Project 1: Mechanisms of sex-specific programming of obesity and type 2 diabetes risk by periconceptional exposure to a maternal obesogenic milieu.

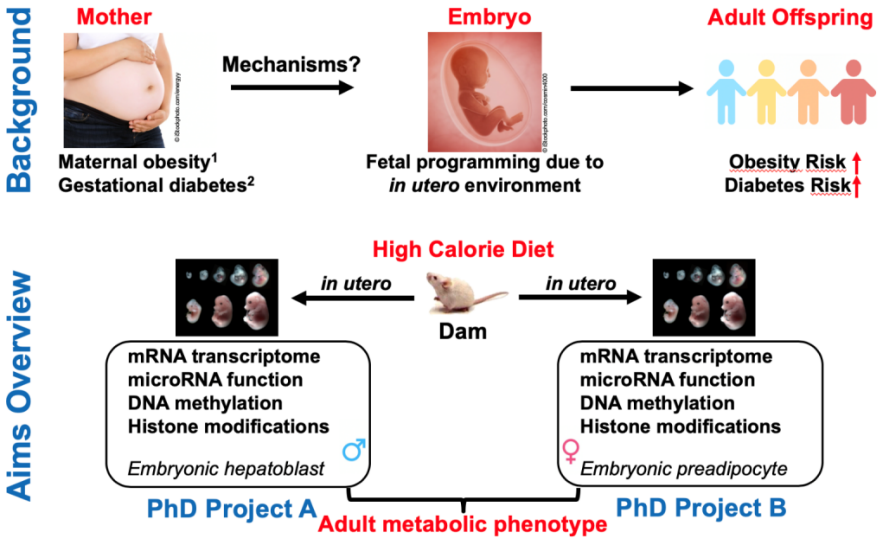
(Supervising Investigators: R. Ensenauer, UKD Pediatrics and B. Belgardt, DDZ)

Background: Maternal obesity continues to increase dramatically in developed countries. Preclinical and clinical data have demonstrated that the offspring born to overweight or obese mothers have an increased risk for metabolic disease such as obesity and type 2 diabetes, which also holds true in animal models. However, the molecular mechanisms linking prenatal obesogenic exposure to the later development of diabetes and obesity in offspring remain poorly defined.

Own previous work: We previously established a mouse model of peri-conceptional maternal diet-induced obesity. We demonstrated that, even in the absence of any postnatal obesogenic influences, adult offspring developed adverse outcomes, i.e. increased body weight, insulin resistance and hepatic steatosis in males and impaired fasting glucose and altered adipose tissue expansion in females, indicating that peri-conceptional obesity induces metabolic disease in offspring in a sex-dependent manner[1]. Moreover, intracellular signaling pathways can be altered by specific bioactive lipids or microRNAs[2]. Nonetheless, it remains unknown how exposure to maternal diet and diet composition *in utero* mechanistically affects development of liver and adipose tissue.

Aim of the project: PhD student A will establish the effects of maternal obesity on the developing fetal liver using a multi-Omics approach, and verify relevance of altered signaling pathways in murine and human hepatoblasts (**PhD Project A**). **PhD student B** will perform parallel studies on the developing adipose tissue, with a key focus on adipocyte precursors (**PhD Project B**).

Work program: Male and female fetal liver alterations will be investigated in our mouse model of maternal obesity, including use of confocal microscopy, transcriptional profiling as well as Mass Spec. lipidomics studies. Regulated pathways will be assessed in mouse and human hepatoblasts by RNA interference and CrispR/Cas9, and development into hepatocytes will be induced. Epigenetic regulation of novel candidate genes will be assayed by e.g. Chromatin immunoprecipitation (ChIP) (**PhD Project A**). To define the molecular alterations leading to sex-specific adipose tissue dysregulation, preadipocyte precursor cells will be purified followed by RNASeq. Upstream regulatory factors will be identified by *in silico* analyses and epigenetic screening. Candidate genes/microRNAs will be assessed using RNAi in murine and human primary preadipocytes, followed by differentiation into adipocytes (**PhD Project B**).



References: [1]Dahlhoff et al., Biochim Biophys Acta. 2014. [2]Belgardt et al., Nat Med. 2015