MARIE SKŁODOWSKA-CURIE POSTDOCTORAL FELLOWSHIPS 2021

EXPRESSION OF INTEREST FOR HOSTING MARIE CURIE FELLOWS

HOST INSTITUTION

NOVA University Lisbon | ITQB NOVA - Instituto de Tecnologia Química e Biológica António Xavier

RESEARCH GROUP AND URL

The Garcia-Santamarina Lab

SUPERVISOR (NAME AND E-MAIL)

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SHORT CV OF THE SUPERVISOR

For her PhD, Dr. Garcia-Santamarina joined Professor Elena Hidalgo laboratory (University Pompeu Fabra (Barcelona) where she worked on mechanisms of oxidative stress signaling and toxicity in fission yeast. There, she focused in understanding how oxidative stress triggers signaling cascades, how cells cope with the excess of oxidants and which are their toxic effects in proteins using the fission yeast as a model organism. After her PhD, she joined the laboratory of Professor Dennis J. Thiele at Duke University (USA) for her first postdoc. In the Thiele lab she worked with a human fungal pathogen, *Cryptococcus neoformans*, in a fungal pathogen-host interface context. Her postdoc focused in understanding how transition metals, essential for all living organisms but toxic when excess, are used by the host immune system as a first line of defense against pathogens [both metal deprivation ("nutritional immunity") and metal bombardment (toxicity)]. As part of her postdoctoral work, she identified the regulatory mechanisms important for *C. neoformans* to thrive in environments that rapidly fluctuate in copper concentrations, such as within the host, and characterized two novel proteins with roles in copper detoxification and copper import, respectively, which are fungal virulence determinants.

She then moved to EMBL (Heidelberg) in 2018, for a second postdoc, with a prestigious Interdisciplinary Marie Curie fellowship (EIPOD). At EMBL, she had shared appointment between the laboratories of Dr. Athanasios Typas, Dr. Kiran R. Patil and Prof. Dr. Peer Bork where she became an expert in the microbiome field. There, she optimized an *in vitro* microbiomics platform to answer the question on whether bacterial members of the gut microbiota behave the same against external perturbations (drugs) when they are alone or as part of a community. By comparing the species behavior in isolation and in the community, she discovered that in several occasions emergent phenotypic traits are only visible in the community context. She followed up these with metabolomics and in-depth molecular biology and biochemistry experiments to dissect how a particular drug becomes inactive in microbial consortia. *In toto*, she uncovered that a combination of drug metabolism, drug bioaccumulation and interspecies interactions are the main drivers of microbial community traits.

As a new faculty at ITQB NOVA, Dr. Garcia-Santamarina research goal is to deepen into the mechanisms of gut microbial metabolism at the gene and strain level in a competitive environment, namely other gut microbes and host cells. Gut microbial metabolism has evolved to take advantage of any metabolite as a potential energy source, and therefore is highly hydrolytic and reductive, mostly relying in metalloenzymes especially suited for electron transfer reactions in anaerobiosis. Thus, in the case of the gut microbiota, metalloenzymes are involved in carbohydrate degradation, pathogen colonization resistance, vitamins and cofactors biosynthesis, reductive amino acid metabolism, or xenobiotics metabolism. She plans to combine her expertise in the metal's biology field with her knowledge in the microbiome field to set-up experimental pipelines that lead to an understanding of the role of metals in driving gut microbial metabolism and its implications in human health and disease, e.g. inflammatory diseases, cancer, aging, or genetic diseases that course with host metal overloading or defects.

5 SELECTED PUBLICATIONS

- García-Santamarina S., Probst C., Festa R.A., Ding C., Smith A.D., Conklin S.E., Brander S., Kinch L.N., Grishin N.V., Franz K.J., Riggs-Gelasco P., Lo Leggio L., Johansen K.J., Thiele D.J. (2020) A Lytic Polysaccharide Monooxygenase-like protein functions in copper import and fungal meningitis. Nature Chemical Biology 16(3):377-344.

- García-Santamarina, S., Festa, R.A., Smith, A.D., Yu, C.H., Probst, C., Ding, C., Homer, C.M., Yin, J., Noonan, J.P., Madhani, H., Perfect, J.R., Thiele, D.J. (2018) Genome-wide analysis of the regulation of Cu metabolism in *Cryptococcus neoformans*. Molecular Microbiology. 108 - 5, pp. 473 - 494.

- García-Santamarina, S., Uzarska, M.A., Lill, R. and Thiele, D.J. (2017) *Cryptococcus neoformans* iron-sulfur protein biogenesis machinery is a novel layer of protection against Cu stress. mBio 8 - 5, pp. e01742-17.

- García-Santamarina, S., and Thiele, D.J. (2015) Copper at the fungal pathogen-host axis. Journal of Biological Chemistry 290(31):18945-18953.

- García-Santamarina, S., Boronat, S., Domènech, A., Ayté, J., Molina, H. and Hidalgo, E. (2014) Monitoring *in vivo* cysteine oxidation in proteins – global maps of reversibly oxidized thiols using ICAT and LC-MS/MS. Nature Protocols. 9(5):1131-45.

PROJECT TITLE AND SHORT DESCRIPTION

Establishing transition metal homeostasis at the gut microbiome-host interface

In recent years there has been an increased awareness of the importance of the human microbiome for our healthy state. By outnumbering our genes by a factor of 150, the human microbiome influences us in a variety of physiological, immunological and metabolic processes. Dysbiosis or alterations of the human microbiome have been implicated in gastrointestinal, cardiovascular, psychologic, respiratory, oncologic, hepatic and autoimmune disorders or diseases.

Ingested substances, including nutrients or xenobiotics, have the greatest influence on the composition and function of the gut microbiome and its interaction with the host. Among ingested substances, metals are particularly interesting. Metals are essential for life; both the microbiota and the host require homeostatic metal concentrations for the correct functioning of about 50% of their proteins. However, although essential, in excessive concentrations metals are toxic. Despite their physiological relevance, not much is known about what are the effects of low or high metal concentrations in the human gut microbiome and how this influences human health. Importantly, millions of people around the world have severe and life-threatening deficiencies in biologically relevant metals due to poor nutrition, low metal absorption rates, or genetic diseases. But also, millions of people are over-exposed to metals (including heavy metals) due to ingestion of contaminated food, pollution, or occupational exposure, making metals environmental toxins of public health concern.

This proposal aims to investigate the effects of metals in the gut microbiota composition and functionality and its effects on the host by combining systems-based approaches (high-throughput experimental platforms coupled to “omics” readouts) and tailored molecular and biochemical experiments to address how transition metals affect gut microbiome composition and function and its interaction with the host. The findings from this research will contribute to a better understanding of microbial physiology and responses to fluctuating micronutrient concentrations, as well as shed light into host-microbial interactions that might have a direct role in host nutrition.

SCIENTIFIC AREA WHERE THE PROJECT FITS BEST*

Life Sciences (LIF)