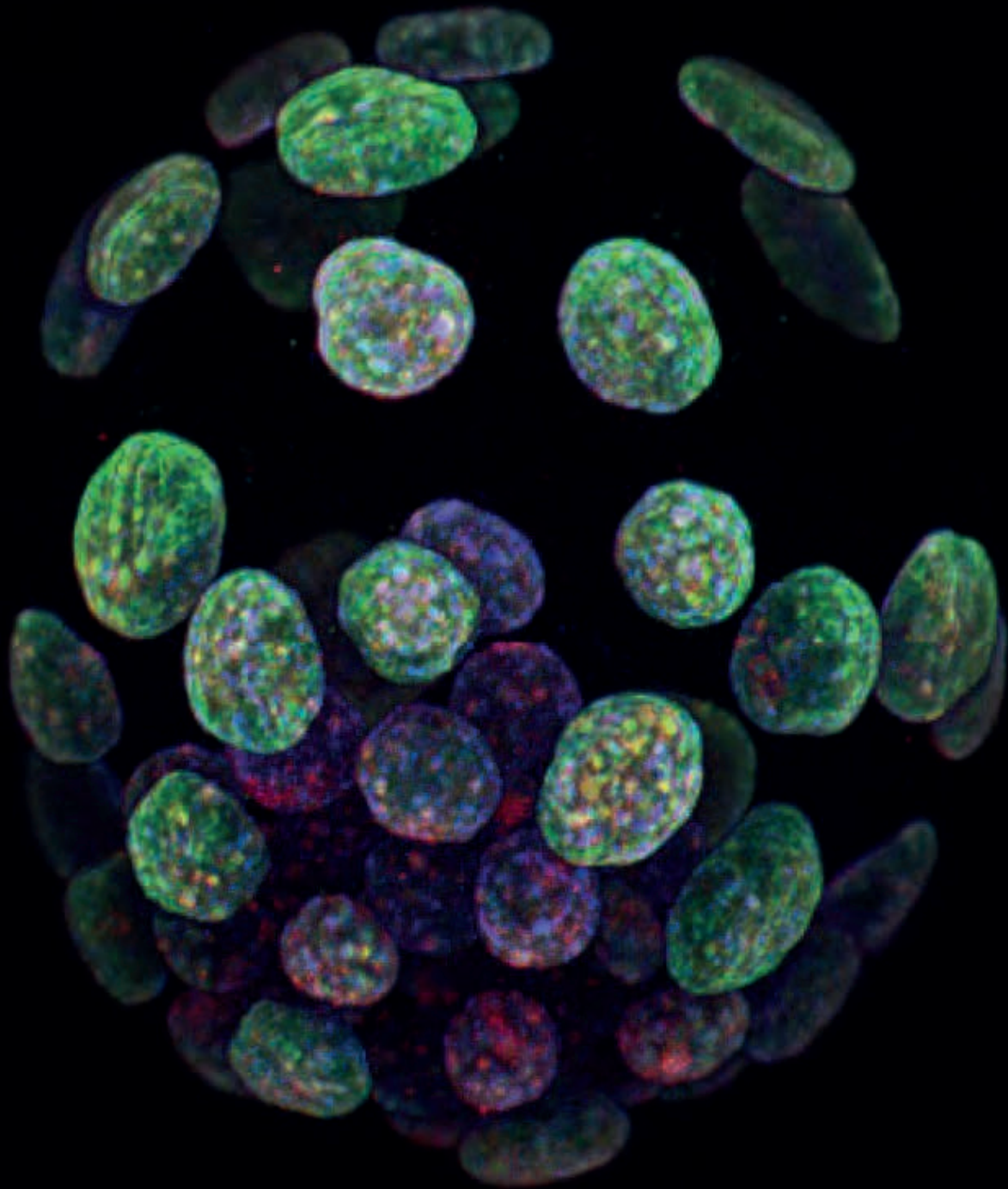


# Centre for Trophoblast Research Annual Report 2021/2022



UNIVERSITY OF  
CAMBRIDGE



# ABOUT THE CTR

The mission of the CTR is to foster collaborations and promote excellence in the study of trophoblast biology. As a virtual centre we bridge trophoblast-related research across the School of Biological Sciences (Departments of Pathology, Genetics, and Physiology, Development and Neuroscience), Clinical School (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).



