Perelman School of Medicine
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Report to Dr. Roberto Bufo and the Italian POHA – December 2019

Research investigations dedicated to finding the cause and establishing a cure for POH are conducted at the University of Pennsylvania School of Medicine (Philadelphia, PA, USA) with the support of the Progressive Osseous Heteroplasia Association. In a key discovery by our research group, heterozygous inactivating mutations in the *GNAS* gene were identified as the cause of POH. *GNAS* has many critical roles in our cells, but heterotopic ossification in POH is a very specific consequence. Identifying the specific downstream molecular and cellular effects of *GNAS* inactivation that lead to ectopic bone formation will identify specific treatment targets for POH.

Studies supported in part by the Italian POHA are:
1. Evaluate the DNA sequence of the *GNAS* gene in patients who have received a clinical diagnosis of POH. These studies investigate the correlation between clinical presentation and specific gene mutations as well as increase our understanding of the range of mutations that cause POH.
2. Investigate the role of the *GNAS* gene in directing the differentiation of cells. To understand the cells and molecular pathways in bone formation that are controlled by *GNAS* gene products, we are investigating the signaling pathways downstream from *GNAS* that regulate osteogenesis, in the skeleton and in heterotopic ossification, in order to identify therapeutic targets.
3. Using a recently developed mouse model, investigate POH heterotopic ossification *in vivo* to further understand the earliest effects of *GNAS* mutation that lead to ectopic bone formation in POH. This animal model is also important for pre-clinical drug testing; we have identified candidates that we expect to begin to test in 2020.

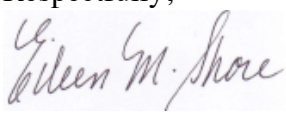
In 2019, we continued to make progress using our POH mouse model as a system to better understand how *GNAS* mutation changes tissues prior to formation of heterotopic ossification. We are currently drafting a manuscript that will report some of our data. Our graduate student, who is mainly supported through a NIH research fellowship, continues to work on POH projects. Her NIH support has allowed us to expand our work on POH.

Financial Report (2019):
Funds available: $17,145 (2019 funds; 15,500 euro, received February 2019)

	Received	Spent	Balance
POH Researchers		$8,180	
Lab experiment support		$8,965	
Total	$17,145	$17,145	$0

Funding through the Italian POHA has been critically important in reaching a better understanding of POH that will lead to therapeutic options. The support of the IPOHA is greatly appreciated.

Respectfully,



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