BIOGRAPHICAL SKETCH

NAME: Jones, Helen Nichola

eRA COMMONS USER NAME (credential, e.g., agency login): HNJONES

POSITION TITLE: Associate Professor

EDUCATION/TRAINING

INSTITUTION AND LOCATION	DEGREE	Completion Date MM/YYYY	FIELD OF STUDY
University of St. Andrews, St. Andrews, U.K	B.Sc.	07/2000	Biochemistry
University of Aberdeen, Aberdeen, U.K	Ph.D.	07/2005	Physiology
University of Cincinnati, Cincinnati, U.S.A		07/2006-06/2009	Postdoctoral training placental function in maternal obesity

A. Personal Statement

My primary research interests lie in the involvement of the maternal-fetal interface in pathological pregnancies and congenital diseases, such as fetal growth restriction, preterm birth, AIP and congenital heart disease. The goal of this proposed research application is to develop a safe, targeted and efficient placental gene delivery mechanism, identify uptake mechanisms involved in the human placental syncytiotrophoblast and assess the impact of in utero therapy in animal models of genetically- or dietary-induced fetal growth restriction. I have the expertise, experience and resources to undertake this study to move the use of placental therapy closer to the clinic. My laboratory has experience in both mouse and human placental studies and analyzing and interpreting altered placental structure in pathological pregnancies. I am a Principle Investigator with expertise in regulation of placental structure and function during pathological pregnancy and the development of an in utero targeted therapy that could be used during pregnancy. I have established collaborations with experts in both polymer chemistry and pharmacology that will consult on the proposed study.

1 **Jones H,** Crombleholme T, Habli M. Regulation of amino acid transporters by adenoviral-mediated human insulin-like growth factor-1 in a mouse model of placental insufficiency in vivo and the human trophoblast line BeWo in vitro. Placenta. 2014 35(2):132-8. PMCID: PMC3951792

2 Noura Abd Ellah, Wes Troja, Chuck Klanke, Giovanni Pauletti, Neil Ayres, **Helen Jones.** (2015) Non-viral Trophoblast-specific gene delivery in a model of Human Trophoblast. PLOSOne 10(10):e0140879.

3 Pavlicev M, Wagner G, Chavan AR, Owens K, Maziarz J, Dunn-Fletcher C, Kallapur SG, Muglia L, **Jones H** (2017). Single-cell transcriptomics of the human placenta; inferring the cell communication network of the maternal-fetal interface. Genome Research 27(3):349-361. PMC5340963

4 Rebecca L. Wilson, Kathryn Owens, Emily K. Sumser, Matthew V. Fry, Kendal K. Stephens, Natalia Schlabritz-Lutsevich, **Helen N. Jones.** (2020) Nanoparticle mediated delivery of insulin like growth factor 1 gene enhances expression and human placenta syncytium function. Placenta 93:1-7.

B. Positions and Honors

Positions and Employment

July 2000-Dec2001 Graduate Research Assistant, Protein Purification, Bayer, Stoke Poges, UK

Aug 2005-May 2006	Research Scientist, Maternal-Fetal Physiology, Rowett Research Institute, Aberdeen, UK
July 2006-June 2009	Post-doctoral Fellow, Obstetrics and Gynecology, University of Cincinnati.
Sep 2009- Dec 2010	Research Associate, Center for Molecular Fetal Therapy, Cincinnati Children's Hospital Medical Center
Dec 2010 – Nov 2013	Res. Assistant Professor, Center for Molecular Fetal Therapy, Fetal Care Center Cincinnati Children's Hospital Medical Center Department of Surgery, College of Medicine University of Cincinnati
Nov 2013 - Aug 2019	Assistant Professor Department of Surgery, College of Medicine University of Cincinnati Divisions of Pediatric and General Thoracic Surgery and Reproductive Sciences, Cincinnati Children's Hospital Medical Center
Mar 2018- June 2020	Head of Research, Center for Fetal and Placental Research Divisions of General Pediatric and Thoracic Surgery & Reproductive Sciences Cincinnati Children's Hospital Medical Center
Sep 2019 – June 2020	Associate Professor Department of Surgery, College of Medicine University of Cincinnati
July 2020 – present	Associate Professor Department of Physiology and Functional Genomics University of Florida