UNIVERSITY OF  
CAMBRIDGE

Department of Obstetrics  
and Gynaecology



Babraham  
Institute



Department of  
genetics



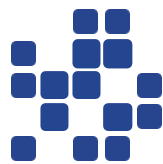
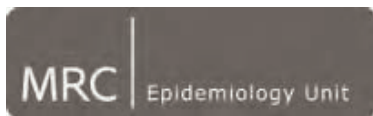
pdn

Department of Physiology,  
Development and Neuroscience



UNIVERSITY OF  
CAMBRIDGE

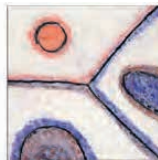
School of Clinical Medicine



wellcome  
sanger  
institute



Gurdon  
INSTITUTE



UNIVERSITY OF  
CAMBRIDGE

School of  
Biological Sciences



wellcome-MRC  
cambridge  
stem cell institute

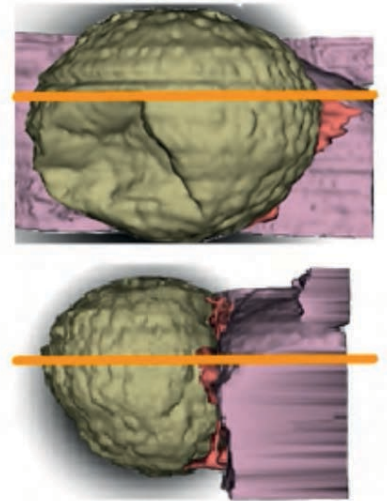
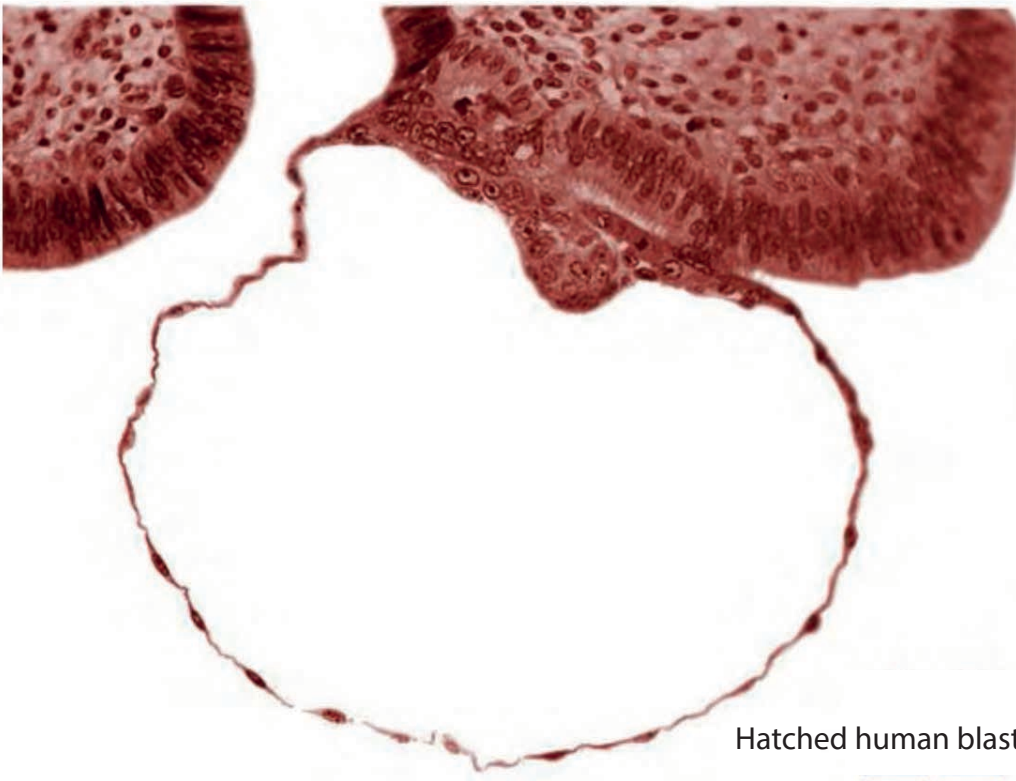


UNIVERSITY OF  
CAMBRIDGE

Department of Pathology



Wellcome - MRC  
Institute of Metabolic Science  
Metabolic Research Laboratories



Hatched human blastocyst undergoing adplantation  
Source: Virtual Human Embryo

## DIRECTOR'S INTRODUCTION

**Welcome to the CTR Annual Review of 2021/2022. Over the past year we have focused on further securing connections the CTR has built, as we establish ourselves as an integral part of a Cambridge Reproduction community, and we have fostered international collaborations to further the missions of the CTR.**

By working in partnership - across Cambridge, the UK, and through international collaborations - it is important to tackle major scientific questions. We highlight examples of how the CTR is leading nationally and internationally recognised research.

We also highlight how the CTR continues to lead the way in training in fundamental and cutting edge trophoblast and placental biology research across the basic and clinical science.

