**PhD position at the Centre National de la Recherche Scientifique, Institut de Mécanique des Fluides de Toulouse (UMR CNRS-INPT-UPS 5502)**

**Deciphering the contribution of abnormal vessel architecture on disease progression in cerebral small vessel disease**

**Keywords:** Blood microcirculation, Microvascular networks, Blood flow, Mass transfers, Discrete models, 3D Image Processing, Amyloid Angiopathy, Inter-species comparison.

**Academic context:** This PhD/Post-doc position is part of an interdisciplinary project funded for 5 years (2018-2023) by the National Institute of Neurological Disorders and Stroke (USA) involving the Biological and Porous Media group of the Fluid Mechanics Institute of Toulouse, France. This group in internationally recognized for its expertise on modelling the structure and function of brain microcirculation at various scales, in health and disease. This project also involves the hemorrhagic stroke group at the Massachusetts General Hospital (MGH) (affiliated with Harvard Medical School), Boston, USA, for its expertise on cerebral amyloid angiopathy (CAA), studied both in the clinics, including the *post-mortem* collection of anatomical material from human patients, and in animal models of vascular amyloid accumulation, studied by advanced *in-vivo* optical imaging of structural and functional alterations to the small vessels in the brain.

**Scientific context:** The cerebral microvascular system is essential to a large variety of physiological processes in the brain, including blood delivery and blood flow regulation as a function of neuronal activity (neuro-vascular coupling). It plays a major role in the associated processes leading to disease (stroke, neurodegenerative diseases) but the comprehension of the basic mechanisms involved is still largely incomplete. For example, in CAA (a common age-related cerebral small vessel disease resulting in dementia and often catastrophic hemorrhagic stroke), microvascular lesions, including vessel occlusions and bleeds, progressively appear, and are associated with abnormal vascular architecture, and possibly with reduced total microvascular density and reduction in blood flow. However, the question whether these vascular abnormalities are involved in the appearance and evolution of microvascular lesions is still fully open. Also, their impact on microvascular function and brain performance is poorly understood. To answer the first question, quantitative knowledge of the three-dimensional brain microvascular network anatomy in healthy and diseased conditions is needed, both in human and mice. Highly quantitative, physiologically informed modeling and analysis is also needed for any coherent understanding and for translating results between species.

**Project summary:** Our first goal is to gain insight on the onset and progression of abnormal vessel architecture in CAA in mice. For that purpose, we will quantify characteristic measures of vessel morphology and topology, such as vessel tortuosity and the number of vessels in capillary loops, from imaging data acquired in healthy, aged, and diseased mice. The models previously developed and validated at IMFT for simulating blood flow and mass transfers in large microvascular networks will then be used to infer the associated functional changes most susceptible to induce both classes of microvascular lesions (i.e. occlusions and bleeds), and their possible spatial inter-relationships. This will help design new experiments enabling the validation of the underlying mechanisms of lesion formation. The results will be translated to humans based on anatomical datasets obtained from the MGH brain bank and clinical data on lesion type and preferential localization in human patients.

**Profile:** Strong background in numerical fluid mechanics and advanced C++, demonstrated motivation for work at the interface between disciplines, in close collaboration with clinicians and researchers performing *in vivo* experiments in mice. Knowledge of numerical algorithms for 3D image processing or graph theory is welcomed. A university Master's Degree or equivalent in Fluid Mechanics, Applied Mathematics or related disciplines is required, as well as fluency in English and willingness to learn French.

**Academic supervisors:** Sylvie Lorthois, Directrice de Recherche CNRS (IMFT), in collaboration with the hemorrhagic Stroke group at the Massachusetts General Hospital, Boston, USA (Profs Greenberg and Bacskai and Dr. Van Veluw).

**Administrative aspects:** The PhD will be awarded by Université de Toulouse, Doctoral School "Mechanics, Energetics, Civil and Process Engineering" (www.ed-megep.fr). The employer is the Centre National de la Recherche Scientifique (National Center for Scientific Research, www.cnrs.fr), the largest fundamental research organization in Europe. The PhD project is funded for 3 years, starting no later than October 2019 (Gross salary: ~ 21 000 €/year; Net salary, including social security: ~ 17 000 €/year).

For more information or to apply, please submit via email your curriculum vitae, copies of recent transcripts, a statement of your future career goals, and the names and email addresses of two references, with "PhD position NINDS" in the subject line, to: Sylvie Lorthois, PhD (lorthois@imft.fr).