Project Details	
Project Code	MRC21IIRBa Murrell
Title	Modelling parity-associated immunity against breast cancer
Research Theme	Infection, Immunity & Repair
Summary	Pregnancy imposes a risk of breast cancer in the mother. Paradoxically if a woman has a first full-term pregnancy before the age of 20, she is protected against some types of breast cancer. This PhD will model the impact of pregnancy on the maternal immune system and susceptibility to breast cancer, using 3D-organoids, quantitative imaging, epigenetic/genome editing and bioinformatics approaches
Description	Pregnancy is a period of physiological interactions between the mother and a fetus who only shares half of the maternal genes. Immunological tolerance during pregnancy is important to prevent the mother rejecting the fetus. In addition to immune evasion, fetal and placental growth rely on several mechanisms that are commonly activated during tumorigenesis which can put the mother at risk for developing cancer, particularly breast cancer. Although there is an immediate risk of breast cancer during pregnancy, paradoxically, pregnancy actually protects against breast cancer in the longer term. Indeed, the younger a woman is when she completes her first full term pregnancy, the more she is protected against developing breast cancer in her lifetime. Several epidemiological studies have corroborated these observations, yet very little is known about the mechanisms that underlie the age related protective effect (known as the "parity effect"). The aim of this PhD project is to investigate the molecular mechanisms of parity-associated breast cancer protection. Our hypothesis is that the hormones and cytokines released by the placenta primes the immune system and the developing mammary gland to resist oncogenic transformation. In order to test this hypothesis, we have access to serum from a cohort of 100 women (ages 18 – 40), taken during the 1st, 2nd and 3rd trimester of their first pregnancies, that we will use to determine the cytokine profiles and assess whether there is an age associated variation in cytokine levels. This will be done as part of a JvdE collaboration with UCB Celltech. In addition, we will develop an in vitro state-of-the-art human mammary organoid cell culture system to study the developing human mammary gland in the presence of defined placental conditioned media, containing placental growth factors and cytokines. The organoids will be characterised using quantitative imaging and mechanobiology techniques (optical tweezers) to investigate how the physical and mechanical properties of cells and tissues contribute to mammary gland differentiation and how this is influenced by placental endocrines and cytokines. Further characterisation will include fluorescence activated cell sorting (FACS) analysis and immunohistochemistry to examine MHCII surface markers as well as gene expression profiling (RNAseq) and DNA methylation analysis to identify epigenetic signatures during mammary organoid development. We will also use these models to test whether pregnancy-conditioned mammary organoids are primed to resist tumour formation compared to unprimed controls. The results of this study will be used to assemble mathematical models for mammary gland development, parity associated immunological resistance to tumorigenesis. This is a particularly pertinent project when women are

	tending to delay childbearing and female breast cancer rates have increased: in 1970, the average age of first pregnancy was 21.4 years; in 2013 it was 30.3 years, during this period, the female breast cancer incidence rates (age standardised) have increased by 12%. Thus understanding the mechanisms whereby pregnancy influences breast cancer risk could lead to improved maternal health outcome and lifelong health.
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