Honors

Physiological Society Affiliate member travel grant	2004
Society for Reproduction and Fertility travel grant	2004
IFPA Y W (Charlie) Loke Young Investigator Awards	2003-2006
Royal Society Partnership, Researcher in Residence Award	2003/2004
European Nutrition Leadership Programme Awardee (ENLP)	2005
NICHD/IFPA New Investigator Award	2007
NICHD Aspen Perinatal Symposium travel award	2007
Perinatal Research Society New Investigator Award	2008
Perinatal Research Society, Early Career Speaker	2013
Program Director, PAA Satellite Symposium, Society for Gynelogical Investigation	2013-2014
Program Director, PAA Satellite Symposium, Society for Reproductive Investigation	2015-2016
Executive Treasurer, International Federation of Placental Associations	2018-

Professional Societies and Public Advisory Committees

Physiological Society	2002-2006
Society for Reproduction and Fertility	2005-2006
International Federation Placental Associations (IFPA)	2003-present
European Placental Group	2002-2006
Placental Association of the Americas (PAA)	2006-present
Society for Gynelogical Investigation (SGI)	2007-2014
American Physiological Society	2009-present

Chair, IFPA Early Career Researchers Committee	2010-2012
ECR Representative IFPA Executive Board	2010-2012
University of Cincinnati, University Research Council, Grant Review Committee Member,	2012-present
Grant reviewer, Medical Research Council, United Kingdom	2013
NIEHS Special Emphasis Panel/ Scientific Review Group 2014/08 ZES1 RAM-D (LP) 1	2014
Society for Reproductive Investigation (SRI)	2015-present
NICHD Scientific Review Group RFA-HD-15-030/031	2015
CIHR Project Grant Program review committee	2016
NICHD Scientific Review Group RFA-HD-16-036/37	2016
NICHD CHHD-B Obstetric and Maternal-Fetal Biology Subcommittee	2015-present
Grant reviewer Society of Reproductive Investigation	2018-
International Scientific Committee member IFPA	2018-
Grant reviewer, Medical Research Council, United Kingdom	2019-

C. Contributions to Science

1. The aim of this study was to investigate the regulation of nutrient transport in placental models of maternal obesity at both functional and molecular levels. This included the development of a murine model of obesity in pregnancy and investigations into the regulation of placental nutrient transport systems in human primary trophoblast cells. Using functional (in vivo radioisotope uptake studies) and molecular studies in the mouse model, we demonstrated an increase of amino acid and glucose transport in the placenta of offspring whose mother was fed a high fat diet and the transport mechanisms responsible for this pathway. Altered adipokine levels in maternal obesity are well known but their effects on placental nutrient transport are not and that was the focus of my studies in the primary human trophoblasts. Our data utilizing siRNA in primary human trophoblasts indicated the altered levels of adipokines in the obese mother would increase placental amino acid transport and likely contribute to the overgrowth of the fetus.

a. **Jones HN,** Woollett LA, Barbour N, Prasad PD, Powell TL, Jansson T. 2009 High-fat diet before and during pregnancy causes marked up-regulation of placental nutrient transport and fetal overgrowth in C57/BL6 mice. FASEB J. 23(1):271-8. PMCID: PMC2626621

b. **Jones HN**, Powell TL, Jansson T. 2009 IL-6 stimulates System A amino acid transporter activity in trophoblast cells through STAT3 and increased expression of SNAT2. Am J Physiol Cell Physiol. 297(5):C1228-35. PMID:19741197

c. **Jones HN**, Powell TL, Jansson T. 2010 Full-length adiponectin attenuates insulin signaling and inhibits insulin-stimulated amino acid transport in human primary trophoblast cells. Diabetes 59(5):1161-70. PMCID: PMC2857896

d. Jansson N, Rosario F, Gacciola F, Lager S, **Jones H**, Roos S, Jansson T, Powell T. Activation of placental mTOR signaling and amino acid transporters in obese women giving birth to large babies (2013) JCEM 98(1):105-13. PMCID: PMC3537112