I am delighted by the appointment of a new exceptional CTR Next Generation Fellow, a recruitment that was made possible by the generous support of The Loke Foundation. Our PhD studentship this year was supported by matched funding by King's College Cambridge and we are also thrilled by the appointment of an excellent candidate.

This year we prioritised restructuring the CTR to align support functions with strategic



**Professor Kathy Niakan**  
Director of the CTR  
Mary Marshall & Arthur  
Walton Proessor of  
Reproductive Physiology  
Cair of Cambridge Repro-  
duction

and academic priorities of the CTR, allied Departments and School of Biological Sciences. The aim of restructuring was to expand and support collaborations across clinical and basic research and to ensure long term financial sustainability of the CTR. Our new structure will enhance collaborative working and improve the scope and effectiveness of CTR support.



# CTR HIGHLIGHTS NGFs

CTR Next Generation Fellows have continued to excel, transitioning to fully independent positions at internationally recognised universities and research institutes.

Courtney Hanna was recently awarded a prestigious Wellcome and Royal Society Sir Henry Dale Fellowship. Courtney will be based at the CTR laboratory in the Department of Physiology, Development and Neuroscience at the University of Cambridge.

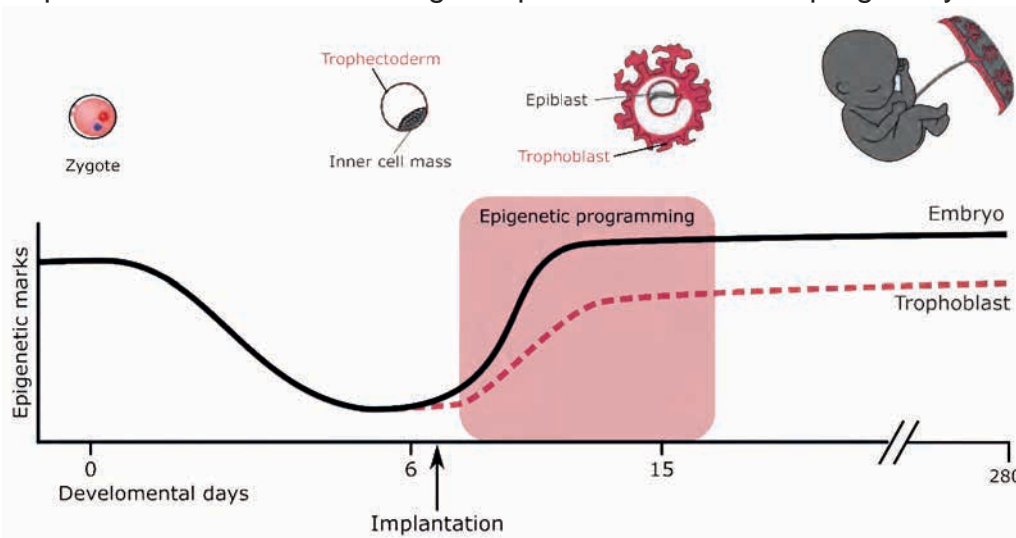
Courtney's research programme will investigate mechanisms of epigenetic programming and gene regulation in early placental trophoblast and reveal how these underpin the development of a functional placenta.

Courtney will be testing the hypothesis that epigenetic programming in placental trophoblast is critical for setting

up the gene regulatory landscapes in placental cell types and directing appropriate differentiation during placentation. Courtney will continue to develop and apply cutting-edge ultra-low input sequencing methodologies to provide novel insights into how errors in epigenetic programming can lead to compromised placental function in pregnancy.



**Dr. Courtney Hanna**  
CTR Next Generation Fellow from 2018 - 2021 where she investigated how DNA methylation is targeted to the placental genome.



**Vicente Perez Garcia was appointed a Group Leader at Centro de Investigación Príncipe Felipe in Spain**



**Dr. Vicente Perez Garcia**  
CTR Next Generation Fellow from 2018 - 2021 where he discovered that placental malformations are highly prevalent in embryonic lethality.

Vicente will decipher the molecular mechanisms of cell invasion shared between the trophoblast and cancer cells. Intriguingly, placental trophoblast cells share some key similarities with carcinomas. These similarities include the ability to invade healthy tissues, the formation of new vessels and the promotion of an immunotolerant environment. Vicente's laboratory will study how do tumour cells repurpose the same genes and mechanisms that are critical for trophoblast invasion?

