Project Summaries for SRF Scholarship Recipients 2017

Academic Scholarship Award Recipients

Name: Professor Jane Morrell
Project title: Physical removal of bacteria as an alternative to antibiotics in boar semen extenders.
Institution: Clinical Sciences, Swedish University of Agricultural Sciences (SLU)

Antibiotics are added to semen extenders used for preparing semen for artificial insemination to counteract bacterial contamination arising during semen collection and processing. Globally there is considerable concern about the development of antibiotic resistance, which can be spread among bacterial species in different hosts, and between animals and human beings. In addition, the bacteria found in semen may be developing resistance to the antibiotics usually added to semen extenders. The purpose of this project is to investigate an alternative to adding antibiotics, namely to separate the spermatozoa from bacteria in seminal plasma by colloid centrifugation. It has been shown previously that a high density colloid can be used to separate boar spermatozoa from bacteria in semen as well as to select functional spermatozoa from the rest of the ejaculate. However, some spermatozoa may be lost during selection, and recontamination of the clean sperm pellet is possible. In the proposed project, the use of a low density colloid will be tested in a modified procedure to see if it can effectively separate spermatozoa from bacteria and without the risk of re-contamination. If successful, the results can be used to develop new procedures and guidelines for semen processing for animal breeding.

Name: Professor Kevin Sinclair
Project title: Sheep as a model species for mitochondrial replacement therapy: Genetic variances between haplotype groups
Institution: School of Biosciences, University of Nottingham

Mitochondrial diseases represent the most common form of inherited metabolic and neurological disorders. Mitochondrial replacement therapy (MRT) by either pronuclear (PNT) or maternal-spindle (MST) transfer was recently licenced for use in the UK by the HFEA as a means of treating women whose oocytes carry a high mutation load. However, there are concerns which relate to issues such as spindle damage and increased risk of aneuploidy, extent of mitochondrial DNA (mtDNA) carryover, preferential amplification of diseased karyoplast-derived mtDNA over host mtDNA, and genetic mismatch of nuclear DNA and mtDNA leading to metabolic complications in offspring. The current proposal seeks to generate pilot data for future RCUK funding that will utilise the sheep as an outbred and precocial animal model of MRT. Specifically, for the current project, we will sequence the mitochondrial genomes of two contrasting breeds of sheep to confirm divergent mitochondrial haplotype groups that we believe will render these animals suitable for study into the genetic effects of MRT on development and metabolic health of offspring. With further funding we would investigate the effects of reciprocal (between breeds) PNT and MST on (i) the extent of mtDNA heteroplasmy in embryonic cells and fetal tissues, (ii) the extent of preferential karyoplast mtDNA-variant proliferation in these cell/tissue types and (iii) neurological and metabolic wellbeing in offspring.

Name: Professor Norah Spears
Project title: Are primordial follicles protected from chemotherapy drug-induced damage in the human ovary?
Institution: University of Edinburgh

With a steady increase in survival rates of many cancers, there is a growing need to improve the quality of life of cancer survivors, reducing the consequences of off-target treatment effects, including on fertility. Fertility problems in female cancer patients are primarily due to a reduced ovarian primordial follicle pool. Much of the research into this area that has used the mouse as a model, including from my laboratory, indicates that chemotherapy drugs may not directly damage primordial follicles, instead specifically targeting growing follicles. This is often termed as ‘burn-out’, with primordial follicle loss due to an increased growth initiation rate, as they leave the resting pool to replace follicles from the growing pool that have undergone atresia due to drug-induced damage. If burn-out occurs, then primordial follicle loss will be a secondary effect of treatment, and, if primordial follicle growth initiation can be blocked, then it might be possible to alleviate follicle loss. This SRF Academic Scholarship will support my sabbatical at the University of Oxford during which time I will investigate the effects of different chemotherapy drugs on primordial follicles in the human ovary, in collaboration with Dr Suzannah Williams.

Name: Dr. Agnieszka Waclawik
Project title: Contribution of prostaglandin F2alpha and prokineticin 1 to embryo-maternal interactions
Institution: Institute of Animal Reproduction and Food Research, Polish Academy of Sciences; Department of Hormonal Action Mechanisms, Olsztyn, Poland

Autocrine and paracrine actions between embryo and uterus play an important role during early pregnancy. Prostaglandins (PGs) are key factors regulating interactions between conceptus and uterus. Recently, we reported that PGF2α which was mainly found as a luteolytic agent, participates in the pregnancy establishment promoting vascular endothelial growth factor synthesis and secretion, as well as increasing the expression of genes involved in embryo-maternal communication in the porcine endometrium. Our latest results indicate that PGF2α acting on conceptus cells alters their transcriptome profile and promotes processes crucial for implantation and differentiation of cells. Moreover, studying another prostaglandin – PGE2, we described universal mechanisms through which PGE2 supports trophoblast adhesion to extracellular matrix proteins both in human and porcine *in vitro* models. After analysis of our results from porcine embryonic transcriptome profile, we decided to study whether PGF2α can also stimulate embryonic function in human trophoblast cells. The aim of planned study will be further exploit and complete unpublished data on effect of PGF2α on human trophoblast cell line. The grant application is intended to retain part of my staff employed in the current project finishing on 19th February 2018. The staff will continue to study interactions between embryo and uterus in the pig, especially on a role of PGF2α and prokineticin 1 (PROK1). The important function of PROK1 has been implicated in processes related with establishment of pregnancy in human. However, it is little known about role of PROK1 expressed in the uterus of farm animals.

