DOCTORAL THESIS

NANTES UNIVERSITE
ECOLE DOCTORALE N° 605
Biologie-Santé
Physiologie, Physiopathologie, Biologie Systémique Médicale

AND UNIVERSITÄT BONN
Mathematisch-Naturwissenschaftlichen Fakultät

Benjamin LE VELY

Macrophages in the pathophysiology of myxomatous mitral valve dystrophy

Thesis defended in Nantes, on March 24th 2026

Research labs: UMR 1087 - L'Institut du Thorax, Nantes
LIMES - Developmental biology of the immune system, Bonn

Reviewers before defense:

Nabila BOUATIA-NAJI	Directrice de Recherche, Paris Cardiovascular Research Center, Paris
Stéphane ZAFFRAN	Directeur de Recherche, Marseille Medical Genetics, Marseille
Elvira MASS	Professor, LIMES - Developmental biology of the immune system, Bonn

Composition of the committee:

President:

Ana Ivonne VAZQUEZ ARMENDARIZ	Professor, LIMES - Organoid biology, Bonn

Examiners :

Nabila BOUATIA-NAJI	Directrice de Recherche, Paris Cardiovascular Research Center, Paris
Stéphane ZAFFRAN	Directeur de Recherche, Marseille Medical Genetics, Marseille
Lucie HENAUT	Ingénieure de Recherche, UR UPJV 7517 - MP3CV, Amiens
Falk NIMMERJAHN	Professor, Chair of Genetics, University Erlangen-Nürnberg, Erlangen
Sebastian ZIMMER	Professor, Herzzentrum Bonn - Universität Klinikum Bonn, Bonn
Ana Ivonne VAZQUEZ ARMENDARIZ	Professor, LIMES - Organoid biology, Bonn

Thesis co-supervision:

Romain CAPOULADE	Chargé de Recherche, UMR 1087 - L'Institut du Thorax, Nantes
Elvira MASS	Professor, LIMES - Developmental biology of the immune system, Bonn

Title: Macrophages in the pathophysiology of myxomatous mitral valve dystrophy

Keywords: Mitral valve dystrophy, macrophages, pathophysiology

Abstract:

Myxomatous mitral valve dystrophy (MVD) is the first cause of mitral valve prolapse (MVP), a common disease affecting 2 to 3 % of the population. The first causal mutation in the FLNA gene (FLNA-P637Q), was associated with MVD in 2007. Recently, the FlnA-P637Q KI rat model was generated and phenotyped. Using multimodality imaging, MVD was diagnosed as early as 3 weeks (D21) and signature of chemotaxis and myeloid cell migration was described at the transcriptomic level. This thesis has attached to determine the role of macrophages in the pathophysiology of MVD. With a combination of histology, flow cytometry and transcriptomic analysis, we clarified the dynamic of MVD development in the FlnA-KI rat model. Extracellular matrix dysregulation, marked with increased expression of the Hyaluronan synthase *Has1*, is present as early as birth, quickly followed by endothelial dysfunction by two days post-natal, marked by overexpression of the endothelial stress marker *Esm1*. Morphological remodeling of the MV is detectable from seven days post-natal, and is accompanied by an upregulation of chemotaxis signaling as assessed in bulk RNA sequencing. However, no differences in the proportion of immune cells is seen at this timepoint. A the age of three weeks, the proportion of macrophages is significantly increase in the MV of KI rats. We also corroborated the contributions of macrophages to MVD in a large cohort of Human MVD samples. We then assessed macrophages core function, phagocytosis, upon FLNA P637Q mutation and found no differences. Finally, using single nuclei RNAseq, we tried to decipher the cellular landscape of the MV at steady state and during MVD and identify the interactions between macrophages and the other cell types contributing to the disease.

Overall, this thesis highlight the contribution of macrophages to the myxomatous remodeling of the mitral valve, and pave the way to the study of macrophages interactions with the MV environment to better understand what role do they play in the development and the maintenance of MVD. This could potentially lead to the identification of new therapeutic target that could greatly improve the quality of treatment offered to patients.