MARIE SKŁODOWSKA-CURIE POSTDOCTORAL FELLOWSHIPS 2023

EXPRESSION OF INTEREST FOR HOSTING MARIE CURIE FELLOWS

HOST INSTITUTION

UCIBIO, Applied Molecular Biosciences Unit, Department of Life Sciences, NOVA School of Science and Technology, Universidade NOVA de Lisboa,

RESEARCH GROUP AND URL

Glycoimmunology Group
https://www.ucibio.pt/people/paula-alexandra-quintela-videira

SUPERVISOR (NAME AND E-MAIL)

Paula Videira p.videira@fct.unl.pt

SHORT CV OF THE SUPERVISOR

I am motivated by understanding the mechanisms that govern glycan expression and recognition and its impact in human biology and disease. I am an expert in Glycobiology and its interface with Immunology and Oncology. I am highly committed to translate research finding into innovative treatments, centered on patient needs. I am currently focused on three interconnected areas: i) mechanisms driving the expression of aberrant sialylated short O-glycans in cancers and its implications for tumour immunity and progression. ii) the role of sialylated glycans in the expression of immunomodulatory molecules and its role in curbing immune responses. iii) the impact of Congenital defects of glycosylation (CDG) in immune response and susceptibility to infection.

I am currently an Associate Professor at Faculdade de Ciências e Tecnologia/ Universidade NOVA de Lisboa (FCT-NOVA) and principal investigator of the Glycoimmunology Group at UCIBIO research unit. In the past few years, our efforts were fruitful in several ways: (A) We published 101 research papers and four patents (as PI) describing various roles of glycans, in several top-ranked journals (e.g. BBA, Molecular Oncology); a featured immunology article (doi: 10.4049/jimmunol.1890012); 11 invited reviews (highly cited doi: 10.3390/ijms19051304), and clinical guidelines (doi: 10.1002/jimd.12024.) (B) Me (plenary, keynote and invited speaker, moderator, chair) and my students have presented unpublished data in several national and international conferences (e.g. EuroCarb, SSIEM, AAI, PEGS). Noteworthy, my students' work was selected for several prestigious meetings. (C) I secured almost 4.5 million EUR for research plus 1.4 million EUR to spin-off our technology, including prestigious EU grants (Twinning, MSCA, EJPRD), prizes and research agreements with biopharmaceuticals. Important, my students and researchers secured individual fellowships. (D) I belonged to the Scientific council of COST, and I am currently part of the IAB of the Slovak Academy of Sciences and RD-Portugal, editorial board of Scientific Report, guest editor of Cancers and reviewer of several journals and international research applications. (E) I organize international courses on Glycosciences as e-learning and Workshops and organized several other meetings. (F) I co-founded the CDG&Allies-PPAIN, a unique patient-centric network, that gathers professionals and patient associations worldwide to foster research and awareness on rare diseases of glycosylation. This network joins almost 100 professionals and has produced several scientific reviews, medical guidelines, and lay language documents for society. (G) In 2019, I co-founded the spin-off CellmAbs, a biopharmaceutical developing immuno-oncology agents for tumour associated glycans. CellmAbs was elected to the top 30 by Biotecnika and

featured by Labiotech and BIO-Europe 2020.
My research is highly multidisciplinary and uses cutting edge methodologies as in vitro and in vivo assays, omics, bioinformatic tools and patient-centric approaches with the ultimate goal of translating research findings into patient benefits.

5 SELECTED PUBLICATIONS

Carlota Pascoal; Mylène A. Carrascal; Daniela F. Barreira; Rita A. Lourenço; Pedro Granjo; Ana R. Grosso; Paula Borralho; Sofia Braga; Paula A. Videira. "Sialyl LewisX/A and Cytokeratin Crosstalk in Triple Negative Breast Cancer". *Cancers* (2023): https://doi.org/10.3390/cancers15030731.

Deschepper, Fanny M.; Zoppi, Roberta; Pirro, Martina; Hensbergen, Paul J.; Dall'Olio, Fabio; Kotsias, Maximillianos; Gardner, Richard A.; Spencer, Daniel I.R.; Videira, Paula A.. "L1CAM as an E-selectin Ligand in Colon Cancer". *International Journal of Molecular Sciences* 21 21 (2020): 8286. http://dx.doi.org/10.3390/ijms21218286.

Loureiro, Liliana R.; Feldmann, Anja; Bergmann, Ralf; Koristka, Stefanie; Berndt, Nicole; Máthé, Domokos; Hegedüs, Nikolett; et al. "Extended half-life target module for sustainable UniCAR T-cell treatment of STn-expressing cancers". *Journal of Experimental & Clinical Cancer Research* 39 1 (2020): http://dx.doi.org/10.1186/s13046-020-01572-4.

