

**Maternal and Fetal Health Research Centre**

**St Mary's Hospital  
University of Manchester**

**Research Performance Indicator Report  
Financial Year 01/04/2006 – 31/03/2007**

**Submitted June 2007**

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**Performance Indicator I1:  
Total grant income.**

1. Itemised grant income from Tommy's and all other sources spent in the year.

Funding Body	Project Title	Total Award (£)	Spend in Financial Year (£)
<b>Tommy's</b>			
	Core budget (incorporating contributions to MAPS study)	362,624.00	358,478.22
National Lottery Charities Board (Community Fund)	Teenage pregnancies: Dietary measures to improve nutrition and pregnancy outcome	151,081.00	39,890.39
GLAXO	A physiological approach to induction of labour: PULSE – a randomized controlled trial of pulsatile versus continuous oxytocin administration	41,580.00	7931.70
<b>Total spend:</b>			<b>406,300.31</b>

Funding Body	Project Title	Total Award (£)	Spend in Financial Year (£)
<b>Research Councils / Government funding</b>			
BBSRC	Dissecting IGF regulation of cell turnover in an integrated cellular system: The human placenta as a model	469,749.00	20,815.62
	Metabolic screening for pregnancy complications	59,623.00	14,905.00
	The role of trophoblast in determining differentiation of stem cells in the human placenta	38,000.00	6330.00
MRC	Mechanisms of homocysteine transport by human placenta: relationship to birthweight and placental vascular distensibility	240,937.00	31,892.07
	Direct effects of cortisol on placental nutrient transfer – implications for IUGR, maternal stress and antenatal administration	171,454.00	11,865.63
	Estrogen / IGF cell signalling in blood vessels of the human maternal / fetal interface	25,000.00	4164.00
	Trophoblast-leukocyte interactions involved in the remodelling of decidual arteries	25,000.00	4164.00
Department of Health	An investigation of pre-eclamptic pathogenesis using a placental perfusion model	228,000.00	41,329.38
	Pharmacogenetics of placental ABC transporters: fetal protection from xenobiotics	238,810.00	7,594.99
	Development of a metabolome screening test for pre-eclampsia	40,087.00	NIL
<b>Total spend:</b>			<b>143,060.69</b>

Funding Body	Project Title	Total Award (£)	Spend in Financial Year (£)
<b>Other charities / Trusts</b>			
Wellcome Trust	An investigation of amino acid transporter activity and expression in blood cells in late gestation and intrauterine growth restriction	183,986.00	66,022.88
	The mechanism of maternal artery smooth muscle cell remodelling by trophoblast cells during pregnancy	423,057.00	36,240.70
	A study of upstream and downstream partners of the RhoA/Rho kinase signalling pathway in human myometrium	138,476.00	51,633.60
	Mechanisms and control of maternofetal calcium exchange in normal and intrauterine growth restricted mouse pregnancy	282,365.00	87,753.63
	Function and regulation of the SNAT4 isoform of the System A amino acid transporter in the human and mouse placenta	226,259.00	69,334.72
	Investigating the role of caveolae in vascular tone regulation by use of gene-specific knockout mice	14,837.00	13,626.29
Action Medical Research	Reactive oxygen species regulation of human myometrial K channels	79,125.00	22,363.04
	Nutrient portioning during pregnancy: the role of the placenta	104,008.00	5,199.85
British Heart Foundation	IGFs and survival signalling in the placenta: towards an in-utero therapy for pre-eclampsia	76,190.00	25,512.90
	Rational metabolome datamining for robust biomarkers of diagnostic and prognostic value in pre-eclampsia	164,333.00	29,732.01
	Extravascular pressure as a modulator of human resistance artery tone; modulation in normal and compromised pregnancy	77,228.00	42,882.07
	The fetoplacental circulation in normal pregnancy and intrauterine growth restriction: a role for hypoxia-induced vasoconstriction	132,682.00	28,592.73
	Interactions between estrogen, endothelial nitric oxide and caveolin-1 and effects on resistance arteries	78,153.00	13,672.55
Diabetes UK	Placental regulation of insulin-like growth factor bioavailability and fetal growth in type 1 diabetic pregnancy	145,840.00	1909.76
Castang Foundation	Placental cell turnover: time to translate knowledge to therapy	73,983.00	7,981.51
Royal Society	Nutrient portioning during pregnancy: the role of the placenta	13,925.00	11,332.08
SPARKS	The characterisation of placentally derived pathogenic factor(s) in pre-eclampsia	108,609.00	36,397.15
<b>Total spend:</b>			<b>550,187.47</b>