# CTR HIGHLIGHTS NGFs



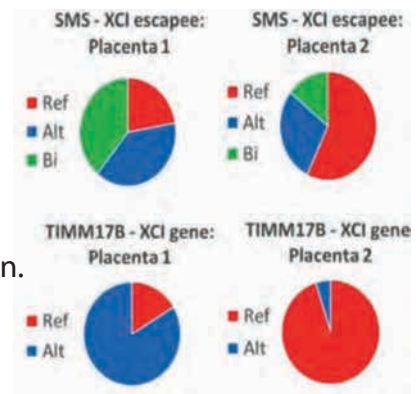
**Dr. Irving Aye**  
CTR Next Generation Fellow from 2018 - 2022 where he investigated fetal sex specific regulation of polyamine metabolism and its role in placental function

Irving Aye was recently awarded a prestigious Medical Research Council Career Development Fellowship and will be a CTR-affiliated Group Leader based in the Department of Obstetrics and Gynecology at the University of Cambridge.

Irving's research programme will establish the mechanisms by which acetyl-coA metabolism regulates trophoblast differentiation in normal and preeclamptic pregnancies.

Irving will be testing the hypothesis that acetyl-coA synthesis enzyme ACLY regulates the fate of cytotrophoblast cells in humans and mice. Irving will testing the effects of ACLY-silencing on histone acetylation in regulatory regions of stemness

genes during differentiation. He will also determine the role of cellular stress and preeclampsia in regulating ACLY activity, acetyl-coA metabolism, histone acetylation and trophoblast differentiation.



Aye et al., *Communications Biology* 2022

**Nick Burton was appointed an Assistant Professor in the Department of Epigenetics at the Van Andel Institute in the USA.**

Nick will investigate environmental impact on health and epigenetics to understand the mechanisms that mediate intergenerational effects and how deleterious consequences can be prevented.



**Dr. Nick Burton**  
CTR Next Generation Fellow from 2016 - 2021 where he investigated how environmental bacteria can affect development, physiology, metabolism and neuronal function of individuals and their offspring

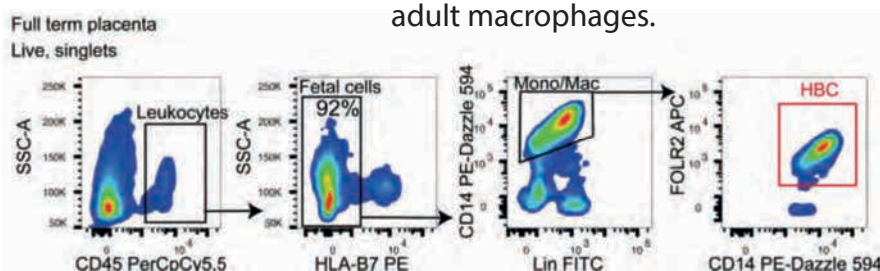


**Dr. Naomi McGovern**

**Naomi McGovern was awarded a competitive 3 year extension of a Wellcome and Royal Society Sir Henry Dale Fellowship in the Department of Pathology at the University of Cambridge.**

Naomi's laboratory has demonstrated that first trimester placental macrophages, Hofbauer cells (HBC), have unique phenotypic and functional properties, in comparison with adult macrophages.

Naomi will now test the hypothesis that the ontogeny and function of HBC changes from first trimester to full term. Understanding the origin of HBCs, their heterogeneity, and changing function are all important for understanding how HBCs assist in placental biology in both health and disease. Naomi will determine if changes observed in HBC from first trimester to full term lead to increased susceptibility to bacterial infection.