Return to Research Award Recipient

Name: Professor Lisa Thurston
Project title: Investigating the role of extracellular vesicles in gamete-oviductal cell communication in the female reproductive tract
Institution: Royal Veterinary College, University of London and University of Sheffield

Beneficial communication between the oviduct and gametes is essential for the successful establishment of fertilisation. It is widely accepted that extracellular vesicles (EVs) are potent vehicles for intercellular communication in a variety of physiological systems, potentially via their transport of microRNAs (miRNAs).

Pilot data from our laboratory have demonstrated that EVs are secreted by oviductal epithelial cells and that these EVs contain miRNAs known to be involved in cell cycle regulation and cell adhesion. More recently, we have obtained data indicating that spermatozoa also secrete EVs that interact with oviductal epithelial cells when in sperm-oviduct co-cultures.

Investigating the role of EV miRNAs in gamete-maternal tract communication will provide important insights into the mechanisms influencing fertilisation by natural conception and assisted reproductive technologies.

This project will also significantly contribute to an exciting collaboration with the Department of Computer Sciences at the University of Sheffield, where we are developing a computational model of the porcine reproductive tract. The secretion of EVs by oviductal epithelial cells and spermatozoa, and the subsequent actions of EV miRNAs, will be included in the computational model as factors influencing the oviductal environment and the predictive success of fertilisation.

Early Career Researcher Award Recipients

Name: Dr Kim Jonas
Project title: Deciphering the role of follicle stimulating hormone glycosylation variants on human ovarian function
Institution: St. George's University, London

The pituitary glycoprotein hormone, follicle stimulating hormone (FSH), is essential for female reproduction. Glycosylation of FSH is imperative for its function; in vivo, two predominant FSH glycosylation variants have identified from pituitary extracts, termed hyperglycosylated FSH (FSH24) and hypoglycosylated FSH (FSH21). *In vitro* analysis has shown FSH21 to have a higher bioactivity than FSH24, with FSH21 displaying a higher binding affinity to FSH receptor, and more potently activating cAMP-dependent pathways. *In vivo*, age-related changes in the ratio of FSH21:FSH24 have been described, with higher FSH21:FSH24 in women of reproductive prime (early 20's) versus low FSH21:FSH24 in menopausal females, suggesting potential functional dichotomy of FSH glycosylation variants. This project aims to determine the effects of FSH21 and FSH24 on FSHR-mediated signalling and steroidogenic output in human granulosa lutein cells. Given the importance of FSH in modulating reproductive function, and its use in assisted reproductive techniques, this study will provide much needed mechanistic insight into how differential glycosylation of FSH regulates human ovarian function.

Name: Dr Sander van den Driesche
Project title: Human masculinization disorders: investigation of mechanistic origins using an animal model
Institution: Centre for Discovery Brain Sciences and Zhejiant / UoE Institute, University of Edinburgh

Formation of a testis and its subsequent production of androgens in early fetal life are prerequisites for masculinisation. Any disruption of these events can have adverse consequences and lead to (common) reproductive disorders that manifest at birth or in adulthood - this has been encapsulated in the testicular dysgenesis syndrome (TDS) hypothesis. To study the mechanistic origins I have used an animal model in which pregnant rats are exposed to high doses of dibutyl phthalate (DBP). This has identified the so-called masculinisation programming window (MPW). Reduced androgen production/action during the MPW results in TDS disorders, but exactly how is unknown.

I have performed a microRNA next generation sequencing experiment using control and DBP exposed testis tissues that were isolated at the end of the MPW or just before birth. The money from this SRF Academic Scholarship will be used to perform the validation experiments of key findings using real-time RT-PCR and in situ hybridisation. Furthermore, detailed bioinformatics analyses will be performed in order to identify interesting microRNA targets to study further.

As study of the role of microRNAs in androgen signalling and masculinisation is largely unexplored, this would continue the foundations for establishing my own research niche, which will be an essential element in the future of my scientific career. The data obtained through this scholarship would generate results that would be expected to provide a solid scientific basis for further studies as part of my tenure track lectureship and it would allow me to obtain pilot data for future research grant applications.

Name: Dr Nick Wheelhouse
Project title: Chlamydia induced progesterone resistance in the endometrium
Institution: School of Applied Sciences, Edinburgh Napier University

Chlamydia trachomatis is the most common sexually-transmitted infection in the world, and is associated with miscarriage, pre-term birth and infertility. However, the understanding of the mechanisms through which infection leads to pregnancy failure is poor. Successful embryo implantation requires the progesterone dependent differentiation of endometrial stromal cells into secretory cells. We recently determined that *Chlamydia* inhibits and prevents the action of progesterone on uterine cells, however we do not yet understand the mechanisms through which this occurs. Using an in vitro system of endometrial decidualisation, this project will determine the pathways underpinning the effects of *Chlamydia* infection on steroid responsiveness of the endometrium.