Summary public summary

Overweight and obesity, defined as abnormal or excessive fat accumulation are major risk factors for a number of chronic diseases, including diabetes, cardiovascular diseases and cancer. Worldwide obesity has nearly tripled since 1975 and, as reports WHO, most of the world's population live in countries where overweight and obesity kills more people than underweight. With all these risks, obesity leads also problems with infertility, which mainly concerns women.

Fat tissue, termed also adipose tissue, produces hormones and one of them is leptin (LEP), which main role is to regulate fat storage and how many calories we eat and burn. LEP is a pleiotropic hormone, meaning that it impacts different organs in our body, including the reproductive system. The uterus, is one of the reproductive organs which is affected by obesity. The inner layer of the uterus, the endometrium, plays an important role in pregnancy in general and in particular in the early steps of pregnancy, like the implantation (stage of pregnancy at which the embryo adheres to the wall of the uterus), or the placentation (stage in which the organ responsible for the transfers between mother and foetus is developed). Data from assisted reproductive clinics show that ovum donations from women with normal body weight donors and obese recipients present reduced implantation success, and pregnancy and live birth rates, which emphasises the role of the endometrium in obesity-related reproductive impairment. A key event for early pregnancy is the decidualisation, a hormonally mediated process in which endometrial stromal cells (ESCs) proliferate and differentiate into decidual cells. Indeed, in obese female mice, decidualisation process was shown to be impaired. Also, in an *in vitro* study with decidualised human endometrial stromal cells, the expression of markers of decidualisation was decreased. Despite all evidences showing the impact of obesity on female infertility, the underlying molecular mechanisms remain still unclear. Thus**, we hypothesise that leptin signalling is altered in the endometrium of obese mice, with consequences for the regulation of the decidualisation process.** Therefore, we wish to characterise **the regulation of LEP signalling in the uterus of obese mice, as a major mechanism leading to endometrial failure.** Moreover we will **characterise the global gene expression profile, or transcriptome, of endometrial stromal cells from the receptive stage of obese mice.**

The present proposal exploits the synergies between two institutes, the Institute of Animal Reproduction and Food Research (IARFR), Olsztyn, Poland and the Babraham Institute (BI), Cambridge, UK. The access to adequate methodology and animal models for the study of obesity is enabled at IARFR. This permits that the animal protocol, samples collections and methods for characterising LEP signalling will be undertaken in IARFR and transcriptomic analyses will be performed at the BI, which provides the methods and state-of-the-art facilities for deep sequencing technologies. Moreover, the candidate supervisor Dr Antonio Galvao has recently finished a Marie Currie Posdoc Fellowship in BI and has broad knowledge and experience in transcriptomic methods which will provide substantive guidance. Knowledge gained from this study will allow us to understand what kind of changes are brought alongside with obesity progression and that might affect the regulation of decidualisation and implantation. It will help us with finding exact molecular mechanism responsible for endometrial failure such important in early pregnancy establishment.