LCHAD RETINOPATHY RESEARCH UPDATE

For the Scully Peterson Family Fund for LCHAD Retinopathy Research | Summer 2019

It has been a year of great breakthroughs for our LCHAD Retinopathy research! Thanks to your generous support, we have been able to create the first LCHAD-deficient mouse who carries the common mutation observed among most human patients with LCHAD deficiency. We are working to establish our mouse colony, breeding more animals, and will begin to test the LCAHD-deficient mouse's vision very soon. This animal model will allow us to test new treatments for LCHAD retinopathy, like gene therapy, in an animal model before we begin human clinical trials. This is a critical and necessary step to get FDA approval for a human clinical treatment trial.

In preparation for clinical trials, we have submitted and received funding for a federal grant, "The Natural History of LCHAD Retinopathy". This trial will be funded by the National Institutes of Health (NIH) and follow up to 44 patients with LCHAD deficiency of various ages over a two-year period of time. The data we gather in this five-year project will lay the groundwork for planning and executing a clinical trial in the future.

A host of new LCHAD-deficient retinal pigment epithelium (RPE) cells has been created. We expanded the number of patient skin fibroblasts that we have converted first to stem cells and then to RPE. Just like there is variation among patients with LCHAD deficiency, there is variation among the cells from patients with LCHAD deficiency. To capture that variation and test our treatment (gene therapy) on several different patient cell lines, we created three different LCHAD deficient RPE, two trifunctional protein (TFP) deficient RPE, and three very long-chain acylCoA dehydrogenase (VLCAD) deficient RPE for a comparison group.

We are currently working on three approaches to reversing the effects of the LCHAD deficiency we have observed in our LCHAD deficient RPE cells. First, we are using CRISPR editing technology to correct the genetic mutation. This technique cuts the DNA and "edits" it back to the normal sequence. We expect this to restore the cells to behave and burn fat like normal cells without LCHAD deficiency. Second, we have created tools that will allow us to turn on an added normal LCHAD gene in our LCHAD deficient RPE when needed. This will help us understand some questions surrounding the TFP complex and how it forms which are important for developing our future treatments. Finally, we are also working on developing the viral gene therapy vectors that will express an additional normal copy of LCHAD in our cells to determine if this can restore the cells to behave and burn fat like normal cells.

We have used all of this new information to prepare and submit a grant to the National Institutes of Health for future continued funding of the cell and mouse experiments. The tremendous strides we have made this year are possible thanks to your very generous support. I'm excited about the possibilities of a novel treatment for LCHAD retinopathy in the future.

- Melanie Gillingham, Ph.D., R.D., L.D.