



CiMUS International PhD Programme

1. Project title:

Inflammatory reprogramming of the Blood–Brain Barrier as an early driver of cancer-associated cachexia

2. Research Project:

Cancer-associated cachexia is a debilitating and multifactorial wasting syndrome characterized by involuntary loss of body weight, adipose tissue, and skeletal muscle mass, accompanied by profound metabolic dysregulation and increasingly recognized neuroinflammation. It affects a large proportion of cancer patients and is associated with reduced survival, impaired quality of life, and poor tolerance to anticancer therapies. Despite its major clinical impact, cachexia remains largely untreatable, reflecting an incomplete understanding of its underlying mechanisms. In particular, the early biological events that initiate cachexia during the precachexia stage, when weight loss is minimal but inflammatory and metabolic abnormalities are already present, remain poorly defined.

Over the past five years, the research group led by Prof. Rosa Señarís (Neuroendocrinology, Metabolism and Cancer) has investigated new targets and therapeutic strategies to preserve fat and muscle mass and improve metabolic function in cancer-associated cachexia using well-established preclinical mouse models. This work has identified multimodal therapeutic approaches targeting hypothalamic signaling together with peripheral inflammatory, immune, and metabolic pathways. While these findings demonstrate therapeutic potential, a critical unmet need remains to elucidate the initiating mechanisms that drive progression from precachexia to overt cachexia. In this context, the blood–brain barrier (BBB), particularly at the hypothalamus, the key metabolic control center, may play a central role.

This PhD project integrates the expertise of Prof. Rosa Señarís' group in cancer cachexia with the expertise of Prof. D. Viña in BBB biology. The central hypothesis is that cancer-associated cachexia is initiated during precachexia by inflammatory reprogramming of BBB endothelial cells in response to tumor- and immune-derived signals. Rather than serving solely as a passive physical barrier, BBB endothelial cells are proposed to act as an active signaling interface that senses circulating factors, including soluble inflammatory mediators and tumor-derived exosomes, and translates these peripheral cues into central nervous system inflammatory responses. This endothelial dysfunction is expected to induce selective alterations in BBB permeability, transport properties, and inflammatory signaling, thereby promoting astrocyte and microglial activation and driving neuroinflammation within hypothalamic regions that regulate energy balance and metabolism.



The project will employ well-characterized mouse models of cachexia, including Lewis lung carcinoma as a cachectic tumor model and MCA207 fibrosarcoma as a non-cachectic comparator. BBB endothelial dysfunction and inflammatory reprogramming will be characterized across precachexia and cachexia using *in vitro* transwell-based BBB tri-culture systems composed of endothelial cells, astrocytes, and microglia exposed to plasma from tumor-bearing mice, tumor-conditioned media, and tumor-derived exosomes. BBB responses to tumor-derived inflammatory cues under physiological shear stress will then be examined using BBB-on-a-chip platforms, enabling dynamic assessment of barrier permeability, tight junction integrity, and endothelial inflammatory signaling. Causality will be addressed by selectively inhibiting identified endothelial inflammatory pathways using complementary pharmacological and siRNA- or shRNA-mediated approaches. Finally, key *in vitro* findings will be validated *in vivo* by assessing BBB integrity, hypothalamic glial activation, and their relationship to body weight loss and skeletal muscle atrophy in tumor-bearing mice.

Overall, this project aims to provide a mechanistic framework linking peripheral tumor-derived signals to central neuroinflammation and metabolic dysregulation, while identifying new opportunities for early, BBB-targeted therapeutic intervention to prevent progression from precachexia to overt cachexia.

3. Job position description:

Key Responsibilities:

The PhD student is expected to design and perform experiments to investigate the role of blood–brain barrier (BBB) endothelial dysfunction in cancer-associated cachexia. This includes establishing and using *in vitro* BBB models, such as endothelial–astrocyte–microglia tri-cultures, implemented both in transwell systems and BBB-on-a-chip platforms under flow conditions, and analyzing the effects of tumor-derived signals, including plasma, conditioned media, and exosomes, on BBB function and inflammatory responses. The candidate will perform molecular and cellular analyses, including transcriptomic data generation and analysis, to assess endothelial and glial activation, and will apply pharmacological and siRNA/shRNA-mediated approaches to modulate inflammatory pathways and explore causal mechanisms. Contributions to *in vivo* studies in mouse models of cachexia will be expected, including validation of key *in vitro* findings. The student will integrate and interpret *in vitro* and *in vivo* data to develop mechanistic insights, prepare scientific reports, figures, and manuscripts, and present results at meetings and conferences. Careful maintenance of experimental documentation will also be essential aspects of the role.

Essential Requirements

We are looking for a motivated and enthusiastic PhD student to join our project investigating how the BBB may act as an early driver of cancer-associated cachexia. This project offers an



exciting opportunity to explore the mechanisms behind cachexia using both *in vitro* and *in vivo* experiments. The successful candidate will gain hands-on experience with advanced techniques, including BBB models, BBB-on-a-chip platforms, transcriptomic analyses, and tumor-derived exosome studies.

Applicants should hold a degree in Biology, Medicine, Pharmacy, Biotechnology, Biochemistry, Biomedicine or a related field, together with a Master's degree (or equivalent) in Biomedical Sciences, Neuroscience, Biology, or a similar discipline. A solid foundation in cellular and molecular biology, physiology, or immunology is essential, along with practical experience in laboratory techniques such as cell culture and protein or RNA analysis. We are looking for someone who can work independently, collaborate well in a multidisciplinary team, think analytically, and communicate clearly in English. Above all, strong motivation to pursue a PhD and an interest in neurobiology, metabolism, and cancer research are key.

Desirable Requirements

It would be an advantage to have previous experience with *in vitro* cell culture models, especially endothelial or neural cells, and familiarity with neuroinflammation, blood–brain barrier biology, metabolism, or cancer biology. Experience with animal models or handling biological samples from animals, as well as knowledge of molecular pathway modulation techniques (e.g., pharmacological treatments, siRNA/shRNA), is also desirable. Additional assets include experience with data analysis, basic bioinformatics or transcriptomic datasets, and previous research experience or publications.

4. Supervisor and Co-Supervisor

Name: Rosa Señarís

Email: rosa.senaris@usc.es

Research group: Neuroendocrinology, metabolism and cancer

Link to the group website: <https://cimus.usc.gal/es/grupo/neuroendocrinology-metabolism-and-cancer>

Name: Dolores Viña Castelao

Email: mdolores.vina@usc.rs

Research group: Pharmacology of chronic diseases

Link to the group website: <https://cimus.usc.gal/es/grupo/pharmacology-chronic-diseases>