Funding Body	Project Title	Total Award (£)	Spend in Financial Year (£)
<b>Industrial</b>			
Novo Nordisk UK Research Foundation	Endothelium-dependent vascular behaviour in pregnancies complicated by diabetes	131,203.00	26,520.38
Pfizer	The role of phosphodiesterase inhibitors in the treatment of pre-eclampsia	105,413.00	25,304.71
Ardana Biosciences	Lysophospholipids and pregnancy: regulation of uterine and vascular contractility by LPA and sphingosine-1-phosphate	143,215.00	30,337.49
	Studies of sulphate at the maternal-fetal interface	30,000.00	11,983.95
University of Manchester Intellectual Property Limited	Screening for pregnancy complications	53,000.00	4783.40
<b>Total spend:</b>			<b>98,929.93</b>

Funding Body	Project Title	Total Award (£)	Spend in Financial Year (£)
<b>University of Manchester / CMMC NHS Trust</b>			
University of Manchester Research Support Fund	Interaction between activin and angiotensin in early pregnancy	15,000.00	3750.00
University of Manchester Stepping Stones Fellowship	The development of a placental perfusion model to investigate the liberation of pathological factors in response to the aberrant placental conditions and haemodynamics of pre-eclampsia	47,000.00	7,981.51
	Role of the angiotensin II type I receptor within the placenta and its interaction with transforming growth factor beta	181,384.00	8,384.58
	Xenobiotic handling by the placenta: the role of mdr and inflammation in fetal brain damage at term	203,062.00	7,594.99
University of Manchester Research Equipment Scheme	Zeiss Axiovert 200M motorized inverted microscope	28,224.00	28,224.00
	Laser capture microscope	87,680.00	87,680.00
Central Manchester & Manchester Children's University NHS Trust	Pharmacogenetics of placental ABC transporters: Fetal protection from xenobiotics	14,950.00	2,716.03
	Impaired placental growth and development in adolescent pregnancies complicated by intrauterine growth restriction: role of glucocorticoids	7,350.00	7,350.00
<b>Total spend:</b>			<b>153,681.11</b>

Funding Body	Project Title	Total Award (£)	Spend in Financial Year (£)
<b>International</b>			
National Institute for Health, USA	Signalling and uterine contractility with human pregnancy	34,240.00	27.30
Canadian Institute of Health Research	Strategic training program in maternal, fetal & newborn health	8,629.00	3,179.21
<b>Total spend:</b>			<b>3,206.51</b>

	Total Award (£)	Spend in Financial Year (£)
<b>Grand Total Including Funding From Tommy's:</b>	<b>5,238,910.00</b>	<b>1,355,366.02</b>
<b>Grand Total Excluding Funding From Tommy's:</b>	<b>4,683,625.00</b>	<b>949,065.71</b>

2. Total and itemised grant income awarded in the year as a direct result of work by Tommy's.

Funding body	Project Title	Total award (£)
BBSRC	The role of trophoblast in determining differentiation of stem cells in the human placenta	38,000.00
MRC	Direct effects of cortisol on placental nutrient transfer – implications for IUGR, maternal stress and antenatal administration	171,454.00
	Estrogen / IGF cell signaling in blood vessels of the human maternal / fetal interface	25,000.00
	Trophoblast-leukocyte interactions involved in the remodeling of decidual arteries	25,000.00
Department of Health	Development of a metabolome screening test for pre-eclampsia	40,087.00
The Wellcome trust	Investigating the role of caveolae in vascular tone regulation by use of gene-specific knockout mice	14,837.00
Action Medical Research	Nutrient portioning during pregnancy: the role of the placenta	104,008.00
British Heart Foundation	Extravascular pressure as a modulator of human resistance artery tone; modulation in normal and compromised pregnancy	77,228.00
Castang Foundation	Placental cell turnover: time to translate knowledge to therapy	73,983.00
The Royal society	Nutrient portioning during pregnancy: the role of the placenta	13,925.00
University of Manchester Intellectual Property Limited	Screening for pregnancy complications	53,000.00
Central Manchester & Manchester Children's University NHS Trust	Impaired placental growth and development in adolescent pregnancies complicated by intrauterine growth restriction: role of glucocorticoids	7,350.00
<b>Grant Total:</b>		<b>643,872.00</b>

**Performance Indicator 12:  
Staff.**

<b>Grand Total:</b>	<b>64</b>
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<b>Principal Investigators</b>	<b>Total</b>	<b>6</b>
Professor John D Aplin, Professor Philip Baker, Dr Rebecca Lee Jones, Dr Michael J Taggart, Professor Colin Sibley, Dr Melissa Westwood.		

