LCHAD RETINOPATHY RESEARCH UPDATE

For the Scully Peterson Family Fund for LCHAD Retinopathy Research | Summer 2018

True to the process of scientific research and discovery, the OHSU team of LCHAD researchers have experienced both successes and some obstacles in their efforts to treat blindness caused by LCHAD Retinopathy. That said, significant progress has been made in the understanding of this disease and how it affects vision, as well as a giant leap in the ability to test effective treatments.

Among the many successes, perhaps the most significant is the development of an LCHAD deficient mouse—the first ever created—AND this mouse has successfully birthed the first litter of mouse pups. These pups and their offspring will be placed on a high fat diet to have their vision evaluated upon maturation at 4 months.

The team has experienced some challenges making more LCHAD deficient retinal pigment epithelium (RPE) from several patient fibroblasts. Treatments will need to be tested for efficacy in human cells, but first the skin fibroblasts need to be reverted back to stem cells which can then be converted into LCHAD RPE for testing. This process has been modified and the issue nearly resolved so that human cells with LCHAD RPE will be available and at the ready for testing the treatment.

The current LCHAD-deficient RPE cells are more resilient than anticipated when exposed to fat. This has made it more difficult to test gene therapies ability to rescue the cells. However, we have embarked on a long-term experiment where we expose the cells to fats every day for 3 months. While labor-intensive and time consuming, this process actually recapitulates the physiologic conditions of the eye in children and adults with LCHAD deficiency and may be very meaningful. This experiment is about 2 months in progress and we hope to have results soon.

Other experiments have also provided very promising and exciting results. We have measured the amount of fatty acid oxidation enzyme proteins in our cells by a technique called a Western Blot. In our LCHAD-deficient and normal or wildtype cells, there are normal and equal amounts of LCHAD protein, as expected, and high amounts of another protein called ACAD9. ACAD9 functions similarly to VLCAD. The presence of the ACAD9 protein may be of particular importance. For many years we have wondered why patients with LCHAD deficiency have retinopathy but patients with VLCAD deficiency do not. It is possible that the first step in fatty acid oxidation in RPE is performed by ACAD9 and not VLCAD. This might be why retinopathy is only seen among patients with LCHAD deficiency and provides another clue about how and why LCHAD retinopathy occurs.

In a toxic clearance assay, we demonstrated that when LCHAD-deficient RPE cells make potentially toxic hydroxy-acylcarnitines, the compounds can be used for energy and degraded by normal or wildtype cells. This is important and we will continue to study this to determine how many normal cells are needed to clear partially oxidized fatty acids such as hydroxy-acylcarnitines. The implication of this clearance experiment is that we may be able to restore LCHAD activity by gene therapy in only a few cells in the retina and those rescued cells would help the whole retina function normally.

Conclusion: To develop a treatment, we need a model in which to test our treatments. Our cell culture models are progressing and we are starting to test treatments in our cell line from one particular patient's skin cells we call J9. We are working on developing other cell lines from other patient's skin cells. The mice are in progress and we should have mice to test our treatments by the end of 2018. We are making progress towards our goal of gene therapy for LCHAD retinopathy and despite progress being slower than anticipated there is more reason for hope than ever before.