THESIS TOPIC

Subject N° (to be completed by the ED):	FUNDING:	☒ Requested ☐ Acquired	Funding origin:

Thesis title: **Mechanosensing and mechanotransduction pathways involved in intracranial aneurysm formation**	3 keywords: aneurysm, signal transduction,cerebral vasculature

Unit / team: **UMR Inserm 1087/Cnrs 6291 – Université de Nantes**

Supervisor's name: **Gervaise LOIRAND / Anne-Clémence VION**	Phone number: +33(0)228080116 Email address : gervaise.loirand@univ-nantes.fr

Socio-economic and scientific context (approximately 10 lines):

Intracranial aneurysm (IA) is a frequent and generally asymptomatic cerebrovascular abnormality affecting 3% of the general population. IA is characterized by a local dilation caused by weaknesses in the wall of a cerebral artery. The devastating complication of IA is its rupture, resulting in subarachnoid haemorrhage that can lead to severe disability and death (40% of rupture case). Risk factors such as hypertension, female sex, increasing age, cigarette smoking, excessive alcohol consumption and familial history of aneurysm predispose to IA formation and rupture. Unfortunately, **there are neither reliable clues nor diagnostic tools to predict the formation and/or the fate of an IA in a given individual**. Also, there is no pharmacological drug available to prevent the rupture of aneurysm and subsequent subarachnoid haemorrhage. Current treatments are invasive (microsurgical clipping or endovascular coiling) with a significant risk of procedural morbidity. Currently, **the management of patients with IA and deciding if a patient needs to be preventively treated or not remain extremely challenging and still controversial.** The present challenge is thus the discovery of tools such as biomarkers that could predict the IA rupture in a given individual, and the identification of relevant targets for pharmacological therapy to prevent it.

Working hypothesis and aims (approximately 8 lines):

The mechanical forces exerted by blood flow on the vascular wall play a major role for vessel maintenance and physiology. IA preferentially arises at the bifurcations of the circle of Willis, where the forces of flow and pressure exerted on the arterial wall by the blood circulation are very strong and subjected to important variations, suggesting that IAs are likely acquired lesions resulting from a defective vascular wall response/adaptation to local hemodynamic stresses. **Why the vascular wall does not respond properly to mechanical stresses in these specific areas leading to IA formation is still unknown. The project aims to answer this question by identifying the signalling pathways activated by mechanical stresses in vascular cells, focusing on the Rho protein signalling pathways.**

Main milestones of the thesis (approximately 12 lines):

AIM 1: Identify which Rho GEFs are regulated by hemodynamic forces both in vascular endothelial and smooth muscle cells.
Task 1 - In vivo regulation of RhoGEFs in cerebral arteries.
Task 2 - In vitro regulation of RhoGEFs activity and expression by mechanical forces.
AIM 2: Evaluate the contribution of the identified GEF to the main functions of both endothelial and smooth muscle cells
Task 1 - Morphological analysis of endothelial and smooth muscle cell:
Task 2 - Functional analysis in endothelial and smooth muscle cells:
Task 3 - Smooth muscle cell differentiation analysis:
AIM 3: Develop and test new drugs targeting the identified GEF on IA development
Taks 1- Rational design of chemical ligands targeting the Rho protein/GEF interactions.
Task 2 - Assessment of the biological activity of chemical ligands targeting the Rho protein/GEF interactions.
Task 3 - Synthesis and optimization of active molecules
Task 4 - Drug effect in vivo
AIM 4: Generation and phenotyping of genetically modified mice

Scientific and technical skills required by the candidate (2 lines):
Vascular biology, signal transduction, cell culture & biology (histology, IH, IF,…), biochemistry (Western blot, Co-IP, …)

3 publications from the team related to the topic (last 5 years):

1. Bourcier R, Le Scouarnec S, Bonnaud, S, the ICAN Study Grp, **Loirand G***, Desal H*, Redon R*. Rare coding variants in ANGPTL6 are associated with familial forms of intracranial aneurysm. *Am J Hum Genet.* 2018, 102(1): 133-141 *(IF=9.025)*

2. Bourcier R, Chatel S, Bourcereau E, Jouan S, Marec HL, Daumas-Duport B, Sevin-Allouet M, Guillon B, Roualdes V, Riem T, Isidor B, Lebranchu P, Connault J, Tourneau TL, Gaignard A, **Loirand G**, Redon R, Desal H; ICAN Investigators. Understanding the Pathophysiology of Intracranial Aneurysm: The ICAN Project. *Neurosurgery.* 2017 Apr 1;80(4):621-626. doi: 10.1093/neuros/nyw135. *(IF=4.889)*

3. **Vion AC**, Alt S, Klaus-Bergmann A, Szymborska A, Zheng T, Perovic T, Hammoutene A, Oliveira MB, Bartels-Klein E, Hollfinger I, Rautou PE, Bernabeu MO, Gerhardt H. Primary cilia sensitize endothelial cells to BMP and prevent excessive vascular regression. *J Cell Biol.* 2018 Mar 2. pii: jcb.201706151. doi: 10.1083/jcb.201706151 *(IF=7.955)*

National and international collaborations:
- Cerebro-vascular and aneurysm field:
  - Dr. Joutel, UMR Inserm 1161, Génétique et physiopathologie des maladies cérébro-vasculaires, Paris, France
  - Dr. Desal, Neuroradiologie diagnostique et interventionnelle, CHU Nantes, Nantes, France
  - Dr. Richard Redon, UMR Inserm 1087 CNRS 6291, IDT-Inserm, Nantes, France

- Vascular paphysiology field:
    - Dr. Boulanger, INSERM U970, PARCC, team 1
    - Dr Rautou, INSERM UMR 1149. Centre de recherche sur l'inflammation. Hôpital Bichat. Paris.

- Vascular development field:
    - Dr Gerhardt, Integrative Vascular biology lab, MDC Berlin, Germany
    - Dr Potente, Angiogenesis and metabolism laboratory, Max Planck Institute for Heart and Lung Research, Germany
    - Dr Caesson-Welsh, Uppsala Universtity, Sweeden
    - Dr Franco, Vascular morphogenesis laboratory, institute of molecular medicin, Lisbon, portugal

- Rheology, mathematical modeling field:
    - Dr Bernabeu, university of Edinburgh, UK

To apply, please email application letter, CV, grade sheets and recommendations to: gervaise.loirand@univ-nantes.fr