APPEL A PROJETS DE THÈSE 2026
CONCOURS DE L'ED 658 – Sciences du vivant

Formulaire à compléter et déposer par les porteurs du projet de thèse HDR via l'adresse mail suivante : ed658@univ-amu.fr OU/ET romane.haddadi@univ-amu.fr
MERCI DE METTRE EN SUJET DU MAIL : Concours ED 658 2026 porteur de projet
Ces dossiers seront publiés pour que les candidats postulent.

au plus tard le 3 mars 2026.

INTITULÉ DU PROJET
Deciphering the therapeutic effect of VEGFB in ischemic heart disease

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SPECIALITE : (Rayer les mentions inutiles)

Bio-informatique et Génomique / Biochimie Structurale / Biologie du Cancer / Biologie du Développement / Biologie Végétale / Biotechnologie / Immunologie / Microbiologie et interactions hôte-pathogènes / Neurosciences

SOUS JURY POUR LE CONCOURS : (Rayer les mentions inutiles)
JURY 1 : BIOLOGIE CELLULAIRE
~~JURY 2 : MICROBIOLOGIE – GENOMIQUE~~
~~JURY 3 : NEURSOCIENCES~~

MERCI DE REMPLIR TOUTES LES INFRORMATIONS EN FRANÇAIS ET EN ANGLAIS

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Description de la problématique de recherche - Project description

Cardiac ischemia, due to the obstruction of a coronary artery, leads to the death of cardiomyocytes, resulting in myocardial infarction (MI) and irreversible scarring. While timely reperfusion is crucial to minimize adverse outcomes, acute MI remains the leading cause of mortality and morbidity worldwide. Hundreds of clinical trials promoting revascularization using angiogenic growth factors have failed to demonstrate an effective therapeutic response in the human heart, as massive neoangiogenesis has led to the formation of leaky and non-functional vessels. We have shown that neonatal mice can restore a functional arterial tree, essential for proper heart function, only during the regenerative period. Therefore, reactivating "arterial-remodeling" pathways in ischemic heart conditions may represent a valid therapeutic approach rather than simply creating a mass of new vessels by angiogenesis. In parallel, others have shown that VEGF-B has a greater therapeutic potential than VEGF-A in improving cardiac function after MI in several animal models. We recently conducted a pilot study whose very encouraging results suggest that VEGF-B is capable of promoting the remodeling of a functional arterial tree in the infarcted heart of a mouse outside the period of cardiac regeneration, giving the first indication of the therapeutic mechanism induced by VEGF-B. The objective of this PhD project is to demonstrate that VEGF-B has clear therapeutic implications in the heart, orchestrating arterial remodeling after myocardial ischemia in order to restore a functional arterial tree. To achieve this goal, the student will 1) decipher the mechanisms by which arteries exposed to VEGF-B develop and remodel following cardiac MI, 2) determine how this remodeling affects cardiac function.

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Mots clés – Keywords

Génétique de la souris ; Chirurgie (MI); Imagerie 3D ; Artères coronaires ; Régénération cardiaque ;

Mouse genetics ; Surgery (MI) ; Coronary arteries; Cardiac regeneration

Thématique / Domaine / Contexte - Theme / Field / Context

Although VEGF-B clearly induces cardiac ischemic protection through revascularization of the heart, it has been demonstrated that transgenic overexpression of VEGF-B in cardiomyocytes induces cardiac hypertrophy. These transgenic animals had preserved cardiac function and were protected against myocardial infarction, suggesting that the cardiac response to VEGF-B is similar to that of physiological cardiac hypertrophy. Thus, the beneficial effect of VEGF-B in the heart remains poorly understood. Interestingly, VEGF-B has been also described for its effect on arteriogenesis and we have shown that arterial remodeling plays a primary role in cardiac regeneration. During development, coronary endothelial cells originate from two spatially distinct sources, sinus venous and endocardium. In adult myocardial infarction, a major remodeling of coronary arteries occurs within the infarcted zone in the adult mouse heart associated with the formation of endocardial flowers. The arterial endothelial structures within the endocardium reveal extensive endothelial cell plasticity in the infarct zone and identify the endocardium as a site of endogenous arteriogenesis. This process in adult hearts is similar to how coronary vessels develop in embryos and neonates. VEGF-B promotes the proliferation and migration of a specific endocardial-derived population following a paracrine and not autocrine mechanism. This PhD project aims to build on these findings to decipher the role of VEGF-B on arterial remodeling during MI.

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Objectifs

1) decipher the mechanisms by which arteries exposed to VEGF-B develop and remodel following cardiac MI,

2) determine how this remodeling affects cardiac function.

Méthode – Method

1) to demonstrate that VEGFB overexpression in cardiomyocytes is capable of restoring a functional arterial tree after MI in adult heart, MI will be induced by ligation of the left coronary artery of transgenic mice in which coronary arteries are fluorescently labelled. VEGFB will be overexpressed by AAV9. 3D images of the arterial tree will be imaged and rebuilt from cleared hearts using Imaris software. To better understand the molecular mechanisms responsible for this repair, scRNA seq and spatial transcriptomic analyses will be performed using 10X genomics and Visium technologies. This approach will enable us to identify overrepresented signaling pathways driving the remodeling of a functional arterial tree.

2) Cardiac function will be analyzed by Echo- and Electrocardiography combined with histological analyses.

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Références bibliographiques

1- **L. Miquerol** et al., Endothelial plasticity drives arterial remodeling within the endocardium after myocardial infarction. Circ Res 116, 1765-1771 (2015).

2- R. Sturny, L. Boulgakoff, R. G. Kelly, **L. Miquerol**, Transient formation of collaterals contributes to the restoration of the arterial tree during cardiac regeneration in neonatal mice. *J Mol Cell Cardiol* **195**, 1-13 (2024).

2- E. Lahteenvuo *et al.*, Vascular endothelial growth factor-B induces myocardium-specific angiogenesis and arteriogenesis via vascular endothelial growth factor receptor-1- and neuropilin receptor-1-dependent mechanisms. *Circulation* **119**, 845-856 (2009).

3- M. Rasanen *et al.*, VEGF-B Promotes Endocardium-Derived Coronary Vessel Development and Cardiac Regeneration. *Circulation* **143**, 65-77 (2021).

4- **G. D'Amato** *et al.*, Endocardium-to-coronary artery differentiation during heart development and regeneration involves sequential roles of Bmp2 and Cxcl12/Cxcr4. *Dev Cell* **57**, 2517-2532 e2516 (2022).

Conditions scientifiques matérielles et financières du projet de recherche - Scientific, material, and financial conditions of the research project

Le projet sera réalisé au sein de l'équipe du Dr Robert Kelly à l'IBDM financée par la FRM et l'ANR.

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Profil et compétences recherchées - Profile and skills required

L'étudiant(e) doit être habile avec les souris, et posséder des qualités techniques fines compatibles avec de la chirurgie de précision.

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