Appios et al., *Bio Protocols* 2021

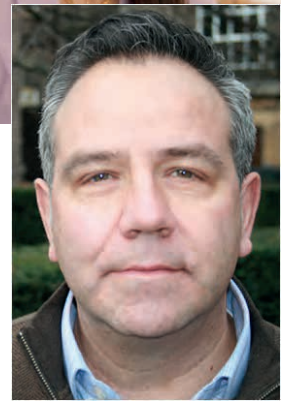


# CTR HIGHLIGHTS PIs

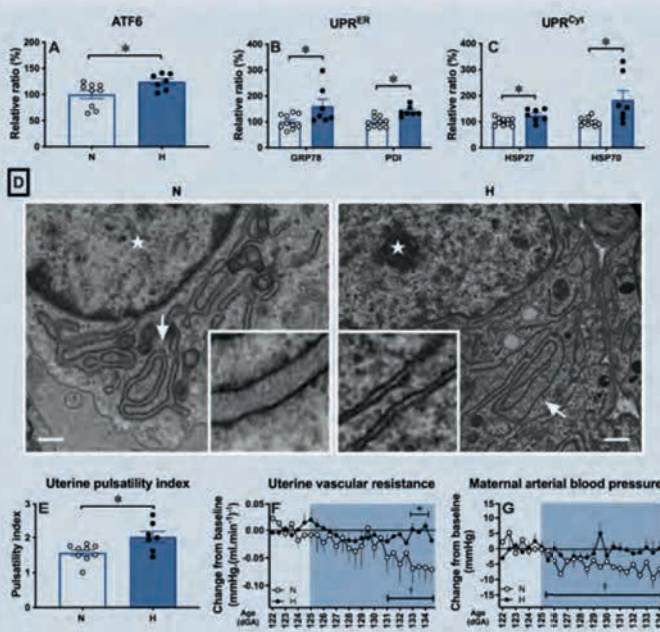
Dr Wen Tong, a CTR-sponsored PhD student in Professor Dino Giussani's laboratory, was successfully awarded a University of Cambridge PhD in 2021. The title of Wen's thesis is: Preeclampsia Links to Gestational Hypoxoxia.

Wen and Dino, along with CTR colleagues based in Graham Burton's lab, showed that chronic hypoxoxia in ovine pregnancies recapitulates physiological and molecular markers of placental diseases.

Their publication described the role of pregnancy complicated by chronic hypoxoxia in preeclampsia and fetal growth restriction, opening avenues for novel predictive biomarker discovery to prevent still birth.



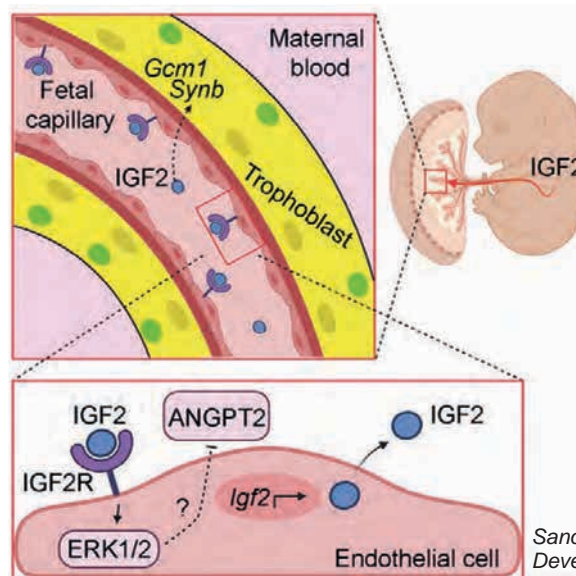
**Dr. Wen Tong**  
CTR PhD student from 2018 - 2021 was trained in the laboratory of Professor Dino Giussani.



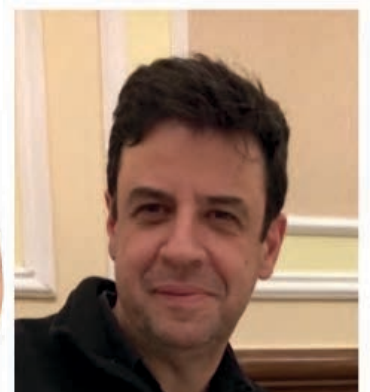
Tong et al., *Hypertension* 2022

A highly collaborative project lead by Professor Miguel Constância demonstrated the importance of a genomic imprinting axis in matching placental microvasculature expansion to cell growth in pregnancy.

Miguel brought together the laboratories of Professors Abby Fowden, Graham Burton, Amanda Sferruzzi-Perri and, former CTR Next Generation Fellow alumni, Miguel Branco to address the question of how the placenta adapts and responds to fetal signals. The groups discovered that fetal and endothelial-derived insulin growth factor is required for the growth and appropriate development of the fetal-placental microvasculature in pregnancy.



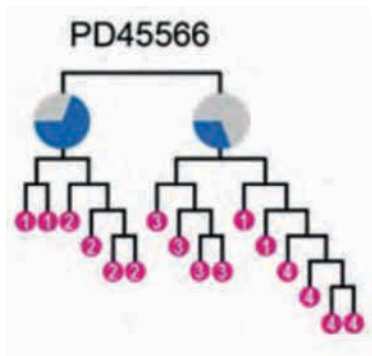
Sandovici et al., *Developmental Cell* 2021



