**PhD PROPOSAL FOR THE**

**PASTEUR - PARIS UNIVERSITY INTERNATIONAL DOCTORAL PROGRAM**

Time for applicants to contact host laboratories: September 13 – November 2, 2017

Deadline for full application: November 13, 2017

Interviews: January 30, February 2, 2018

Start of the Ph.D.: October 1, 2018

**Title of the PhD project:** Left-right patterning of heart morphogenesis

**Keywords**: left-right patterning, asymmetric morphogenesis, congenital heart defects, mouse genetics, transcriptomics

**Department:** of Developmental & Stem Cell Biology

**Name of the lab:** Heart Morphogenesis

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Presentation of the laboratory and its research topics:

The acquisition of a specific shape is key for organ function. The group of Heart Morphogenesis studies how cells are coordinated at the level of the tissue and how their local behaviour generates global changes of organ shape. We address these questions in the context of heart development, which provides a striking model of morphogenesis in 3D. We use a combination of approaches to address these questions, including genetics, transcriptomics, embryology, primary cultures of cardiac cells, 3D imaging and computer modelling.

We have previously characterized the lineages and behaviour of cardiac muscle cells during heart morphogenesis [1, 2]. We have also developed interdisciplinary tools for the quantification of tissue anisotropy in 3D and revealed that myocardial cells coordinate locally their orientation of division during cardiac chamber expansion [3, 4]. Recently, we have studied the atypical cadherin Fat4, a cell adhesion protein, which was initially discovered in the fly as a major regulator of organ size. However, how the Fat pathway is connected to the Hippo pathway in mammals remained poorly understood. We have shown that Fat4 is required to restrict heart growth at birth, by modulating the nuclear translocation of the effector of the Hippo pathway Yap1, in a non-canonical way [5]. In addition to investigating the mechanism of heart growth, we are interested in the looping of the heart tube in the early embryo, which provides an example of how left-right patterning is sensed by cells to drive asymmetric morphogenesis.

Our work in the mouse is relevant to congenital heart defects and heart repair in humans. The laboratory is affiliated to both the Department of Developmental Biology of the Institut Pasteur as well as the Institut *Imagine*, within the Hospital Necker-Enfants Malades, in which the national reference centre for congenital heart defects is located.

Description of the project:

The mammalian heart has four cardiac chambers, two atria and two ventricles. The alignment of cardiac chambers is key for the correct plumbing of the blood, so that carbonated blood in the right heart is separated from oxygenated blood in the left heart. Initially, in the heart primordium, the right ventricle is positioned cranially to the left ventricle. It is during the process referred to as cardiac looping, that the right ventricle acquires its position to the right of the left ventricle. Cardiac looping corresponds to a rapid change in heart geometry, from a straight tube to a helical tube [see 6]. Heart looping, which is oriented rightward, is the first morphological sign of left-right asymmetry during embryo development. It has been shown to depend on left-right patterning, initiated one day earlier in the left-right organiser of the embryo [7]. In humans, mutations disrupting the left-right organiser are associated with heterotaxy, including defects in visceral organs and also complex cardiac malformations. However, how information from the left-right organiser is transposed into cardiac cells remains poorly understood.

The laboratory has recently developed a computer model of heart looping, as well as tools to stage heart looping and quantify in 3D the associated morphological changes. These are applied to study in mouse mutants the role of the major left determinant Nodal, a secreted factor of the TGFβ family, in heart looping.

As other factors than Nodal have been proposed to control heart looping in the fish [8], the PhD project aims at characterising novel markers of left-right asymmetry during heart looping. Which markers are asymmetrically expressed at precise stages of heart looping ? Are they dependent on Nodal signalling ? What is the proportion of cardiac cells that have expressed Nodal on the left side ? Molecular markers will be identified by transcriptomics, in control and Nodal mutant embryos. Transgenic mouse models will be developed to track cells which have expressed an asymmetric marker, including Nodal.

The project is expected to provide novel insight into how heart morphogenesis is imprinted by left-right signalling, which is relevant to congenital heart defects in humans.

References:

1- Oriented clonal cell growth in the developing mouse myocardium underlies cardiac morphogenesis, S. Meilhac, M. Esner, M. Kerszberg, J. Moss and M. Buckingham, The Journal of Cell Biology 2004, 164(1) : 97-109.

2- Asymmetric fate of the posterior part of the second heart field results in unexpected left/right contributions to both poles of the heart, Domínguez JN, Meilhac SM, Bland YS, Buckingham ME, Brown NA, Circ Res. 2012, 111(10):1323-35.

3- Extracting 3D cell parameters from dense tissue environments: Application to the development of the mouse heart, S. Pop, A. Dufour, J-F. Le Garrec, C. Ragni, C. Cimper, S. Meilhac and J-C. Olivo-Marin, Bioinformatics 2013, 29(6):772-9.

4- Quantitative analysis of polarity in 3D reveals local cell coordination in the embryonic mouse heart, J-F. Le Garrec, C. Ragni, S. Pop, A. Dufour, J-C. Olivo-Marin, M. Buckingham and S. Meilhac, Development 2013, 140(2):395-404.

5- Amotl1 mediates sequestration of the Hippo effector Yap1 downstream of Fat4 to restrict heart growth, C. Ragni, N. Diguet, J-F. Le Garrec, M. Novotova, T. Resende, S. Pop, N. Charon, L. Guillemot, L. Kitasato, C. Badouel, A. Dufour, J-C. Olivo-Marin, A. Trouvé, H. McNeill and S. Meilhac, Nature Communications 2017, 8:14582.

6- The anatomy of cardiac looping: a step towards the understanding of the morphogenesis of several forms of congenital cardiac malformations, Männer J., Clin Anat. 2009, 22(1):21-35.

7- Nodal activity in the node governs left-right asymmetry, Brennan J, Norris DP, Robertson EJ., Genes Dev. 2002, 16(18):2339-44.

8- A Nodal-independent and tissue-intrinsic mechanism controls heart-looping chirality, Noël ES, Verhoeven M, Lagendijk AK, Tessadori F, Smith K, Choorapoikayil S, den Hertog J, Bakkers J., Nat Commun. 2013, 4:2754.

Expected profile of the candidate:

A strong interest in developmental biology is required, as well as previous lab experience in molecular or cellular biology. You work with rigour and creativity and enjoy team work.

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