Board of examiners

Prof. Katarina Vukojevic
Department of Anatomy, Histology and Embriology
University of Split, Split-Croatia

Dr. Pau Sancho-Bru
Liver cell plasticity and tissue repair group
Institut d´Investigacions Biomédiques August Pi I Sunyer, Barcelona-Spain

Prof. Lindsey Devisscher
Basic and Applied Medical Sciences-Gut and Liver Immunopharmacology
Universiteit Gent

Prof. Ron Kooijman
Department of Pharmacology
Vrije Universiteit Brussel

Prof. Dimitri de Bundel
Research group Experimental Pharmacology
Vrije Universiteit Brussel

Prof. Debby Mangelings, Chair
Department of Analytical Chemistry, Applied Chemometrics and Molecular Modelling
Vrije Universiteit Brussel

Prof. Mathieu Vinken (Promoter)
Department of *In Vitro* Toxicology and Dermato-Cosmetology
Vrije Universiteit Brussel

Prof. Bruno Cogliati (Promoter)
Department of Pathology of the School of Veterinary Medicine and Animal Science
University of São Paulo, São Paulo-Brazil

VRIJE UNIVERSITEIT BRUSSEL

UNIVERSIDADE DE SÃO PAULO

PhD in Pharmaceutical Sciences
2018-2019

INVITATION to the public defence of

Sara CRESPO YANGUAS

To obtain the academic degree of **'DOCTOR IN PHARMACEUTICAL SCIENCES'**

The role of connexins, pannexins and their channels in liver fibrosis.

Thursday 25 October 2018
Auditorium **Piet Brouwer**, 17:00
Faculty of Medicine and Pharmacy, Laarbeeklaan 103, 1090 Brussel

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Summary of the dissertation

While connexin-based gap junctions have been historically considered as goal keepers of tissue physiology, connexin hemichannels and pannexin channels have lately gained considerable attention as drivers of pathological processes, including cell death and inflammation. The objective of this doctoral thesis project was to investigate the role of the latter 2 channel types, in particular hemichannels consisting of connexin32 (Cx32) and connexin43 (Cx43) as well as pannexin channels built up by pannexin1 (Panx1), in chronic liver disease. Focus was hereby put on liver fibrosis, which is characterized by scar formation in response to liver damage, oxidative stress and inflammation associated with several types of chronic liver disease. In a first study, it was found that administration of a specific Cx43 hemichannel inhibitor or a general connexin-based channel inhibitor to mice with liver fibrosis reduced hepatic oxidative stress and inflammation, respectively. Furthermore, both treatments alleviated liver fibrosis, thus underscoring the involvement of Cx43 hemichannels in chronic liver disease. In a second study, genetic ablation of Cx32 in mice revealed enhanced scar formation, liver damage and oxidative stress in a mouse model of liver fibrosis, pointing to a protective role for Cx32 signaling in liver fibrosis. In a third study, genetic ablation of Panx1 in 2 mouse models of liver fibrosis showed a different outcome with respect to scar formation, liver damage and inflammation, suggesting that the involvement of Panx1 in liver fibrogenesis is etiology-dependent. Collectively, the outcome of these 3 studies confirms the pathological role of connexin hemichannel and pannexin channel signaling and opens new perspectives for the clinical treatment of liver fibrosis.

Curriculum Vitae

Sara Crespo Yanguas was born on 17th March 1987 in Madrid-Spain. She obtained a bachelor's degree in biological sciences from the *Universidad de Alcalá de Henares* in 2011 and a master's degree in microbiology and parasitology: research and development from the *Universidad Complutense de Madrid* in 2012. Before starting her PhD project, Sara was shortly employed by the pharmaceutical company Eli Lilly & Company in Alcobendas-Madrid, where she contributed to the research activities related to the discovery of new drugs against neurodegenerative diseases. She joined the research group of *In Vitro* Toxicology and Dermato-Cosmetology at the Faculty of Medicine and Pharmacy at the Vrije Universiteit Brussel (VUB) in 2014 to investigate the role of connexin and pannexin (hemi)channels as drug targets in liver fibrosis. This project, part of a double PhD diploma program established between the VUB and the University of São Paulo-Brazil (USP) and supervised by Prof. Mathieu Vinken (VUB) and Prof. Bruno Cogliati (USP), was funded by the European Research Council (ERC) and the São Paulo Research Foundation (FAPESP). During this PhD research, Sara participated in 2 other research projects focused on the role of connexin and pannexin (hemi)channels in acute liver failure and non-alcoholic steatohepatitis. The results obtained during her doctoral research were presented at several national and international congresses. Sara authored as much as 20 scientific publications in international peer-reviewed journals, among which 9 as first author. She is also co-author of 5 book chapters. She obtained a certificate corresponding to the FELASA C degree to supervise and conduct animal experiments. Sara has supervised a master thesis project and assisted in several practical courses for bachelor and master students in pharmaceutical sciences at the VUB. In addition, she has given some lectures for postgraduate, master and PhD students in veterinary sciences at the USP.