Zélia Silva; Tiago Ferro; Danielle Almeida; Helena Soares; José Alexandre Ferreira; Fanny M. Deschepper; Paul J. Hensbergen; et al. "MHC Class I Stability is Modulated by Cell Surface Sialylation in Human Dendritic Cells". *Pharmaceutics* (2020): https://www.mdpi.com/1999-4923/12/3/249.

Liliana R Loureiro; Diana P Sousa; Dylan Ferreira; Wengang Chai; Luís M. P. Lima; Carina Pereira; Carla B Lopes; et al. "Novel monoclonal antibody L2A5 specifically targeting sialyl-Tn and short glycans terminated by alpha-2-6 sialic acids". *Scientific Reports* 8 1 (2018): 12196-12196. doi: 10.1038/s41598-018-30421-w

PROJECT TITLE AND SHORT DESCRIPTION

Title: The gut-immune system crosstalk in PMM2-CDG

Congenital disorders of glycosylation (CDG) are a family of ultra-rare genetic diseases with defects in the glycosylation machinery causing multi-system involvement with severe and life-threatening consequences. CDG have high unmet diagnostic and therapeutic needs which stem from the lack of understanding on the disease mechanisms underlying the symptomatic spectrum and its evolution over time. PMM2-CDG is the most frequent of these disorders with a major neurologic involvement but also other multi-system manifestations often leading to severe clinical presentations and life-threatening consequences. Importantly, it was reported that 20% of infant mortality happens in the first year of life due to frequent and recurrent infections, but the underlying causes remain undeciphered. We previously identified, by a transcriptomics and experimental validation approach, that PMM2-CDG patients have molecular and signaling defects when challenged with inflammatory stimulus which compromise the synthesis of key immune players. Besides, we previously found that infections of the gastrointestinal (GI) tract are more prevalent in PMM2-CDG patients compared to the healthy population, with a higher frequency of frequent or chronic infections. We were also able to associate the presence of infections to higher phenotypic severity and lower quality of life, particularly in day-to-day activities; and to identify the occurrence of food allergies and celiac disease among PMM2-CDG patients. While a vast list of GI manifestations is known to afflict PMM2-CDG patients, our findings suggest the existence of an immune system-gut crosstalk in PMM2-CDG which remains to be unravelled.

In fact, the GI tract and its defence is dependent on physical and chemical structures and highly regulated mechanisms for each glycosylation is of extreme importance. On the one hand, in the gut, the first line of defence against pathogens is the mucus mostly composed by by mucins which are responsible for the protection of the underlying epithelial cells against external insults and serves as a physical gel to inhibit and entrap invading microbes and aid clearance; while the second line of defense is the glycocalyx, a layer of highly diverse glycoproteins and glycolipids expressed on the membrane of epithelial cells that limits the colonization by pathogens. On the other hand, the homeostasis of the gut depends on regulated interactions of the immune system components with dietary and bacterial antigens as well as their and host glycosylation.

Given the fact that glycosylation is essential for the correct functioning of the immune system and GI protection, we hypothesize PMM2-CDG patients have functional defects in the interplay between the immune system and the gut that cause a high prevalence of infections mostly associated with the GI tract. Therefore, this project aims to decipher the molecular mechanism of such interplay by using GI cellular models and applying a multi-omics approach.

Specifically, we aim to:

1. Characterize a cohort of PMM2-CDG patients by the analysis of clinically relevant biomarkers (e.g., GI infections, fecal calprotectin, lactoferrin levels) as well as of patient-reported data (e.g., diet, lifestyle, symptomatic care, and management).
2. Resorting to non-invasive *in vitro* (e.g., knock-out of commercially available gastrointestinal cell lines, IPSCs-derived organoids and/or microfluidic organ chips) and *in vivo* (i.e., zebrafish), we will access the glycosylation-dependent adhesion/invasion/colonization of commensal or pathogenic microorganisms as well as to perform co-cultures with immune cells to test the gut-related immune response resorting to several imaging, immunodetection techniques and single-cell RNA-sequencing.
3. Test potential therapeutics derived from the previous results using a drug repositioning approach. Drug candidates (and therapeutic already used for other diseases of the GI tract, like IBD will also be tested).

Deciphering the GI pathological alterations will allow to build scientific knowledge in an extremely rare disease and possibly find new therapeutic targets and consequently improve the symptomatic management, care and QoL of CDG patients. We also foresee the involvement of several stakeholders and fomenting work in network complemented by a sound science communication strategy with the disease community, general public, to make scientific results accessible and understandable by all.

SCIENTIFIC AREA WHERE THE PROJECT FITS BEST*

Life Sciences (LIF)

*Scientific Area where the project fits best – Please select/indicate the scientific area according to the panel evaluation areas: Chemistry (CHE) • Social Sciences and Humanities (SOC) • Economic Sciences (ECO) • Information Science and Engineering (ENG) • Environment and Geosciences (ENV) • Life Sciences (LIF) • Mathematics (MAT) • Physics (PHY)