Master 2 Internships

Modeling the dynamics of NMDA receptor interactions in vascular remodeling leading to Pulmonary Arterial Hypertension

Context of the project

Pulmonary Arterial Hypertension (PAH) is a rare disease associated with high morbidity and mortality despite the available treatments, which are essentially vasodilators while the cause of the increased pressure in the lung is a mechanism of vascular remodeling. Starting from scratch, with just the intuition of the target, the ambition of Sylvia Cohen-Kaminsky's team at Inserm UMR_S999/Université Paris Saclay, was to propose a new active ingredient for a disease-modifier treatment of PAH, centered on the mechanisms of pulmonary vascular remodeling. With €3 million raised (LabEx LERMIT, ANR NUTS, FRM, SATT Paris Saclay) the team has developed a breakthrough innovation based on (1) the discovery of the NMDA receptor (NDMAR), mainly known in the central nervous system, as an unexpected target in vascular remodeling leading to PAH *(Dumas & al Circulation 2018)* and (2) the development of a "first-in-class" drug candidate, selective antagonist of the peripheral NMDA receptor without central effects, protected by 3 patent families granted worldwide, and whose mechanism of action validated in pre-clinical models *in vivo* targets pulmonary vascular remodeling. The mission of the start-up ALSYMO created on September 1st 2022 is now to drive the regulatory and clinical development of the first asset in its pipeline, targeting peripheral NMDAR. Its first strengths: an exclusive worldwide license negotiated with SATT Paris Saclay for the use of its first-in-class drug candidate, a project Winner of the i-Lab 2021 competition and nominated for the Galien Price 2021 and 2022.

Rational

Targeting NMDAR in PAH would represent a major breakthrough in the treatment of PAH. First, because this target is involved in pulmonary vascular remodeling leading to PAH with an unprecedented mechanism. Secondly, because this target has a definite advantage over all other competitors under development. Indeed, a systems biology approach underway at Inserm UMR_S999, based on the construction and integration of the knowledge bases of NMDAR (mainly from the central nervous system) and PAH, has revealed that NMDAR is engaged (phosphorylated) and activated downstream - and at the crossroads - of many known PAH pathways. NMDAR proved to be a very highly connected node, providing evidence of its importance as a target, and suggesting that NMDAR is a molecular hub at the crossroads of PAH pathways. As NMDAR is downstream of all these pathways, it can be hypothesized that NMDAR targeting will affect all these pathways activated in PAH (multiplying efficiency), without affecting the major players in these pathways involved in otherwise important functions (increasing safety). The non-crossing of the blood brain barrier of the drug candidate should contribute to its safety (no central effects, cognitive functions preserved). However, the molecular network built is static and not dynamic, and does not make it possible to test/predict *in silico* the importance of NMDAR as a molecular hub and the consequences of its targeting, on the known PAH pathways.

Objectives

The challenge is to design a model of the interactome network involving NDMAR in the causal pathways of vascular remodeling (disease progression) that can be in silico manipulated by a therapeutic tool leading to the cure of PAH through a controllability analysis. The internship has 2 distinct parts: 1) Molecular network synthesis involving NDMAR, 2) controllability analysis to study the causal pathways involved in vascular remodeling and their phenotypic implications.

The interactome comprising NMDAR and the corresponding identified PAH pathways, comprises 344 entities/nodes, 1000 signaling pathways and 8500 interactions. This analysis will focus on a subset of these nodes that will have to be selected according to their functional relevance in the remodeling mechanism. On this network model, we will then

evaluate the consequences of the effect of an NMDAR antagonist to model its mechanism of action on known PAH pathways connected to NMDAR.

Methodology & Candidate Profile

The theoretical framework chosen will be boolean networks, constituting a recognized framework for modeling the interactome. The intern will use the ACTONET platform developed within the COSMO team for controllability synthesis and analysis. The expected candidate will have competences in the fields of biology and modelling. Knowledge of lung diseases and Boolean networks would be appreciated but is not required for the application.

Expected results and prospects

This work is expected to provide a dynamic model of the interaction of NMDAR with the main pathways of vascular remodeling leading to PAH and the modeling of the mechanism of action of NMDAR antagonists on the NMDAR as a molecular hub at the crossroads of these pathways. Such a demonstration could give a competitive advantage to NMDAR as a major player in vascular remodeling leading to PAH.

Supervisors

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Bibliography

DUMAS S.J, G. BRU−MERCIER, A. COURBOULIN, M. QUATREDENIERS, C. RÜCKER−MARTIN, F. ANTIGNY, B. NAKHLEH M, RANCHOUX, E. GOUADON, M. VINHAS M, VOCELLE, N. RAYMOND, P. DORFMÜLLER, E. FADEL, F.PERROS, M. HUMBERT, S COHEN−KAMINSKY. Vascular NMDA receptor activation promotes arterial remodelling and pulmonary hypertension, Circulation 2018,137:2371-2389.

Top 1% of the specialty, cited F1000 https://f1000.com/prime/732674650#

Editorial associated https://www.ncbi.nlm.nih.gov/pubmed/29844072,

Podcast with the Publisher: Circulation on the Run https://circulation.libsyn.com/circulation-may-29-2018-issue

CNRS Innovation Letter 18/11/2021: A drug candidate to treat pulmonary arterial hypertension
https://www.cnrs.fr/lettre-innovation/actus.php?numero=803

CNRS and INSB press review 19/02/2018: The NMDA receptor, an unexpected target in Pulmonary Arterial Hypertension
https://www.insb.cnrs.fr/fr/cnrsinfo/le-recepteur-nmda-une-cible-inattendue-dans-lhypertension-arterielle-pulmonaire

Célia Biane, Franck Delaplace Causal reasoning on Boolean control networks based on abduction: theory and application to Cancer drug discovery. IEEE/ACM Trans Comput Biol Bioinform. 2018 Dec 21.
https://pubmed.ncbi.nlm.nih.gov/30582550/

Sara Sadat Aghamiri, Franck Delaplace. TaBooN Boolean Network Synthesis Based on Tabu Search. IEEE/ACM Transactions on Computational Biology and Bioinformatics, 2021.
https://ieeexplore.ieee.org/abstract/document/9369896