work was selected for the SRI President's Plenary Award (Top 4 abstracts) by the Society for Reproductive Investigation (SRI), which she presented in-person in Brisbane, Australia.

Dylan Siriwardena, a CTR-funded PhD student working in the laboratory of Dr Thorsten Boroviak, identified 15 essential factors for human trophoblast stem cell self-renewal

Dylan and colleagues in the Boroviak lab combined six published single-cell transcriptomic datasets into a unified atlas of human trophoblast development from zygote to mid-gestation and showed that trophoblast stem cells correspond to early cytotrophoblast in the periimplantation embryo. By screening the cytotrophoblast transcription factor network using siRNA, Dylan identified the gene regulatory network controlling cytotrophoblast identity and reveal a set of 15 essential factors for human trophoblast stem cell self-renewal.

Chen and Siriwardena et al., 2022, PMID: 35792865



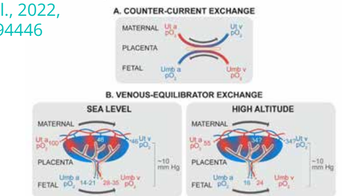


Dr Dylan Siriwardena
CTR PhD student from 2017-2022 who trained trained in the laboratory of Dr Thorsten Boroviak. Dylan's paper was shortlisted for 2022 outstanding paper prize by Development.

Highlight: Perspectives

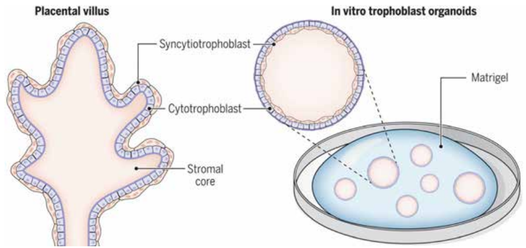
Professor Andrew Murray undertook a visiting Florence Crozier Cobb Visiting Professorship at the University of Colorado, resulting in a new perspective on why human uterine arterial blood flow is so high during human pregnancy.

The ideas in the piece directly arose during virtual discussions at the University of Colorado in May 2021. The team questioned why human convective oxygen delivery apparently exceeding the oxygen demand of the fetal-placental unit. Considering principles developed by exercise physiologists, they propose that uterine venous partial pressure of oxygen (PO2) sets the upper limit for oxygen diffusion to the fetus. Concomitantly, arterial blood flow serving to narrow the arterial-venous difference. Following the publication of a perspective in the American Journal of Physiology, Professor Andrew Murray and colleagues were awarded an R01 award by the NIH to test these concept in high-altitude dwelling populations in the Andes and Colorado. The work will include novel, simultaneous measurements of blood flow and oxygen tension in 4 vessels (uterine and umbilical arteries and veins) alongside placental mitochondrial respiratory function and metabolism.
Moore et al., 2022, PMID: 36094446



Dr Catherine Aiken (CTR PI), together with colleague Sarah Stock, Program Director at the Wellcome Leap In Utero programme, presents a case for the urgency of research on pregnancy complications, highlighting the limited availability of therapies to improve pregnancy outcomes.

Catherine and colleagues explain that one of the reasons for this lack of therapies is our incomplete understanding of fundamental processes involved in pregnancy, including the basic mechanisms of placentation, the safety of diabetes drugs for use in gestational diabetes, and the mechanisms controlling the onset of human labour. However, recent advancements, including the use of trophoblast organoids to model placental development and the integration of data-science techniques to study longer-term outcomes, promise to address these gaps. This is a crucial first step towards identifying potential therapeutic targets for pregnancy disorders.
Stock and Aiken, 2023, PMID: 37053324



Awards

Professor Anne Ferguson-Smith

Professor Anne Ferguson-Smith was appointed the Commander of the Order of the British Empire (CBE) for services to Medical Research in the King's Birthday Honours List in 2023 in recognition of her fundamental discovery research in the field of genomic imprinting and epigenetic inheritance. She was also awarded Mabel Fitzgerald Lecture and Medal University of Oxford (2022) and received the Anne McLaren Distinguished Scientist rose vase from the Society of Reproduction and Fertility (2021).

