Research Program for Progressive Osseous Heteroplasia
at the University of Pennsylvania Research
Annual Report 2022

In people with POH, heterotopic bone typically begins within the adipose (fat) tissue beneath the skin. At the University of Pennsylvania in Philadelphia, our goal for POH research is to determine the cellular mechanisms though which the extra bone formation (heterotopic ossification; HO) in POH occurs and use this knowledge to identify specific treatment targets for preventing the initiation and progression of HO in POH.

The Penn POH research program has accomplished important milestones including the discovery that inactivating mutations in the *GNAS* gene cause POH. In people who have POH, *GNAS* inactivating mutations cause heterotopic bone that often arises within the subcutaneous fat layer (adipose tissue) of the skin. Our research has determined that mesenchymal stem cells (MSCs) – progenitor cells that reside in many tissues and that have the potential to differentiate into cell lineages such as bone, cartilage, and fat (adipose) cells – more readily become bone cells (osteoblasts) than fat cells (adipocytes) when they carry a *Gnas* mutation, even under conditions that would normally promote differentiation to fat cells. In other words, our work indicates that progenitor cells in the tissues of people with POH have lost their normal control mechanisms for cell differentiation, leading to osteoblast differentiation and bone formation in places where bone does not normally form.

A genetically-engineered mouse with GNAS inactivation models POH HO bone formation, providing an excellent system for lab research studies on determining how the HO first begins to form in POH. We have used this mouse model to show that even before HO begins to form, the adipose tissue where HO eventually forms changes dramatically over time, with the adipose tissue becoming depleted followed by progressive formation of heterotopic bone.

In order to examine how the tissue and cells change during HO development, in 2022, we began to conduct a series of studies to define the time course of HO in our POH mouse model and develop methods to isolate the tissue where HO is forming. We then began to conduct initial studies using a relatively new technology known as single cell RNA sequencing (scRNAseq). This is a high-throughput technology that allows us to conduct sequencing of individual cells to examine the gene expression information in each cell. By examining the gene expression patterns of the populations of cells over time, we can construct a history of their changes and fates, and thereby identify the cell activities in specific types of cells that lead to HO formation.

We continue to be highly committed to our work on POH; the studies that are supported by all of the members of the POHA, the Italian POHA, and the Rice Family allow us to make continued progress toward identifying treatments and cures.

Best regards,
Eileen M. Shore
December, 2022

I thought you might be interested in ‘meeting’ some of our POH researchers so I’m attaching a photo of the three students who have been working on POH over the last couple of years – from left to right in the photo: Aparna Sumanth, Jianing Xu, and Niambi Brewer. Niambi graduated with her PhD in May 2021 but has stayed engaged with our ongoing work – she’s currently doing postdoctoral studies in clinical genetics at Penn. Aparna is a Bioengineering grad student who plans to work full time during the summer and into the next school year. Jianing is a Penn Vet student who will continue to work with us on the scRNAseq data analysis.

Eileen