<b>Clinical Lecturers</b>	<b>Total</b>	<b>2</b>
Dr Jenny Myers, Dr Clare Tower.		

<b>Research Fellows</b>	<b>Total</b>	<b>8</b>
Dr Diane Atkinson, Dr Helen Bond, Dr Ian Crocker, Dr Jo Glazier, Dr Susan Greenwood, Dr Carolyn Jones, Dr Mark Wareing, Dr Gregor Fyfe (until March 2007).		

<b>Post Doctoral Research Associates</b>	<b>Total</b>	<b>12</b>
Dr Xillian Bai, Dr Richard Blankley, Dr Marie Brown, Dr Michelle Desforges, Dr Mark Dilworth, Dr Karen Forbes, Dr Lynda Harris, Dr Nicola Hudson, Dr Nicola Robinson, Dr Paul Speake, Dr Nita Solanky, Dr Michelle Sweeney (until Nov 2006),.		

<b>Post-Graduate Students</b>		<b>Total</b>	<b>20</b>
Ph.D. Students			
<b>Clinical Research Fellows</b>		<b>Basic Scientists</b>	
Dr Patrice Arthur		Paul Brownbill	
Dr Alex Heazell		Jemma Corcoran	
Dr Justine Nugent		Jayne Fitzimmons	
Dr Chibuikwe Iruloh (until Sept 2006)		Christina Hayward (started January 2007)	
		Elizabeth Hutchinson	
		Ali Khashan	
		Tracey Mills	
		Naseem Sheikh	
		Harmeet Singh	
		Samantha Smith	
		Karen Spencer	
		Joanna Stanley	
		Eleni Tsitsiou	
		Joanna Williams	
Sub Total:	4	Sub Total:	14
MD Students			
Dr Fatima Soydemir , Dr Alexandra Solomon (started March 2007)			
		Sub Total:	2

<b>Master of Research Students</b>	<b>Total</b>	<b>4</b>
Christine Beck, Vicky Cookson, Sally Jewsbury, Sarah Moll.		

<b>Research Midwives (part time)</b>	<b>Total</b>	<b>5</b>
Georgina Bennett, Lorna Carruthers, Jane Guarino, Gemma Wild, Clare Stanley (until August 2006).		

<b>Technical Support</b>	<b>Total</b>	<b>7</b>
Bernadette Baker (part-time), Nicola Charlesworth (part-time), Liz Cowley (part-time), Millie Cretney (part-time), Becky Garside, Maureen O'Hara, Alicia Requena-Jiminez (part-time).		

**Performance Indicator P3:  
Number of applications submitted.**

1. Total number of grants submitted: 42

Decision pending: 9 (21%)

Decision made: 33 (79%)

Awarded: 15 (45%) **£1,472,242**

Rejected: 18 (56%)

**Performance Indicator P4:  
Success rate of grant applications.**

2. Success rate: approximately 1 in 2

**Performance Indicator P5:  
Time spent preparing applications.**

1. Number of man hours spent preparing applications:

Information not collected during 2006-2007 financial year.

2. Number of man hours per successful application:

N/A

**Performance Indicator P6:  
Projects finishing on time.**

1. Number of projects finishing on time and to budget:

11

2. Number of projects finishing late and/or not on budget:

0

**Performance Indicator O7:  
External Audit every two years.**

Next due date – 04<sup>th</sup> December 2007

**Performance Indicator O8:**

**Number of peer reviewed scientific papers, field weighted.**

1. Number of papers produced with high impact factor, medium impact factor and low impact factor;

Impact	Number of Papers
<b>HIGH</b> (Top 25% of Journals in Research Field)	<b>30 (71%)</b>
<b>MEDIUM</b> (Middle 50% of Journals in Research Field)	<b>8 (19%)</b>
<b>LOW</b> (Bottom 25% of Journals in Research Field)	<b>4 (10%)</b>
<b>Total:</b>	<b>42</b>