2. Our group initially developed a surgical model of placental insufficiency which I utilized to investigate the effects of direct intra-placental injection of adenoviral-mediated human IGF-1 on placental function, signaling and fetal growth. Intra-placental delivery was able to maintain normal fetal growth, despite surgical interruption of placental blood supply. For comparison to the human I conducted experiments using into an in vitro trophoblast model and investigated the regulation of nutrient transport mechanisms following Ad-IGF-1 treatments. Since establishing my independent laboratory I have further developed this therapy using a non-viral delivery system, a polymer nanoparticle, which can both successfully and specifically deliver transgenes to both mouse placenta in vivo and human trophoblast in vitro and maintain normal fetal growth in the mouse model of placental insufficiency. Current investigations are underway using a guinea pig model of maternal nutrient restriction to identify treatment in longer gestation and impact on fetal organ development as well as in the Non-Human Primate to establish a safety protocol for the nanoparticle delivery mechanism and assessment of specificity of transgene delivery/expression.

a. **Helen Jones**, Timothy Crombleholme, Mounira Habli. Placental Glucose Transport Mechanisms in IUGR and following Ad-IGF-1 gene therapy. PLoS ONE (2013) 8(9): e74632. PMCID: PMC3760855
b. **Jones H,** Crombleholme T, Habli M. Regulation of amino acid transporters by adenoviral-mediated human insulin-like growth factor-1 in a mouse model of placental insufficiency in vivo and the human trophoblast line BeWo in vitro. Placenta. 2014 35(2):132-8. PMCID: PMC3951792
c. Noura Abd Ellah, Wes Troja, Chuck Klanke, Giovanni Pauletti, Neil Ayres, **Helen Jones.** (2015) Non-viral Trophoblast-specific gene delivery in a model of Human Trophoblast. PLOSOne 10(10):e0140879.
d. Rebecca L. Wilson, Kathryn Owens, Emily K. Sumser, Matthew V. Fry, Kendal K. Stephens, Natalia Schlabritz-Lutsevich, **Helen N. Jones.** (2020) Nanoparticle mediated delivery of insulin like growth factor 1 gene enhances expression and human placenta syncytium function. Placenta 93:1-7.

3. Placental abnormalities in cases of congenital heart disease are unknown and understudied. This project aims to identify potential mechanisms and targets for clinical intervention in the placenta from fetuses with congenital heart disease. Comparison of placentas from a CHD cohort with age-matched controls identified abnormal parenchymal morphology, suggesting immature structure and villous vascular abnormalities. While vascular abnormalities are common amongst subtypes of CHD, impaired fetal growth appears associated with impaired trophoblast development. Utilizing murine models of Hand1 disruption we are elucidating the development in the placenta in early pregnancy that may contribute to both the etiology of CHDs as well as placental remodeling in later pregnancy that may impact fetal development and growth throughout gestation.

a. HN. Jones, SK. Olbrych, KS. Smith, O. Gonzales-Ramos, M. Faust, M. Habli, JF. Cnota, AC. Hinton, WJ. Polzin, LJ. Muglia, RB. Hinton (2015). Hypoplastic left heart syndrome and related fetal growth abnormalities are associated with placental vascular micropathology and leptin dysregulation. Placenta 36(10):1078-86. doi: 10.1016/j.placenta.2015.08.003
b. Courtney JA, Cnota JF, Jones HN. (2018) The Role of Abnormal Placentation in Congenital Heart Disease; Cause, Correlate, or Consequence? Frontiers in Physiology, 9:1045 doi:10.3389/fphys.2018.01045
c. Troja W, Owens K, Courtney J, Brockway H, Hinton R, Hinton A, Cnota J, Jones HN (2018). Placental mechanisms of disrupted fetal growth in congenital heart disease. BioRxiv doi: https://doi.org/10.1101/388074

4. Abnormal placental maturation is associated with several pathologies, including placentas from spontaneous preterm birth. Understanding the alterations in the placenta in spontaneous preterm birth may elucidate potential predictors earlier in pregnancy as well as potential therapeutic targets. Utilizing human placental tissues and animal models we are building an understanding of normal maternal-fetal interface communication and placental maturation, as well as disruptions in spontaneous preterm birth.

