Human epidemiological and animal experimental studies have convincingly demonstrated a link between nutrition and the optimal reproductive performance. However, proximate causes of the reproductive outcomes are not well known, especially when developmental programming and multi/transgenerational transmission of favourable reproductive traits are considered. Leptin has been proposed as an important candidate for developmental programming, because it displays epigenetic variation and is involved in the development of several metabolic disorders in adults, including obesity and insulin resistance. Leptin deficiency is also known to cause reproductive impairments in males and females, but nothing is known about underlying mechanism of milk-borne leptin involvement in programming of reproductive performance over generations. Recently, we have demonstrated that undernutrition leads to a sex-specific molecular programming of hypothalamus of F1 generation that is subsequently transmitted to both male and female F2 generation, defining their future reproductive capacity. Leptin was identified among top upstream regulators of the transcriptomic changes occurring in the hypothalami of undernourished animals, affecting major elements of the neuroendocrine axis controlling reproduction. On the other hand, our preliminary studies showed altered levels of leptin in maternal milk of nursing, undernourished F0 and F1 mothers. These results provide the initial evidence of lactational programming of the reproductive fitness over generations.

The overarching goal of this proposal is to discover the molecular and physiological underpinnings of this phenomenon. We will focus on lactocrine-based mechanism responsible for the programming of reproductive fitness over generations, deciphering the multiple layers of signalling pathways (Central Nervous System, gonads, and adipose tissue, and leptin) leading to successful outcomes. Our study will determine the epigenetic and neuroendocrine alternations, as well as reproductive system development impairments caused by a milk-borne factors deficiency at the postnatal window of developmental programming. Description of neuroendocrine and epigenetic alternations will allow to reveal mechanisms responsible for the transmission of adverse reproductive phenotypes over multiple generations, which have been already observed by our team.

Our project will provide a comprehensive view of the role of milk-borne factors, such as leptin, in the programming of reproductive performance over generations, and a basis for the further research on use of milk-borne factors in personalized strategies preventing forthcoming disorders induced by malnutrition. Results of this studies have the high potential to shed a new light on possible mechanisms underlying reproductive disorders, such as precocious puberty, hypogonadotropic hypogonadism, infertility and reduced reproductive capacity.