2. List of papers published and impact factor;

Journal	Impact factor	Publication Details
<b>Research Field: Obstetrics and Gynaecology</b>		
Reproductive Biomedicine Online	3.206	Quenby S, Anim-Somuah M, Kalumbi C, Farquharson R, <b>Aplin JD</b> . Different types of recurrent miscarriage are associated with varying patterns of adhesion molecule expression in endometrium. (2007) 14(2):224-34.
		<b>Aplin JD</b> . Embryo implantation: the molecular mechanism remains elusive. (2006)13(6):833-9.
Placenta	2.969	Mayhew TM, Manwani R, Ohadike C, Wijesekara J, <b>Baker PN</b> . The placenta in pre-eclampsia and intrauterine growth restriction: studies on exchange surface areas, diffusion distances and villous membrane diffusive conductances. (2007) 28(2-3):233-8.
		Lewis RM, <b>Glazier J</b> , <b>Greenwood SL</b> , Bennett EJ, Godfrey KM, Jackson AA, <b>Sibley CP</b> , Cameron IT, Hanson MA. 1-serine uptake by human placental microvillous membrane vesicles. (2007) 28(5-6):445-452.
		<b>Crocker IP</b> , <b>Arthur P</b> , <b>Heazell AE</b> , <b>Baker PN</b> . The mitotic manipulation of cytotrophoblast differentiation in vitro. (2007) 28(5-6): 408-411.
		<b>Atkinson DE</b> , <b>Sibley CP</b> , Fairbairn LJ, <b>Greenwood SL</b> . MDR1 P-gp expression and activity in intact human placental tissue: upregulation by retroviral transduction. (2006) 27(6-7): 707-14.
		<b>Brownbill P</b> , <b>Sibley CP</b> . Regulation of transplacental water transfer: the role of fetoplacental venous tone. (2006) 27(6-7): 560-7.
		<b>Wareing M</b> , <b>Greenwood SL</b> , <b>Fyfe GK</b> , <b>Baker PN</b> , <b>Taggart MJ</b> . Glibenclamide inhibits agonist-induced vasoconstriction of placental chorionic plate arteries. (2006) 27(6-7):660-8.
		<b>Sweeney M</b> , <b>Jones CJ</b> , <b>Greenwood SL</b> , <b>Baker PN</b> , <b>Taggart MJ</b> . Ultrastructural features of smooth muscle and endothelial cells of isolated isobaric human placental and maternal arteries. (2006) 27(6-7):635-47.
		<b>Aplin JD</b> , Straszewski-Chavez SL, Kalionis B, Dunk C, Morrish D, Forbes K, Baczyk D, Rote N, Malassine A, Knofler M. Trophoblast differentiation: progenitor cells, fusion and migration -- a workshop report. (2006) 27 Suppl A:S141-3.

Placenta	2.969	<b>Bond H, Baker B, Boyd RD, Cowley E, Glazier JD, Jones CJ, Sibley CP, Ward BS, Husain SM.</b> Artificial perfusion of the fetal circulation of the in situ mouse placenta: methodology and validation. (2006) 27 Suppl A:S69-75.
		Carter AM, Enders AC <b>Jones CJ</b> , Mess A, Pfarrer C, Pijnenborg R, Soma H. Comparative placentation and animal models: patterns of trophoblast invasion – a workshop report. (2006) 27 Suppl A: S30-3
		<b>Cooper EJ, Wareing M, Greenwood SL, Baker PN.</b> Oxygen tension and normalisation pressure modulate nifedipine-sensitive relaxation of human placental chorionic plate arteries. (2006) 27(4-5):402-10.
		Jansson T, Cetin I, Powell TL, Desoye G, Radaelli T, Ericsson A, <b>Sibley CP.</b> Placental transport and metabolism in fetal overgrowth -- a workshop report. (2006) 27 Suppl A:S109-13. .
		Angiolini E, Fowdon A, Coan P, Sandovici I, Smith P, Dean W, Burton G, Tycko B, Reik W, <b>Sibley CP</b> , Constanca M. Regulation of placental efficiency for nutrient transfer by imprinted genes. (2006) 27 SupplA:S98-102.
American Journal of Obstetrics & Gynecology	2.805	<b>Myers JE</b> , Hart S, Armstrong S, Mires GJ, Beynon R, Gaskell SJ, <b>Baker PN.</b> Evidence for multiple circulating factors in preeclampsia. (2007) 196(3):266.e1-6.
Journal of the Society for Gynecological Investigation	2.379	Settle P, <b>Sibley CP</b> , Doughty IM, Johnston T, <b>Glazier JD</b> , Powell TL, Jansson T, <b>D'Souza SW.</b> Placental lactate transporter activity and expression in intrauterine growth restriction. (2006) Jul; 13(5):357-63.
Ultrasound in Obstetrics & Gynaecology	2.288	Ben Nagi J, Ofili-Yebovi D, Sawyer C, <b>Aplin JD</b> , Jurkovic D. Successful treatment of a recurrent Cesarean section scar ectopic pregnancy by surgical repair of the uterine defect. (2006) 28(06):855-6.
British Journal of Obstetrics & Gynaecology	2.126	<b>Nugent JL, Baker PN.</b> Periodontal disease and adverse pregnancy outcomes. (2006) 113(7):848.
Pediatric & Perinatal Epidemiology	1.833	Clark JM, Hulme E, Devendrakumar V, Turner MA, <b>Baker PN, Sibley CP, D'Souza SW.</b> Effect of maternal asthma on birthweight and neonatal outcome in a British inner-city population. (2007) 21(2):154-62.
European Journal of Obstetrics & Gynecology and Reproductive Biology	1.273	<b>Jewsbury S, Sheikh N, Crocker I, Baker PN, Myers JE.</b> Plasma uric acid levels do not correlate to plasma-evoked changes in endothelial function in women with preeclampsia. (2006).
		<b>Wareing M, Myers JE, O'Hara M</b> , Kenny LC, <b>Taggart MJ</b> , Skillern L, Machin I, <b>Baker PN.</b> Phosphodiesterase-5 inhibitors and omental and placental small artery function in normal pregnancy and pre-eclampsia. (2006)127(1):41-9.
Gynecologic and Obstetric Investigation	0.874	Bischof P, <b>Aplin JD</b> , Bentin-Ley U, Brannstrom M, Casslen B, Castrillo JL, Classen-Linke I, Critchley HO, Devoto L, D'Hooghe T, Horcajadas JA, Groothuis P, Ivell R, Pongrantz I, Mackon NS, Sharkey A, Vicovac L, White JO, Winterhager E, von Wolff M, Simon C, Stavreus-Evers A. Implantation of the Human Embryo: Research Lines and Models. From the Implantation Research Network 'Fruitful'. (2006) 62(4): 206-216.
Hypertension in Pregnancy	0.871	<b>Mills TA, Baker PN, Wareing M.</b> The effect of mode of delivery on placental chorionic plate vascular reactivity. (2007) 26(2):201-10.
Australian & New Zealand Journal of Obstetrics & Gynaecology	0.835	<b>Jones RL</b> , Findlay JK, Salamonsen LA. The role of activins during decidualisation of human endometrium. (2006) 46(3): 254-9.
		Rombauts L, Donodhue J, Cann L, <b>Jones RL</b> , Healy DL. Activin-A secretion is increased in the eutopic endometrium from women with endometriosis. (2006) 46(2): 148-53.