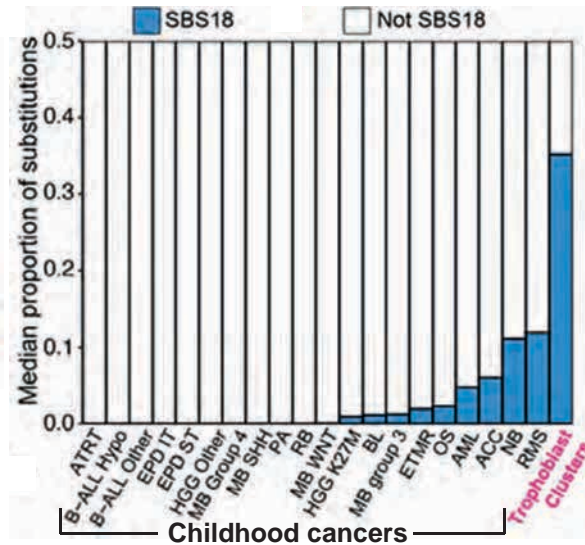
**Professor Miguel Constância**

# CTR HIGHLIGHTS PIs

Professors Gordon Smith and Steve Charnock-Jones, together with colleague at the Sanger Institute, discovered that human placental cells exhibit a mutational landscape that is remarkably similar to childhood cancer.



Coorens et al., Nature 2021



Professors Steve Charnock-Jones and Gordon Smith

The groups performed detailed whole genome sequencing of placental biopsies and, by using phylogenetic analysis, the team were able to retrace the evolution of cell lineages. They found evidence indicating that the placenta tolerates major genetic changes. Intriguingly, each placental biopsy was a distinct

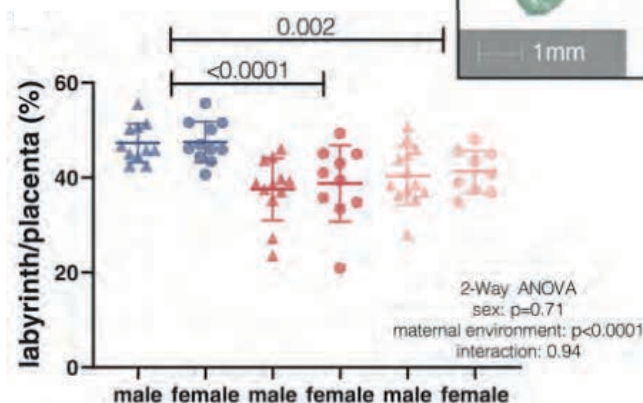
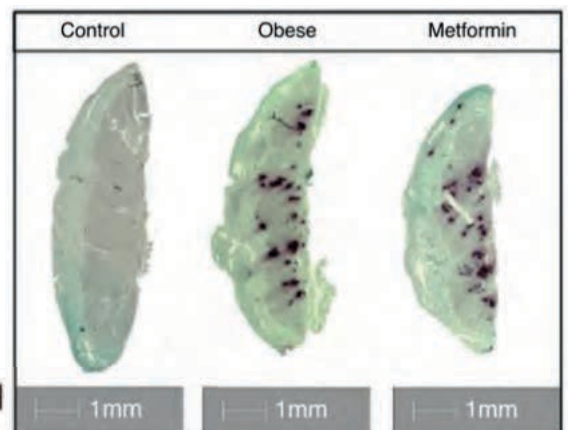
clonal expansion of cells that descended from a common ancestor. This is a feature of human placental cells that is shared with cancer cells. The mutational patterns observed in human placental cells were especially reminiscent of childhood cancers such as neuroblastoma. The findings highlight the importance

of studying how genetic mutation in not only fetal, but also placental cells, impacts on birth outcomes in order to better understand pregnancy complications such as preeclampsia or the causes or stillbirth.

Professor Susan Ozanne, together with CTR colleague Dr. Catherine Aiken, showed that metformin treatment improves maternal, but not fetal or placental, health.

The impact of metformin, a medication commonly used to treat gestational diabetes, during pregnancy remains incompletely understood. In a mouse models of diet-induced (high fat and sugar) maternal obesity, Sue's laboratory demonstrated that metformin treatment has a significant maternal benefit. However, fetuses are significantly smaller and the placental is calcified and complexity is reduced.

This work highlights the importance of further studies on the risks and benefits of interventions during pregnancy and the impact of obstetric medical treatments.



