UNIVERSITÀ DEGLI STUDI DI TORINO

I@UNITO – Visiting Scientists

Scientific area	Scientific responsible	Host Department	Type of activity	Start of mobility	Language
Area 6 – Biological Sciences	Prof. Saverio Francesco Retta	Clinical and Biological Sciences	Basic and translational research	January 2017	English
Type of fellowship	Junior (less than 40 years old) 3 months fellowship				
Title of the research project	Characterization of Defective Autophagy as Pivotal Player in Cerebral Cavernous Malformation Pathogenesis and Development of Novel Targeted Therapeutic Strategies				
Description of the research project	Cerebral Cavernous Malformation (CCM) is a major cerebrovascular disease of proven genetic origin affecting 0.3-0.5% of the general population. It is characterized by abnormally enlarged and leaky capillaries, which predispose to seizures, focal neurological deficits and intracerebral hemorrhage (ICH). Despite significant progress and breakthroughs in the understanding of CCM disease natural history and pathogenesis over the last decade, no direct therapeutic approaches for CCM disease exist so far, besides surgical removal of accessible lesions in patients with recurrent hemorrhage or intractable seizures. In particular, novel pharmacological strategies are required for preventing the most severe disease phenotype in susceptible individuals, including the development of numerous and large symptomatic lesions and ICH (Trapani and Retta, 2015; Choquet et al., 2016). Causative loss-of-function mutations have been identified in three genes, KRIT1 (CCM1), CCM2 and PDCD10 (CCM3). While providing new options for the development of pharmacological therapies, recent advances in knowledge of the functions of these genes have clearly indicated that they exert pleiotropic effects on several biological pathways (Trapani and Retta, 2015; Marchi et al., 2016a). Recently, we found that defective autophagy is a common feature of loss-of-function mutations of the three known CCM genes, and underlies major phenotypic signatures of CCM disease, including endothelial-to-mesenchymal transition and enhanced ROS production, suggesting a novel pathogenetic mechanism that may reconcile apparent differences and discrepancies in the literature (Marchi et al., 2016a,b; Marchi et al., 2015; Gibson et al., 2015). To gain further insights into CCM pathogenetic mechanisms and their translational implementation, we will address the possibility that defective autophagy constitutes a convergence nexus for the multiple disease-associated molecular and cellular dysfunctions reported to date as well as for the effectiveness of the distinct therapeutic approaches proposed so far. To this end, we will use an integrated research approach based on studies in available cellular and animal models of CCM disease, and surgical samples of CCM lesions, taking advantage of experimental procedures optimized in our previous work, as well as of ongoing multidisciplinary cooperation among distinct units of the CCM_Italia research network (www.ccmitalia.unito.it). In addition, we will take advantage of international collaborators with specific expertise and interests in the characterization of the physiopathological functions of canonical and non-					

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	canonical forms of autophagy in order to provide novel mechanistic insights into CCM disease pathogenesis and facilitate the identification of new therapeutic options.
Profile Description	The Visiting Scientist should possess documented competencies and interests in research topics related to CCM disease, including the characterization of molecules and molecular mechanisms underlying the role of autophagy in the pathogenesis of human diseases and the development of novel targeted therapeutic approaches.
Research objectives	Integrated research efforts for further investigation of the emerging areas of CCM biology research are likely to pave the way for novel, safe and effective therapeutic strategies to prevent or reverse adverse clinical outcomes of CCM lesions. In this light, we aim to take advantage from a young and motivated Visitor Scientist with specific expertise and interest in the characterization of the psychopathological functions of canonical and non-canonical forms of autophagy in order to provide novel mechanistic insights into CCM disease pathogenesis and facilitate the development of innovative approaches for disease prevention and treatment, including identification of novel therapeutic compounds and development of novel drug repurposing and combination strategies as basis for personalized medicine approaches.
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