Journal	Impact Factor	Publication Details
Research Field: Reproductive Biology		
Human Reproduction	3.769	Ayling LJ, Whitley GS, <b>Aplin JD</b> , Cartwright JE. Dimethylarginine dimethylaminohydrolase (DDAH) regulates trophoblast invasion and motility through effects on nitric oxide. (2006) 21(10):2530-7.
		<b>Jones CJ</b> , Denton J, Fazleabas AT. Morphological and glycosylation changes associated with the endometrium and ectopic lesions in a baboon model of endometriosis. (2006) 21(12):3068-3080.
Biology of Reproduction	3.498	<b>Wareing M, Greenwood SL, Fyfe GK, Baker PN</b> . Reactivity of human placental chorionic plate vessels from pregnancies complicated by intrauterine growth restriction (IUGR). (2006) 75(4):518-23.
		Hannah NJ, <b>Jones RL</b> , White CA, Salamonsen LA. The chemokines, CX3CL1, CCL14, and CCL4, promote human trophoblast migration at the feto-maternal interface. (2006) 74(5): 896-904.
Reproduction	2.958	<b>Jones RL</b> , Stoikos C, Findlay JK, Salamonsen LA. TGF-beta superfamily expression and actions in the endometrium and placenta. (2006) 132(2): 217-32.
		<b>Jones RL</b> , Kaitu'u-Lino, TJ, Nie G, Sanchez-Partida LG, Findlay JK, Salamonsen LA. Complex expression patterns support potential roles for matrix-derived activins in the establishment of pregnancy in mouse. (2006) 132(5):799-810.

Research Field: Physiology		
American Journal of Physiology – Cell physiology	4.334	<b>Iruloh CG, D'Souza SW, Speake PF, Crocker I</b> , Fergusson W, <b>Baker PN, Sibley CP, Glazier JD</b> . Taurine transporter in fetal T lymphocytes and platelets: differential expression and functional activity. (2007) 292(1):C332-41.
American Journal of Physiology – Regulatory Integrative and Comparative Physiology	3.685	<b>Wareing M, Bai X</b> , Seghier F, Turner CM, <b>Greenwood SL, Baker PN, Taggart MJ, Fyfe GK</b> . Expression and function of potassium channels in the human placental vasculature. (2006) 291(2):R437-
		<b>Roberts VH, Greenwood SL</b> , Elliott AC, <b>Sibley CP, Waters LH</b> . Purinergic receptors in human placenta: evidence for functionally active P2X4, P2X7, P2Y2, and P2Y6. (2006) 290(5): R1374-86.