Hufnagel et al., The Journal of Physiology 2021

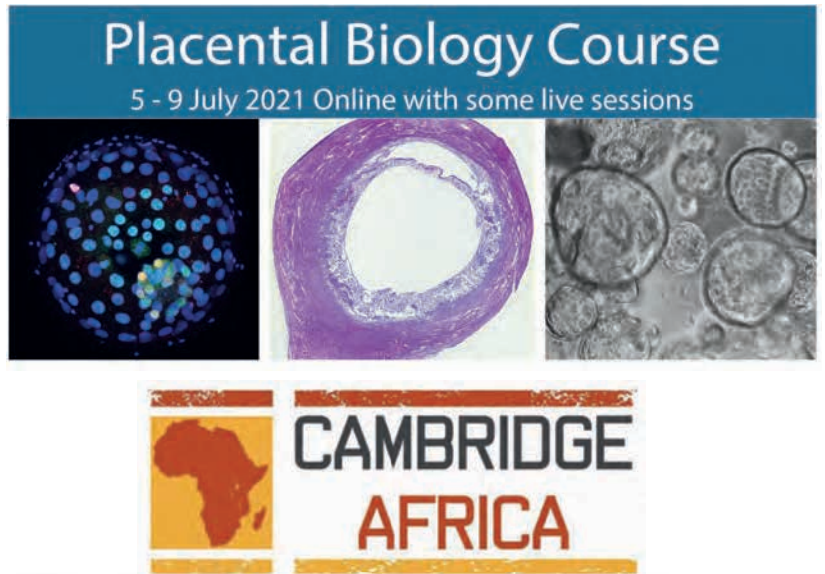


Professor Susan Ozanne



# CTR OUTREACH & POLICY IMPACT

The CTR Placental Biology Course is historically highly oversubscribed. Travel restrictions in early 2021 forced us to rethink how to provide the content of the course and we quickly adapted to providing online virtual teaching. Despite the challenges, one of the major advantages was that we were able to reach broader and more diverse group of attendees. The CTR course had 226 attendees from countries around the world including: Brazil, Canada, Sudan, USA, Uganda, UK, Germany, Australia, Germany, Mexico, China, India, Argentina, Philippines, Israel, Turkey, Iran, Spain, Pakistan, Poland, Ghana and more! In partnership with Cambridge Africa we offered bursaries to international students, researchers and healthcare professionals to take part in the course. The feedback was so positive that we ran a similar virtual course in 2022 and are exploring hybrid options in the future.



**Dr Dorotheah Obiri, Research Fellow, Department of Immunology at the Noguchi Memorial Institute for Medical Research at the University of Ghana.**

My interest in placental research stems from a poor pregnancy experience which made me realise that this poor pregnancy experience was not just unique to me but with most pregnant women in sub-Saharan Africa. I began to explore possible biological reasons for this occurrence which led to my recent transition into placental immunobiology research. It was therefore an exciting opportunity to participate in the CTR placental biology course with full sponsorship from the Cambridge Africa Programme. The course was extremely insightful and a very satisfying hub to my curiosity in placentology. Today, I have **in-depth understanding** and practical knowledge of human placental development and the immunological interplay during normal and complicated pregnancies. In addition, the course structure prompted **new ideas** for my future research and I am hopeful this will open **new avenues for collaborations**. I highly recommend this

educative course to anyone with interest in placental research.



INTERNATIONAL SOCIETY  
FOR STEM CELL RESEARCH

As a consequence of CTR research groups expertise, we have helped to lead on discussions and provide expert advice that impacts on policy, governance and public opinion. For example, Kathy Niakan was a member of the International Society for Stem Cell Research (ISSCR) Guidelines Working Group that developed revised international guidelines on the use of stem cells and human embryos in research and clinical applications (May 2021).

These changes led to an international impact on research policy and governance because most countries use the ISSCR guidelines to guide their Research Ethics Committees. The revised ISSCR guidelines were followed by a call in December 2021 from the UK's HFEA to revisit their regulations on use of embryos in research and clinical settings.

A number of CTR groups are feeding into policy and regulatory discussions on the use of stem cell integrated models of human embryos that use placental and yolk sac cells, the extension of the limit of human embryos in culture and *in vitro* derived gametes (egg and sperm cells).



# CTR GRANTS AWARDED

Value of grants awarded in 2021 - 2022:  
**£20,820,350**



Investigator Award: Kathy Niakan  
**Genetic approaches to studying early lineage specification in human embryos**

Sir Henry Dale Fellowship: Courtney Hanna  
**Placental epigenetic programming: elucidating a role in cellular identity and transcriptional plasticity**

Wellcome Supplement Support: Gordon Smith and Steve Charnock-Jones  
**POPS2 randomised controlled trial**

Sir Henry Dale Fellowship Renewal: Naomi McGovern  
**Characterisation of the human extra-embryonic macrophage population, Hofbauer cells, phenotype and function**



Project Grant: Dino Giussani  
**Maternal obesity during pregnancy: Translatable programmed cardiovascular dysfunction in offspring**

Project Grant: Erica Watson  
**Investigating the multigenerational link between sperm RNA content and birth defects caused by abnormal folate metabolism**

Project Grant: Gordon Smith & Steve Charnock-Jones  
**Pre-labour invasion of the human uterus by Streptococcus agalactiae**

