

Division of
Bone Marrow Transplantation
and Immune Deficiency

March 7, 2014

To: Liam's Lighthouse Foundation

From: Michael Jordan, MD

Re: Progress report to LLF on supported research project:

"Developing Gene therapy for Hemophagocytic Lymphohistiocytosis"

Investigators: Michael Jordan, Kim Risma, and Punam Malik

We are very grateful to the Liam's Lighthouse Foundation for supporting our efforts to develop transformational therapies for hemophagocytic lymphohistiocytosis (HLH). Your support has allowed us to continue this project during a critical time of extremely tight NIH funding. Below is a description of why we are conducting this research and what we have achieved thus far:

Rationale: HLH treatment consists of two phases: initial immunosuppressive treatment (to halt the destructive disease process), and bone marrow transplant (to prevent recurrence of HLH). We believe that strategies to improve outcomes for children affected by HLH should focus on three goals:

1. Improving diagnosis: this includes raising awareness and research into better understanding and recognizing the HLH disease process.
2. Improving therapies to control HLH: Current therapies to suppress the dangerous immune activation seen in HLH are derived, quite literally, from trial-and-error and are far from optimal. New scientific insights are pointing to better strategies for controlling HLH.
3. Improving and/or replacing bone marrow transplant (BMT) as a long term cure for HLH: BMT carries substantial risks of infection and GVHD (where the donor bone marrow attacks the recipient). Instead of receiving a transplant from another individual, if one could correct the underlying genetic defect (using 'gene therapy') in the patient's own bone marrow, these risks could largely be avoided.

LLF has supported our ongoing research efforts to develop gene therapy for HLH. Our current studies are one step in the long road towards creating this new therapy for patients with HLH.

Gene therapy for HLH: Current gene therapy strategies rely on special viruses (called 'vectors') to transfer a corrected version of the gene of interest into bone marrow stem cells. Once stem cells are corrected, they are transplanted back into the host where they give rise to properly

functioning immune cells. In the case of HLH, abnormalities in several related genes can lead to disease, and more genes are likely to be found as not all patients with HLH have identified defects. However, mutations in the perforin gene are the most common cause of HLH, found in up to half of cases.

All genes have unique patterns of regulation. Because viral vectors transfer an entirely new copy of a gene, they also have to carry their own regulation elements. Thus, it is important to use a vector with not only the corrected gene, but one which also regulates this gene appropriately. When correcting gene defects which block development of immune cells and cause many severe immune deficiencies, this regulation is relatively simple. However, no one has previously tried to correct an immune regulatory disorder, such as HLH, with gene therapy. The regulation of perforin gene expression is quite complex, so we knew that a rigorous test of vector design would be needed prior to proceeding to clinical trials with any vector.

Fortunately, some years ago, we developed the first animal model of HLH in order to better understand this disorder. This sort of model is exactly what is needed to carefully test a gene therapy strategy. Because of our expertise, we are uniquely well situated to develop gene correction strategies, amongst all interested labs in the world. In collaboration with additional experts in gene therapy and perforin function (Drs Malik and Risma in Cincinnati and Drs Baum and Gaspar in Hannover and London) we have been developing and testing perforin gene therapy vectors. Initial studies conducted in tissue culture have been very promising. Over the last 1-2 years we have also been assessing various vectors in our animal model. These studies are quite lengthy, each one taking approximately 6 months. We have found that current generation vectors allow for significant correction of perforin and restoration of immune regulation. However, when we subject these vectors to the most rigorous testing, including challenge with viral infection in experimental animals, we find that they do not completely protect animals from developing HLH.

Thus, we have spent much of the last year working to develop and test a new generation of improved vectors. We believe that we have now found the optimal combination of control elements and are preparing a grant application for resubmission to the NIH later this Spring. If funded, this grant will carry our project to the next level, where we can begin the long process of clinical testing of our approach. During this last year we have also completed and submitted a manuscript for publication (currently under review) detailing our initial findings. Publication will help to spread the word of our initial successes and will be helpful for obtaining funding from the NIH. We anticipate that this year we will complete studies detailing our findings with current vectors and submit a second paper for publication. Both of these manuscripts will acknowledge the important support of Liam's Lighthouse Foundation.

Sincerely,



Michael Jordan MD

Associate Professor of Pediatrics

Divisions of Immunobiology, Bone Marrow Transplant and Immune Deficiency,

Cancer and Blood Diseases Institute, Cincinnati Children's Hospital

(513) 636-7287