Research Field: Endocrinology & Metabolism		
Endocrinology	5.2365	<b>Jones RL</b> , Findlay JK, Farnworth PG, Robertson DM, Wallace E, Salamonsen LA. Activin a and inhibin A differentially regulate human uterine matrix metalloproteinases: potential interactions during decidualization and trophoblast invasion. (2006) 147(2):724-32.

Research Field: Cardiac & Cardiovascular Systems		
Circulation Research	9.854	Keogh RJ, <b>Harris LK</b> , Freeman A, <b>Baker PN, Aplin JD</b> , Whitley GS, Cartwright JE. Fetal-derived trophoblast use the apoptotic cytokine tumor necrosis factor-alpha-related apoptosis-inducing ligand to induce smooth muscle cell death. (2007) 100(6):834-41.
Journal of Molecular Cell Cardiology	4.859	Calaghan SC, <b>Taggart MJ</b> . Compartmentalized signalling in cardiomyocyte lipid domains – do structure and function match up? (2006) 41(1): 1-3

Research Field: Pathology		
American Journal of Pathology	5.917	<b>Harris LK</b> , Keogh RJ, <b>Wareing M, Baker PN</b> , Cartwright JE, <b>Aplin JD</b> , Whitley GS. Invasive trophoblasts stimulate vascular smooth muscle cell apoptosis by a fas ligand-dependent mechanism. (2006) 169(5):1863-74.

Journal	Impact Factor	Publication Details
Research Field: Medicine, General & Internal		
European Journal of Clinical Investigation	2.847	Jewsbury S, <b>Baker PN, Wareing M</b> . Relaxation of human placental arteries and veins by ATP-sensitive potassium channel openers. (2007) 37(1):65-72.
Research Field: Cell Biology		
Frontiers in Bioscience	2.771	<b>Arthur P, Taggart MJ</b> , Mitchell BF. Oxytocin and parturition: a role for increased myometrial calcium and calcium sensitization? (2007)12:619-33.
Research Field: Pharmacology & Pharmacy		
Vascular Pharmacology	1.718	<b>Chirayath HH, Wareing M, Taggart MJ, Baker PN</b> . Acute hyperglycemia in uterine arteries from pregnant, but not non-pregnant mice, enhances endothelium-dependent relaxation. (2007)

**Performance Indicator O9:  
Number of patents.**

1. Number of patents granted in the year.

0

2. Number of patents pending.

“Diagnostic marker for pre-eclampsia”

Application number 0701817.9 (filed 31/01/2007)

## Performance Indicator 010:

### Findings that could make a significant contribution to improvements in maternal and fetal health

#### Significant improvements in the prediction of pregnancy problem:

- In pre-eclampsia, a circulating factor(s) is thought to be crucial to the pathogenesis of the disease. **We provided the first demonstration that circulating factor(s) predate clinical manifestations of the disease** - and have demonstrated that this is not merely an epiphenomenon. This has led to the development of antenatal screening strategies.
- **We have established a laboratory model for identifying differences in proteins secreted by placental tissues from normal and pre-eclamptic pregnancies. We have shown preeclamptic secretions have adverse effects on maternal vascular cells** and we are now using modern proteomic techniques to identify and characterise the proteins responsible, which will greatly facilitate clinical screening for at-risk mothers and facilitate the design of effective and targeted therapies.
- We are using metabolomic and proteomic strategies designed to identify proteins/metabolites that accurately predict the onset of major pregnancy complications: pre-eclampsia, preterm labour and fetal growth restriction. **We have identified 15 highly discriminatory biomarkers of established pre-eclampsia and identified metabolites that predict pre-eclampsia in high-risk pregnancies.** Accurate screening is required to enable intervention and prevention. Whilst considerable economic benefit would accrue from streamlined healthcare, accurate risk assessment is also urgently required because of the benefit of recognised interventions. Known therapies could prevent at least a third of cases, if at-risk women could be identified.
- Phospholipids are involved in the maintenance of successful pregnancies, and this role may be altered in problem pregnancies. **Our research has now shown they regulate vascular constrictors in both the uterus and the placenta through different intracellular mechanisms.** This research has two possible clinically relevant endpoints; the development of a diagnostic tool for pregnancy complications, and/or identification of specific molecules which may be targeted by therapies to alleviate/control symptoms of these diseases. This work is also relevant to [treatment of patients](#).
- The human placenta protects the fetus from drugs and toxic substances present in maternal blood by a class of transporter proteins called the ABC transporters. **We have identified sequence variations in the genes for these proteins which result in their reduced expression and function in placental cells.** This work could enable the prediction of adverse outcomes in those patients who need to take medication during pregnancy and it may also allow the development of counselling strategies for those patients for whom medication is unavoidable. This work is also relevant to [management of patients](#).