Professor Dino Giussani

Professor Dino Giussani was awarded the Physiological Society GL Brown Prize Lecture in 2023. Dino delivered a lecture on 'Healing Tiny Hearts Across Generations,' addressing a gap in our knowledge around how the risk of developing heart disease is determined in the intrauterine environment experienced before birth.

Dr Roser Vento-Tormo

Dr Roser Vento-Tormo was a finalist for the Michelson Philanthropies & Science Magazine Prize for Immunology Award in 2023. She was commended for research on understanding how cell-cell communication and the tissue microenvironment regulate cell identity and function in the context of immunity and development.

Professor Magdalena Zernicka-Goetz

Professor Magdalena Zernicka-Goetz was awarded the European Society of Human Genetics Award in 2023 in recognition of her pioneering work in generating embryo-like structures to model early mammalian development.

Professor Andrew Murray

Professor Andrew Murray was awarded the 2023 Annual Public Lecture by the Physiological Society in recognition of his research on the study of placental metabolic function at altitude, including in adapted populations. The Annual Public Lecture is designed to bring exciting and outstanding physiological research to the public. Andrew Murray was also promoted to full professorship in 2023.

Professor Francesco Colucci

Professor Francesco Colucci was awarded two visiting professorships in 2023 at the University of Milano, Department of Medicine and at The University of Torino, Department of Biotechnology.

Grants

Value of grants awarded in 2022- 2023: £27,271,428

Wellcome Leap | In Utero

- "Maternal serum proteomics to understand and to predict pregnancy complications leading to stillbirth" Prof Gordon Smith and Prof Steve Charnock-Jones

Wellcome Trust

- "Defining the epigenetic principles that instruct the development of human embryos" – Dr Peter Rugg-Gunn, Wellcome Discovery Award
- "Functional interrogation of primate gastrulation and body patterning: building the embryo outside the womb" –Dr Thorsten Boroviak, Wellcome Career Development Award
- 'Heat exposure on pregnancy outcomes: studies in The Gambia' – Prof Amanda Sferruzzi-Perri
- "The role of hypoxia and HIF-2 in sympathoadrenal development" – Prof Dino Giussani

British Heart Foundation

- Maternal Obesity During Pregnancy: Translatable Programmed Cardiovascular Dysfunction in the Fetus – Prof Dino Giussani

UKRI: Medical Research Council

- "Genomic imprinting and the epigenetic control of genome function: regulation, redundancy, resilience" – Prof Anne Ferguson-Smith
- "Maternal Obesity During Pregnancy: Translatable Programmed Cardiovascular Dysfunction in Offspring" – Prof Dino Giussani
- "Amelioration of aberrant glycosylation and maternal adaptation to pregnancy" – Prof Steve Charnock Jones and Prof Sue Ozanne

ERC (European Research Council)

- "Dissecting the regulatory mechanisms driving trophoblast cell fate" – Dr Roser Vento-Tormo, ERC starting grant

Chan-Zuckerburg Initiative

- Cell-cell signalling shaping reproductive function – Dr Roser Vento-Tormo
- A single-cell map of the paediatric ovary in 3D – Dr Roser Vento-Tormo

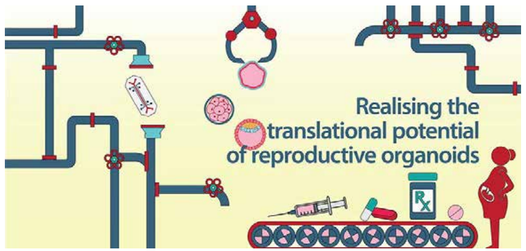
Cambridge-Africa ALBORADA

- 'Understanding placental malaria pathogenesis for the development of simple, sensitive, diagnostic strategies for improving outcomes in asymptomatic placental malaria' – Dr Amanda Sferruzzi-Perri

