MARIE SKŁODOWSKA-CURIE POSTDOCTORAL FELLOWSHIPS 2024

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)

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SHORT CV OF THE SUPERVISOR

I am Paula Videira, leader of the Glycoimmunology Research Group at UCIBIO, Associate Professor with habilitation in Immunology and Glycobiology at the Life Sciences Department of NOVA School of Science and Technology, Universidade NOVA de Lisboa (NOVA-FCT, PT). I am highly motivated to comprehend the intricate roles of glycans in diseases, dedicated to translating Glycosciences into innovative glycan-based immunotherapies, centered on patient needs. I am currently focused on i) mechanisms and clinical implications of aberrant sialylated short O-glycans in cancers. ii) glycan's role in immunomodulatory molecules and immune responses. iii) immunity and novel therapies for Congenital defects of glycosylation (CDG). iv) anti-glycan antibodies and glycan-based therapeutic technologies.

In the past few years, my efforts were fruitful in several ways: (A) We published 108 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 2 clinical guidelines (B) Me (plenary, keynote and invited speaker, moderator, chair) and my students have presented unpublished data in several international conferences (e.g. EuroCarb, SSIEM, AAI, PEGS).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 Reports, guest editor and reviewer of several journals and international research applications. (E) I organize international courses and congresses, including the Glyco- e-learning course. (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, producing several outcomes including lay language documents for society. (G) In 2019, I co-founded the spin-off CellmAbs, a biopharmaceutical developing immuno-oncology agents for tumour glycans. Awarded several times, CellmAbs secured investments and closed in 2024 a historic negotiation with a

big pharmaceutical to step our technology into clinics. In 2024, I co-founded Valvian a novel biopharmaceutical centered on AI-driven novel immune therapies.
My research is highly multidisciplinary and uses cutting-edge in vitro and in vivo assays, omics, bioinformatic tools and patient-centric approaches to translate 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

GlycoCARE: Unraveling the Role of glycans in Immunosuppression and Enhancing Therapy in Pancreatic Cancer

Pancreatic cancer (PC) is rapidly becoming more prevalent and expected to become the second-leading cause of cancer-related deaths, within the next few years. Unfortunately, PC has the poorest prognosis due to its resistance to therapy and late diagnosis, typically detected in metastatic stages. In addition, due to aggressive care needs, it is one of the cancers with highest cost estimates for health care systems.

Pathophysiologically, PC has a immunosuppressive microenvironment characterised by immature dendritic cells (DC) and immunosuppressive cytokines. Recent studies on clinical samples and disease models are consensual that overcoming immunosuppression improves survival of PC patients. Yet, current immunotherapies have limited effectiveness in PC, and better therapeutic targets are needed.

The sialyl Tn (STn) is a short sialylated O-glycan expressed in PC but not in healthy cells. It is associated with poor prognosis, contributing to cancer progression and metastasis. We showed that STn induces immature DC and suppressive cytokines, undermining immune activation. These observations suggest a previously unknown STn–immunosuppressive loop driving PC carcinogenesis. Yet, robust multiparametric studies at tumour microenvironment and confirmation

in meaningful PC cohorts are needed. Preliminary results by our group indicate that anti-STn antibodies lead to anti-tumour activity, strongly suggesting STn as a promising therapeutic target.
Herein, we hypothesise that STn induces immunosuppression, which drives PC carcinogenesis. Thus, targeting STn can be the first step towards an effective anti-PC immune response. Accordingly, the project aims to answer the following questions:
1-How does STn correlate with PC progression in patients?
2-Can we recapitulate STn role in a PC animal model?
3-What triggers STn expression?
4-How can we overcome the immunosuppression in STn+ PC to reduce tumour progression?
These questions are aimed to be addressed using an innovative and integrative approach combining clinical samples, relevant animal models, and transcriptomics.
For the first time we will: i) screen STn in a meaningful patient cohort from two hospitals, including precursor lesions and metastasis, and compare STn phenotype with transcriptome; ii) use mice models that truly recapitulate STn expression in PC to analyse into detail the STn-related environment. This approach will allow us to gather reliable insights into how STn impacts PC aggressiveness/carcinogenesis, which is still unclear. In addition, our functional assays with relevant cell line models will allow us to confirm the drivers controlling the expression of STn in PC. Finally, we will evaluate the efficacy of anti-STn antibodies in attenuating PC progression and metastasis. Furthermore, by integrating all data, we will establish a network model illustrating drivers of STn expression in PC and their correlation with clinical features. This model is foreseen to be useful for the medical community to improve therapy in PC in the clinical setting.
We anticipate generating a significant number of Scientific & Medical documents on the preclinical validation of STn in PC and immunophenotype. We also foresee the involvement of several other stakeholders interested in exploiting our know-how, tools and technology, by applying a strong science communication with the general lay public, making scientific discovery accessible to 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)