UNIVERSITE BIOLOGIE BRETAGNE SANTE LOIRE

Year 2019/2020

THESIS TOPIC

Subject N° (to be completed by the ED):	**FUNDING:** ☒ **Requested** ☐ **Acquired**	**Funding origin:**
Thesis title: **Role of a susceptibly gene variant in intracranial aneurysm formation**		3 keywords: aneurysm, angiogenesis, cerebral arteries
Unit / team: **UMR Inserm 1087/Cnrs 6291 – Université de Nantes**		
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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 hemorrhage. 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 1) molecular mechanisms involved in IA formation, 2) tools such as biomarkers that could predict the IA rupture in a given individual, and 3) relevant targets for pharmacological therapy to prevent it.

Working hypothesis and aims (approximately 8 lines):

The understanding of the pathophysiologic mechanisms of IA is a prerequisite for improving disease evaluation and patient management. Recent studies have demonstrated the usefulness of familial approaches based on whole-exome sequencing to improve knowledge on the molecular mechanisms underlying IA formation and rupture. We have set up such an approach and recently succeeded in identifying two rare coding variants that are causally related to familial forms of IA in *ANGPTL6* (Ref 1 below) and another gene *X*. The protein X encoded by this gene belongs to a protein family, the members of which have been shown to be expressed in endothelial and/or vascular smooth muscle cells and involved in vascular remodeling and atherosclerotic diseases. Some of them have been found in cerebral aneurysm. Except for its gene and sequence, almost nothing is known about X. The present project aims at (i) deciphering the role of X in vascular structure and function and (ii) understanding why the identified *X* variant predispose to IA**.**

Main milestones of the thesis (approximately 12 lines):

Relevant complementary *in vitro*, ex- and *in vivo* approaches will be developed to identify the role of X in the vasculature and answer the following specific questions:

- **WP1: Defining the role of X in the vasculature**

Aim 1: Is X expressed in arterial endothelial (EC) and smooth muscle cells (SMC)? (Cerebral and extra-cerebral rodent and human arterial cells)
Aim 2: Does deletion of X affect arterial wall structure? (X knock-out (KO) (available at IMPC) and control mice)
Aim 3: Does deletion of X predispose to or potentiate IA? (In vivo mouse models)
Aim 4: Does X play a role in angiogenesis? (cell and mouse models)

- **WP2: Understanding the consequence of the expression of the *X* variant**

Aim 1: Does the expression of the identified variation in the X gene affect the expression and/or the activity of the protein? (Expression of the WT and the variant in cell models)
Aim 2: What are the functional consequence of the X variant in VSMC and EC function?

Scientific and technical skills required by the candidate (2 lines):
Vascular biology, animal model, 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