Policy & Outreach

Governance of Stem Cell-Based Embryo Models (SCBEMs)

The CTR, Cambridge Reproduction, the Cambridge Academy of Therapeutic Sciences (CATS) co-organised a workshop in July 2022 focused on realising the translation potential of reproductive organoids. Building on the event, Cambridge Reproduction initiated the Governance of Stem Cell-Based Embryo Models (G-SCBEM) project. It aims to establish a voluntary framework for the permissible use of stem cell-based embryo models in research. Presently, there is no specific regulatory framework in place for SCBEM research, though the transfer of such models into a woman's womb is prohibited by UK law. The absence of clear guidance in this area hampers research and undermines public confidence. The G-SCBEM working group includes current CTR members (Kathy Niakan Peter Rugg-Gunn) and CTR alumnae Jennifer Nichols. The G-SCBEM guidance will be launched in the late autumn and regularly reviewed to ensure that it keeps pace with new scientific developments.



Modernising the Human Fertilisation & Embryology Act

The Human Fertilisation and Embryology Act, enacted in 1990, has established the UK as a world leader in regulating fertility treatment and human embryo research. To adapt to advancements over the past three decades, the HFEA recently conducted a public consultation on proposed amendments to the law. The CTR coordinated a response to the consultation to express support for many of the proposed amendments. We particularly advocated for streamlined consent for embryo donation to allow for research embryo banking, drawing on the pioneering research enabled by our Human Tissue Authority (HTA)-regulated CTR tissue bank. A centrally-managed human embryo bank would bring similar benefits for basic and translational research and the CTR is well-positioned to develop and manage such a bank. Streamlined consenting would not only advance research, but also bring benefits for donors, patients and collaborating clinics. The outcomes of the consultation response will be reported during the HFE Authority meeting in July 2023.

New partnerships and appointments

In partnership with Churchill College, the Sir Robert Edwards Trust and the Cambridge Trust who provided £118,858 in matched funding, we appointed Ana Ribeiro Orsi to a CTR PhD studentship.

Ana will be co-supervised by Kathy and Dr Thorsten Boroviak and will study the molecular mechanisms that regulate early human development, in line with the legacy of Bob Edwards's work in developing IVF.

Ana's project is entitled '**Understanding the molecular mechanisms that control human yolk sac progenitor (hypoblast) cell development'.**

In partnership with Newnham College, who provided £116,218 in matched funding, Natasha Cavell was appointed to a CTR PhD studentships co-supervised by Dr Geula Hanin in the laboratory of Prof Anne Ferguson-Smith and Prof Amanda Sferruzzi-Perri.

Natasha's project is entitled **'Investigating the role of imprinted genes in pre- and post-natal stages, and the links between maternal diet, placental signalling and lactation'**.

The CTR was awarded a Scientific Meeting and Sustainable Conferencing donation from the Company of biologists to support the 2023 hybrid Annual Meeting. This funding supports the virtual element of our programme in order to make the conference accessible to a larger and more diverse audience and promoting inclusivity, accessibility and sustainability.

List of publications

Catherine Aiken

1. Schoonejans JM, Blackmore HL, Ashmore TJ, Pantaleão LC, Pellegrini Pisani L, Dearden L, Tadross JA, Aiken CE, Fernandez-Twinn DS, Ozanne SE. **Sex-specific effects of maternal metformin intervention during glucose-intolerant obese pregnancy on body composition and metabolic health in aged mouse offspring**. *Diabetologia*. 2022 Dec;65(12):2132-2145. doi: 10.1007/s00125-022-05789-0. Epub 2022 Sep 16. PMID: 36112170; PMCID: PMC9630251.

