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Dr. Marco Giovannini and Dr. Jeremie Vitte awarded CDMRP NF Grant February 26, 2018

Schwannomatosis is a rare form of neurofibromatosis that has only recently been identified. The genetic disorder affects less than 1 in 40,000 people, and causes the development of benign tumors, called schwannomas, that usually grow on spinal and peripheral nerves. These tumors develop when Schwann cells, which form the insulating cover around nerve fibers, grow abnormally. These tumors may cause pain that may be hard to manage. Tumor development appears to be primarily related to a change, or mutation, in certain genes that help regulate cell growth in the nervous system. So far, two of these genes have been identified as mutated in schwannomatosis patients (*SMARCB1* and *LZTR1*). In addition, the *NF2* gene is mutated in schwannomatosis tumors. These mutations prevent the genes from making the normal proteins that control cell proliferation, allowing cells to multiply excessively and form tumors.

Despite the recent successes of familial studies to uncover the genetic mutations in schwannomatosis, understanding of the molecular consequences of loss of *NF2* and *SMARCB1* or *LZTR1* that give rise to schwannomas is still in its infancy. The central hypothesis of this study is based on the observation that, in contrast to neurofibromatosis type 2 (NF2), schwannomas in schwannomatosis patients are typically distinctly painful. Thus, *SMARCB1* or *LZTR1* gene inactivation, that is not typically present in NF2 schwannomas, could be responsible for the pain phenotype that is not associated to schwannomas in NF2.

The team led by Dr. Giovannini and Vitte will test this hypothesis by: 1) Using genetically engineered mouse models to determine the mechanisms of schwannoma development in schwannomatosis; and 2) Defining the role of *Smarcb1* or *Lztr1* gene inactivation in pain associated with schwannomatosis (collaboration with Dr. Michael Caterina, Johns Hopkins School of Medicine).

This work will provide the research community with novel model systems and databases of gene expression profiles from each model that can be used to design and perform pre-clinical tests of agents to relieve pain and tumor growth in schwannomatosis. The successful completion of this study will lead to a major leap forward in our understanding of schwannomatosis manifestations and in the availability of tools that can be used over the next decade, to develop novel, efficacious therapies to control tumorigenesis and treat this pain.