Project Grant: Wolf Reik  
**Generation of an in vivo senescent cell atlas: Across the life-course and in pathology**

Career Development Fellowship: Irving Aye  
**Metabolic determinants of early placental development: Acetyl-coA metabolism and histone acetylation during trophoblast differentiation**

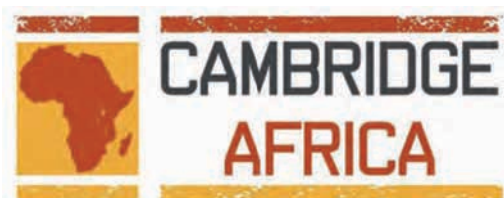


Starting Grant: Marta Shahbazi  
**Impact of tissue morphology on pluripotent stem cell identity and fate**

Advanced Grant: Wolf Reik  
**Epigenetic regulation of cell fate during early mammalian development**



Project Grant: Sue Ozanne  
**Does metformin in obese pregnancy programme long-term cardiac and metabolic dysfunction in adult offspring?**



ALBORADA Research Fund: Irving Aye  
**Biomarkers of placental dysfunction to predict preeclampsia in women with sickle cell trait and sickle cell disease**

# CTR AWARDS



Emeritus Professor Graham Burton was elected as a Fellow of the Royal Society (2022) for identifying that the human placenta initially develops in a protective low-oxygen environment supported by the secretory lining of the uterus. Graham was also celebrated for showing how aberrations in establishing the placenta lead to later complications of pregnancy, ranging from miscarriage to preeclampsia.



Professor Susan Ozanne was awarded an Academy of Medical Research (2022) for her outstanding contributions to biomedical and health science and the generation of new knowledge to improve the health of people.



Professor Anne Ferguson-Smith was appointed Pro-Vice-Chancellor for Research at the University of Cambridge in 2021. Anne was awarded the Society for Reproduction and Fertility Distinguished Scientist Anne McLaren Award (2021) and the Buchanan Medal (2021) for her pioneering work in epigenetics, her interdisciplinary work on genomic imprinting, and for her contributions to understanding how genetic and environmental influences affect development and human diseases.



Professor Magdalena Zernicka-Goetz was awarded the NOMIS Distinguished Scientist and Scholar Award (2022) and the Society for Developmental Biology Edwin G. Conklin Medal (2022) in recognition for her innovative and groundbreaking research and her outstanding contributions to developmental biology and excellent mentorship.



Professor Amanda Sferruzzi-Perri was awarded the Rolly Simpson Frontiers in Reproduction Distinguished Alumni Award (2022) for her outstanding research achievements and was promoted to Professor in the Department of Physiology, Development and Neuroscience at the University of Cambridge.



Professor Azim Surani was awarded the Mendel Medal (2022) by the Genetics Society for his outstanding contributions to science including the discovery of genomic imprinting and the genetic basis for mammalian germ cell specification in mice and humans.



# CTR NEW PARTNERSHIPS & APPOINTMENTS



In partnership with King's College Cambridge, who provided £58,000 in matched funding, we appointed PhD student Andreea Cristian who will be working in the laboratories of Professor Sue Ozanne and Dr. Catherine Aiken.



Andreea Cristian

The title of Andreea's project is:  
**Understanding mechanisms underlying the impact of metformin on placental, fetal and maternal health**

## THE LOKE FOUNDATION

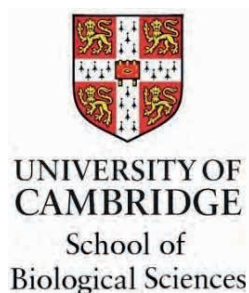


Dr. Priscilla Day

Through the generous support of £210,000 from The Loke Foundation the CTR was able to appoint Dr. Priscilla Day as a 2022 CTR Next Generation Fellow.

Priscilla will be mentored by Professor Steve Charnock-Jones.

The title of Priscilla's project is:  
**Mechanistic understanding of the role of maternal gut microbiota derived metabolites on placental function in relation to pregnancy complications**



By leveraging £282,000 from a Wellcome Investigator Award (Niakan lab) and £179,000 CTR-funded technician support we were awarded matched funding of £172,000 from the School of Biological Sciences and £120,000 from the Department of Physiology, Development and Neuroscience to establish a CTR placental, endometrial and human embryo shared facility. The shared facility will support basic and clinical scientists to gain access to and training in placental, endometrial and human embryo culture and organoid culture.

Space is currently being refurbished in the Physiology Building to establish this unique facility to foster collaborations across the CTR and Cambridge.

## Catherine Aiken

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## Irving Aye

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## Thorsten Boroviak

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## Steve Charnock-Jones

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