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Irving Aye

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William Colledge

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Francesco Colucci

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Priscilla Day-Walsh

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Abby Fowden

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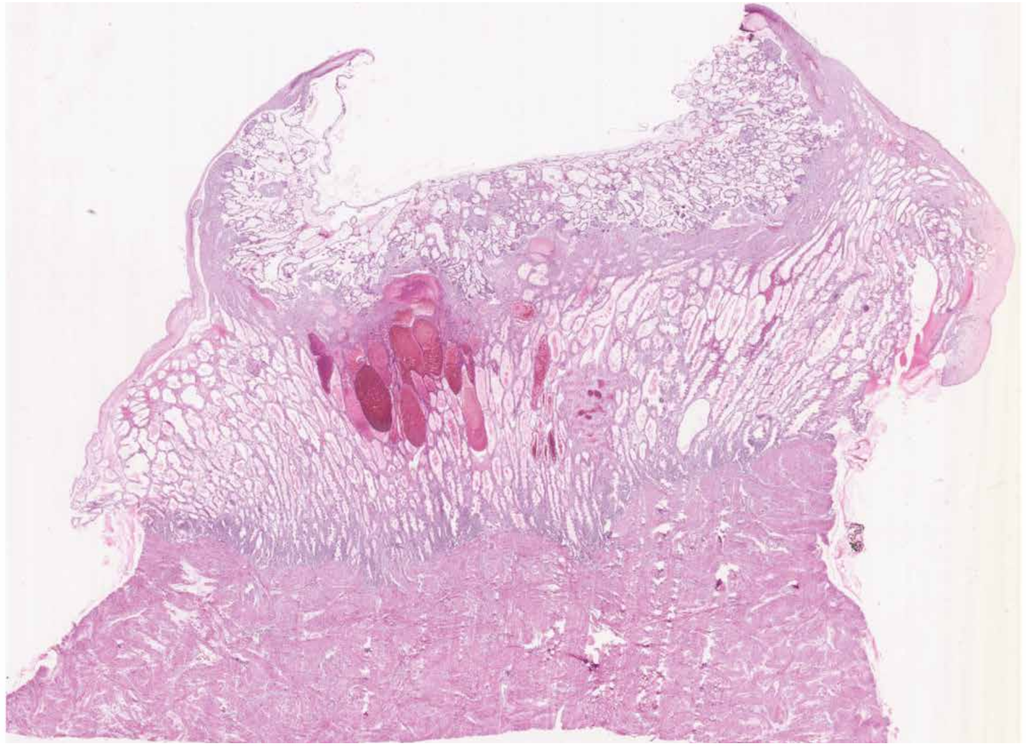

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Images credits

Front cover: Section of an implanted Carnegie Stage 5 marmoset embryo labelled for TFAP2C (yellow, trophoblast), SOX17 (cyan, endometrial glands), and OCT4 (magenta, embryonic disc and amnion). Credit: Sophie Bergmann and Erin Slatery.

Page 12: Image of bovine in vitro fertilisation (IVF). Credit: Niakan lab.

Page 14: Cells of the placenta. Credit: Kenny Roberts, Wellcome Sanger Institute.

Page 15: 3D rendering of spatial transcriptomic sampling of an implanted marmoset embryo. Credit: Erin Slatery.

Page 16: Left – MCT1 and MCT4 staining of an E12.5 placenta. Credit: Courtney Hanna; Right – Fetal Macrophages. Credit: Naomi McGovern.

Page 17: Left – Natural and stem cell-derived embryo models side by side to show comparable brain and heart formation. Credit: Gianluca Amadei and Charlotte Handford.

Right, Fluorescent microscopy image of a human blastoid, which is an embryo-like structure formed from stem cells that can model early embryogenesis in a dish. Cells corresponding to the early placenta are marked in blue, and cells corresponding to the early embryo are marked in yellow. Credit: Photo courtesy of Alok Javali, Heidar Heidari Khoei and Nicolas Rivron, Institute of Molecular Biotechnology of the Austrian Academy of Sciences (IMBA), Vienna, Austria.

Page 18: Image of Dylan Siriwardena. Credit: Timo Kohler

Page 49: Boyd collection - Pregnant hysterectomy, six-week.

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