### Significant improvement in early diagnosis:

- Epidemiological evidence has suggested a connection between the levels of the amino acid homocysteine and pregnancy complications, for example intra-uterine growth restriction. **We have now provided a cellular mechanism for this phenomenon by demonstrating that homocysteine can inhibit the transfer of other amino acids across the placenta.** Homocysteine levels can be lowered by folic acid and B-vitamin supplementation; therefore, measurement and if necessary, manipulation of homocysteine levels during early pregnancy may provide a useful diagnostic tool, and therapeutic strategy, to reduce the incidence of low birthweight and its associated complications. This work is also relevant to **management of patients** and the **treatment of patients**.

### Significant improvement in the management of patients:

- **Current data from the 'About Teenage Eating' study suggests that insufficient weight gain, poor diet and continued smoking during pregnancy are key risk factors for teenagers delivering low birthweight babies.** Better antenatal monitoring of weight gain, together with healthy lifestyle education targeted at teenagers, is a potential and straightforward intervention to improve pregnancy outcome in this vulnerable population. This work is also relevant to **long term health of mother and/or child**.
- The About Teenage Eating project has also **provided an in-depth analysis of the socio-cultural context of teenage pregnancy and of the multiple individual, social and environmental factors shaping food choice and eating patterns among pregnant teenagers.** Understanding these factors offers the basis for making suitable policy recommendations on the provision of services to this vulnerable group of pregnant women in order to improve their own and their baby's immediate and longer term health. This work is also relevant to **long term health of mother and/or child**.
- Glucocorticoids are administered to pregnant women at risk of preterm labour in order to prevent respiratory distress syndrome of premature newborns; however this carries an increased risk of fetal growth restriction in those pregnancies that continue to term. **Our in vitro studies demonstrate that glucocorticoids significantly impair placental growth and alter function of placental vessels, potentially causing abnormal blood flow in the placenta.** Understanding the effects of glucocorticoids on placental function is critical to enable educated assessment of the risk-to-benefit ratio in a clinical setting.
- Diabetes is the most common complication of pregnancy and may have severe consequences for both mother and child. **Our studies have shown that uterine arteries from women whose pregnancies are affected by diabetes show impaired endothelial-dependent relaxation compared to normal pregnant women and we have now developed an animal model of diabetic pregnancy in order to improve our understanding of the ways in which diabetes impacts on pregnancy.** This will allow us to improve the management of diabetes during pregnancy, leading to improvements in the long-term health of both mother and child.

- Laboratory studies of both vascular function and myometrial conductivity have led to clinical trials (for example of oxytocin regimes to augment labour on the delivery ward, and of phosphodiesterase inhibitors in the management of pre-eclampsia) and then to improvements in clinical practice (for example the **maintenance of hydration in labour to ensure adequate contractions**).
- We have undertaken a review of the methods used by UK obstetricians and midwives to count fetal movements. **We have found that practice is chaotic and non-evidence based and that maternal perception of reduced fetal movement is a reliable prediction of perinatal morbidity and mortality.** We now wish to investigate if providing information to educate women about fetal movements and when to present to healthcare services can reduce the incidence of perinatal morbidity and mortality.

#### Significant improvements in the treatment of patients:

- Implantation is the crucial first step in establishing human pregnancy. Inappropriate interactions between the embryo and uterus in these early stages lead to early miscarriage or placental complications later in gestation. **We have established an in vitro model that replicates the early stages of implantation and importantly, have identified a set of molecular makers / drug targets, involved in the attachment of the embryo.** This work paves the way for future therapeutic strategies for optimising early pregnancy events.
- Within the placenta, new blood vessels progressively form, grow and mature into a network that can extract sufficient nutrients from maternal blood to supply the increasing needs of the fetus. Evidence from animal models indicates that incomplete vascularisation leads to problems with fetal development and growth. **We have shown that trophoblast and macrophages are important sources of signals that enable the development of the placental vascular tree** and are now investigating the nature of the signals in order to identify therapeutic targets for intervention in growth restricted pregnancies.
- During pregnancy the blood vessels in the uterus are widened to increase the flow of blood to the baby; if this does not occur, the risks include miscarriage, pre-eclampsia or having a baby born too small or too early. **We have identified the factors, released by the trophoblast cells of the placenta, that allow this process to happen** and are now considering strategies to improve blood vessel widening in pregnancies where this is impaired.
- Surprisingly little is known about how blood flow through placental blood vessels is controlled or why flow is reduced in fetal growth restriction. **We have shown that the hormone estrogen stimulates the relaxation of placental vessels** and are currently investigating the cellular mechanisms involved in regulating and mediating this response in order to ultimately develop innovative approaches for targeting abnormal vascular functions in problem pregnancies. Also, **our preliminary studies have shown that small proteins called potassium channels are key players for normal**