a. Pavlicev M, Wagner G, Chavan AR, Owens K, Maziarz J, Dunn-Fletcher C, Kallapur SG, Muglia L, **Jones H** (2017). Single-cell transcriptomics of the human placenta; inferring the cell communication network of the maternal-fetal interface. Genome Research 27(3):349-361. PMC5340963
b. Dunn-Fletcher CE, Muglia LM, Pavlicev M, Wolf G, Sun M-A, Hu Y-C, Huffman E, Tumukuntala S, Thiele K, Mukherjee A, Zoubovsky S, Zhang X, Swaggart KA, Lamm KYB, **Jones HN**, Macfarlan TS, Muglia LJ (2018) Anthropoid primate-specific retroviral element THE1B controls expression of CRH in placenta and alters gestation length. PLOS Biology: 16(9):e2006337 DOI: 10.1371/journal.pbio.2006337
c. Brockway HM, Ackerman WA, Buhimschi IA, Buhimschi CS, Kallapur SG, Muglia LJ, **Jones HN.** (2019) Unique transcriptomic landscapes identified in idiopathic spontaneous and infection related preterm births compared to normal term births. PLoS One. 8;14(11):e0225062. doi: 10.1371/journal.pone.0225062

5. Understanding the underlying mechanisms of regulating trophoblast invasion is critical to developing mechanisms for diagnosis and treatment of Placental Accreta Spectrum. Following a screening protocol for NK phenotypes with ENU mutagenesis, my collaborators identified frequent dystocia when attempting to expand their colony. We went on to demonstrate that the SNP present in the GAB3 protein in uterine NK cells was detrimental for successful pregnancy and characterized the maternal-fetal interface throughout gestation. Throughout pregnancy abnormal trophoblast invasion occurred via both endovascular and interstitial routes, with abnormal spiral artery remodeling in early pregnancy and trophoblast reaching the uterine wall by 18.5 days. Importantly, the risk of carrying this SNP or one of 27 in the same region, which are proposed to be as deleterious to proper GAB3

function, is 1:900 in humans. The phenotype could be rescued by transferring wildtype peripheral NK cells into the maternal circulation during pregnancy.

a. Anna Sliz, Kathryn C. Sullivan, Kristin Lampe, Alzbeta Godarova, David R. Plas, Edith Janssen, Helen Jones, Andrew Herr, Kasper Hoebe (2019) The GRB2-associated binding protein 3 is required for IL-2- and IL-15-induced NK cell expansion and successful pregnancy. Science Immunology, 4(38). pii: eaav3866. doi: 10.1126/sciimmunol.aav3866.

Complete List of Published Work in MyBibliography:

http://www.ncbi.nlm.nih.gov/sites/myncbi/helen.jones.1/bibliography/43240083/public/?sort=date&direction=descending

D. Research Support
Ongoing Research Support

NICHD R01HD09057 Jones (PI) 7/01/2017- 6/30/2022
Placental-specific therapy for fetal growth restriction
The goal of this project is to develop a polymer-based nanoparticle that can be taken up by the human syncytium and result in transgene expression and allow tracking and targeting developments for non-placental injection of the nanoparticle utilizing both animal and ex vivo models.
Role: Principal Investigator

NICHD R01HD091527 Jones (PI) 3/30/2017-2/28/2022
Harnessing "omics": A Systems Biology approach to discovery of biological pathways in placental development and parturition
The major goals of this project are to identify placental pathways involved in the length of gestation and timing of birth in humans using transcriptomics, metabolomics and genomics.
Role: Co-Investigator

NIAID R21AI135380 Jones (PI) 06/01/2019 – 05/31/2020
The molecular analysis of Gab3 in NK cell function
The goal of this project is to determine the mechanism of GAB3 function in NK cells and investigate its role in over-invasive placentation
Role: Principal Investigator

Completed Research Support

NICHD K99/R00 HD068504 Jones (PI) 4/1/12-3/31/17
Gene Therapy for the Correction of Placental Insufficiency
The goal of this project was to investigate the effects of nanoparticle-mediated gene therapy on the placenta using human cell culture and also murine models of altered fetal growth as well as investigation into the downstream signaling pathways regulated following IGF-1 gene therapy. Role: PI

NIH/NICHD R21HD087536 Woollett (PI) 07/01/16-06/30/18
PRE-CONCEPTION OBESITY PROGRAMS PLACENTAL INFLAMMATION AND FUNCTION
Determine if pre-conception obesity programs placental inflammation and function and determine the role of post-conception maternal obesity on placental inflammation and function. Once again using embryo transfer technology, we will determine if pre-conception oocyte environment programs how placentas are affected by post- conception environment. We will examine inflammation and function in placentas derived from embryos of lean or obese females and transferred into MIO surrogate mothers. Role: Collaborator