

SUMMARY SHEET OF THE INTERNATIONAL RESEARCH PROJECT (IRP)

Title: Ancestral Causes of Obesity: Understanding epigenetic transmission by spermatozoa,

Duration: 5 years,

Coordinator: Prof. Romain Barrès

1) Project summary, main goals and expected results (1 to maximum 2 pages)

State of the art

Our understanding of the mechanisms of heritability has undergone a paradigm shift. Prof. Barrès and his team have contributed extensively to the landmark discovery that pre-fertilization feeding factors modulate the offspring phenotype (de Castro Barbosa et al., 2019; de Castro Barbosa et al., 2016; Donkin and Barres, 2018; Ng et al., 2010). These observations indicate that the preconceptional lifestyle influences metabolism and offspring health. The team was the first to identify that sperm epigenetic signals are sensitive to environmental factors like weight loss and exercise (Donkin et al., 2016; Ingerslev et al., 2018). In human sperm, we have identified areas of epigenetic variability near genes controlling central nervous system development (Donkin et al., 2016; Ingerslev et al., 2018). We name these regions Gametic Hotspots of Epigenetic Variation (GHEV) and postulate that these regions have the capacity to be remodeled in response to environmental stresses. We hypothesize that in response to environmental factors, epigenetic variation on GHEVs contributes to the predisposition to develop metabolic and central nervous system disorders such as obesity and autism.

Objectives

This research aims to study the mechanisms by which environmental factors before conception modulate the phenotype of offspring. We will use a nutritional geometry approach (Aim Ia) to identify the macronutrient composition of the paternal diet that is critical in inducing epigenetic heritability. Using a comparative strategy (Aim Ib), we will attempt to identify, if it exists, the common denominator of epigenetic heritability that may be conserved between animal species. We will combine our chromatin conformation data and epigenomic analyzes to (Aim Ic) identify the effect of nutritional stress on chromatin conformation and enhancer activity in offspring tissues. We will use state-of-the-art biotechnological tools to modify the epigenome in a targeted way and (Aim Id) determine the role of GHEV methylation on cell differentiation and function. This line of research will allow a detailed understanding of the mechanisms controlling epigenetic inheritance and will open the way to new nutritional strategies before conception. It benefits from the partnerships established in the context of the GECKO consortium (Gametic Epigenetics Consortium against Obesity) that Prof. Barrès leads. This consortium, organized in partnership with the University of Chicago, the University of Sydney, the University of Copenhagen and recently the CNRS – IPMC, employs around twenty staff and integrates a bioinformatics platform made up of 6 full-time bioinformatics researchers. It has a comfortable budget of 8 million euros allocated over the period 2019-2025.

Perspective and impact

A detailed understanding of the mechanisms controlling epigenetic inheritance in obesity will pave the way towards preclinical strategies to prevent obesity. At completion of the Programme, the team will have identified the essential preconceptional diet components that influence the sperm epigenome and which may influence the risk to develop obesity in the next human generations. This new knowledge will be a foundation for defining safe preconceptional dietary recommendation, which carries important societal implications. By providing insight into the effect of DNA methylation on de novo DNA mutations, this research will also address fundamental questions beyond the field of obesity research, such as the

plasticity of vertebrate genomes, which has potential to revolutionize current dogmas about species adaptation and evolution.

2) **List of Participants** (specify the scientific coordinator in each country)

a) in France

Name	Laboratory	Institutional affiliation (employer)
Coordinator Prof. Romain Barrès	Institut de Pharmacologie Moléculaire et Cellulaire (IPMC)	CNRS – Université Côte d’Azur
Dr. Jean-Louis Nahon	Institut de Pharmacologie Moléculaire et Cellulaire (IPMC)	CNRS – Université Côte d’Azur
Dr. Carole Rovère	Institut de Pharmacologie Moléculaire et Cellulaire (IPMC)	CNRS – Université Côte d’Azur

b) in Denmark

Name	Laboratory	Institutional affiliation (employer)
Coordinator Prof. Romain Barrès	Center for Basic Metabolic Research (CBMR)	University of Copenhagen, Denmark
Assistant Prof. Kristine Williams	Center for Basic Metabolic Research (CBMR)	University of Copenhagen, Denmark
Assistant Prof. Ali Altintas	Center for Basic Metabolic Research (CBMR)	University of Copenhagen, Denmark