**placental blood vessel responses and that their behaviour is altered in diseased tissue.** Our current studies are aimed at developing novel ways to change potassium channel activity and offer the possibility of rescuing blood vessel function in compromised pregnancies. **We have also demonstrated that oxidative stress, which characterises pre-eclampsia and fetal growth restriction, induces dysfunction in fetoplacental blood vessels.** Current studies aim to characterise the mechanism underlying altered function, thus aiding design of effective antioxidant therapies.

- Blood flow within the placenta is aberrant in pre-eclampsia and this may affect placental function and structure, leading to intrauterine growth restriction and the liberation of cell and tissue components, implicated in the vascular complications of the pre-eclamptic condition. **We are using a placental perfusion system, which replicates abnormal placental blood flow in pre-eclampsia to model this process and have shown that in this work, material liberated from the placenta adversely affects endothelial cells, the target cells for pre-eclamptic induction.** Identifying these liberated components will provide the basis for novel therapeutic options.
- Animal studies have shown that two hormones, insulin-like growth factor (IGF) -I and -II are key regulators of placental and fetal growth in utero. **We have now shown that these hormones also enhance human placental cell proliferation and survival and importantly, have identified the intracellular signalling pathways involved in mediating their actions,** offering the potential for drug targets in therapeutic strategies to correct the altered placental growth and survival that is known to occur in placentas from complicated pregnancies.
- There is strong evidence that the early stages of placental development are abnormal in women with pre-eclampsia; however it is impossible to study these events in vivo. **Using novel in vitro models we have generated compelling evidence to show that placental cells work in concert with maternal white blood cells to remodel and adapt the uterine vessels for pregnancy,** a key event for healthy pregnancy. These experiments provide important new understanding about the early processes involved in the development of pre-eclampsia and are critical for the future development of new clinical treatments. **We have found that in such placentas, there is an imbalance in two of the proteins that are important in determining cell fate. We have also shown that low oxygen and oxidative stress, environments implicated in pre-eclampsia, can induce cell death in vitro and that treatment with a survival factor can reduce these adverse effects.** We are now investigating whether survival factors (such as heparin) and drugs that are already in use for other diseases associated with abnormal cell turnover, can reduce apoptosis in placental tissue with the aim of developing novel therapeutic approaches to reducing the incidence and progression of pre-eclampsia. **We have also found that in pre-eclampsia a protein called TRAIL is overproduced within cells of the placenta.** This factor may be the cause of the placental anomalies observed in this condition and thus we are now defining the importance of this protein in pre-eclampsia and identifying ways of manipulating or blocking its effects, which may give rise to a therapeutic tool.

- Transfer of amino acids from mother to fetus is required for normal fetal growth but the relative importance of the different systems in the placenta and the ways in which they are regulated, remain unclear. **We have shown that reduced system A amino acid transporter activity in the placenta is associated with fetal growth restriction** and we are now focusing on the regulatory mechanisms responsible for this alteration. The project therefore forms an essential step on the path to discovering new diagnostic or therapeutic strategies for this pregnancy complication.
- Transfer of nutrients from mother to fetus occurs across the syncytiotrophoblast layer of the placenta; this cell layer must be constantly renewed and disruption of this process leads to fetal growth restriction. In many tissues, cellular turnover is regulated by K<sup>+</sup> channels **and we have shown that voltage gated K<sup>+</sup> channels participate in trophoblast cell turnover, and some have a lower expression in the placentas of growth restricted compared with normally grown babies.** Our aim is to pursue this family of K<sup>+</sup> channels as potential targets at which to aim therapeutic interventions for treatment of the placenta in fetal growth restriction.
- The activity of amino acid transporters is reduced in placentas from intra-uterine growth restriction pregnancies. **We have shown that amino acid transporter activity is unaltered in fetal T lymphocytes from intra-uterine growth restricted infants, suggesting that fetal cells do not elicit a generalised response to intra-uterine growth restriction, and that the impairment of transporter function is restricted to the placenta.** Understanding how these transport processes are regulated will enable the development of therapeutic strategies to stimulate their activity and consequently, promote fetal growth.
- Pre-term labour occurs when the muscle cells of the uterus are stimulated to contract too soon. **We have identified a molecule within the intracellular signalling pathway mediating muscle contraction that appears to be responsible for uterine quiescence through pregnancy,** thereby offering a potential drug target in the development of an effective treatment for pre-term labour.