September 23, 2013

Dear AILA family,

I am summarizing our progress. I will start by explaining the strategies.
Firstly, Lafora disease is caused by Lafora bodies. We have now proven this without question. Therefore to cure Lafora disease we have two possibilities:

1) Remove Lafora bodies.

2) Prevent further Lafora body formation. For this point, it must be noted that if we stop Lafora body formation, we believe that the brain will itself clear what was already accumulated. We believe that the accumulation of Lafora bodies is a NET accumulation between making and removal. That is, we believe Lafora bodies are being made and removed at the same time, but in Lafora disease more is being made than is being removed, leading to a NET accumulation. Therefore is we stop the making of new Lafora bodies, we will have a NET removal of Lafora bodies, and therefore a cure. Again, we believe there is a good chance that if we stop Lafora body formation, the natural Lafora body removal process will clear the Lafora bodies and result in a cure.

>>>>>>>>>>>>>> Now, where are we in our work in number 1 and in number 2?

1) Remove Lafora bodies.

The only outside thing that can remove Lafora bodies is the enzyme amylase. We are working on finding ways to get this enzyme across the blood-brain barrier into the brain. First we have to show that we can get the enzyme from outside to the inside of cells in Petri dishes, before we try in mouse and then in patients. I am happy to report that we have successfully been able to get from outside to inside the cell. Now, we have to show whether the enzyme, crossing the cell membranes, will maintain its activity and be active inside the cell. This is what we are working on now for this point. If the enzyme is active inside the cell, we will then try our method on the mouse.

2) Stopping Lafora body formation.

We know how to stop Lafora body formation. We now know exactly what enzyme to target for this. The enzyme is called Glycogen Synthase. We are therefore constantly looking for a medication that blocks this enzyme. here, I am happy to report two important progresses:

A) we already have a medication that works in petri dishes. We already know that this medication is safe to use. We are now feeding this medication to mice to see if it will work in the

mice. If it works, we will be extremely happy, because then we can use it directly in our patients. Every day we feed the mice this medication, and we pray that all will go well, day after day. The mice have to be fed by gavage (like they do for ducks to make foie gras). This is necessary to make sure the correct dose is taken by the mouse. This places risk to the life of the mice, and therefore we are constantly anxious that our mice will survive the daily feeding. The poor mice are always scared when we enter the room. But they are getting used to it, and we are very hopeful that they will survive. We have treated them now for 1 month. We need three more months, and then we will sacrifice the mice and study their brains. Of course for our patients, the medication can be given simply by mouth as a normal pill.
At the same time we are constantly looking for other inhibitors of the enzyme in case the one we already found does not work. We have a second potential one right now which we are preparing for mouse study.

B) Another way to bring down the enzymes that make Lafora bodies is to introduce a genetic tool that brings them down. We are collaborating with a company in the US to make this, and I am happy to report that they have succeeded in making one that works in Petri dishes. We will soon try on our mice once they make a sufficient supply.
So, I think we have made great progress. Again, like always, this is only possible with the fundraising help of our families. Almost all our funds come from the families, and the more you help us, the faster we move.
I do realize fundraising causes great difficulties on some of the families, and therefore I hate to ask, but I think we all understand that we need to be open and clear with each other for our common goal.
I hope these notes are helpful to all of you, and my team and I thank you very much and have you and the children always in our hearts and minds.

Berge

April 14, 2013

Dear Linda, dear Chelsea's Hope,

here is an update on our work, in no small part fueled by your efforts.

I will remind you that the great shift in our understanding of what needs to be done to cure Lafora disease happened in 2010, when it became clear from our mouse studies that we need to do one of two things to stop and cure the disease:

1) Reduce the activity of the glycogen synthase enzyme

and/or

2) Introduce amylase into the brain to clear Lafora bodies

For number (1) above we are doing the following:

A) Screen for and test small molecules, including medications already on the market for other diseases, as inhibitors of glycogen synthase. We have identified multiple compounds and are presently testing one in our mice, and will start testing several others within weeks. Meanwhile we are screening continuously and identifying more and more molecules, each of which will go through the now well-established pipeline of testing in mice.

B) We are collaborating with a large company and making antisense oligonucleotides against glycogen synthase and two of its activator molecules. Progress has been great, and we will soon be testing the first oligo in our mice, and the other two to follow shortly thereafter.

For number (2)

To get amylase into the brain to clear Lafora bodies, which we would need to do once every 15 years or so, we are following the following approaches:

A) We are capitalizing on the property of certain bacterial proteins to penetrate across cell and blood brain barrier membranes. We have replaced the bad part of the bacterial protein with amylase. We have shown entry into cells in culture. We are working to translate this into the mouse and see if we can clear Lafora bodies in the mouse.

B) Since we need entry into the brain only once, every 15 years or so, we have started discussions with a well-established lab with proven success in crossing the blood brain barrier using viral vectors. The problem for other brain diseases is that the gene replaced has to be functional for the rest of the patient's life on a daily basis, and most replaced genes get shut down by the brain. In our case, we need the amylase to express briefly, clear the Lafora bodies, and then it would actually be preferable if it shut down. The viral vector approach is therefore perfect for us, and we hope to have the experiments attempting this up and running shortly as we organize the logistics with the collaborating laboratory.

Dear friends, we are not there yet, but our problems are technical in nature, and not fundamental. We hope to overcome them and fulfill Chelsea's, and all the other kids', hopes.

With warmest regards and thanks from all our team.

Berge A. Minassian, MD

January 10, 2013,

Dear parents and friends who care for Lafora patients,

Each of you as a group or individually asked me for an update. I will not write long, because I explained to all of you our therapy projects. 1) We have to find a way to reduce glycogen synthase activity. We know from the mice that if we do this, the disease will stop, and we believe that if the accumulations of Lafora bodies stop, the brain will clear those bodies already formed. We are constantly screening small molecules to find a compound that will do the job. We were very excited with one compound that we had brought to the level of testing in mice. Unfortunately, and you should have seen our sadness that day, it did not work. We have not given up on this compound, we are now testing it at much higher doses. We will see. Meanwhile we continue screening for lots more molecules, and have several good candidates, which are moving up the pipeline towards testing in mice. We hope we will be lucky and get the right drug ASAP. 2) We are working with a company in San Diego, USA who are making for us an siRNA. This is a small piece of RNA (like DNA), which will specifically reduce glycogen synthase activity. They have made great progress, and the compound will likely be ready to be tested in mice within a few months. I am going to San Diego in March to review all the pre-mouse data and bring the compound to Toronto to start testing in our mice. We are very excited with this. 3) We are working to get the amylase into the brain. We have made good progress getting it into cells. We are now testing whether having passed the membranes into the cells, the amylase will work or not. We have good hope that it will. If it does, we can start injecting it into our mice and seeing if it enters the brain and clears the Lafora bodies. This amylase is specially engineered to cross the blood brain barrier and the cell membranes and enter the brain cells. If this approach works, we will need one injection every 15 years or so to keep our children healthy. This is the most challenging of our experiments, but we if it works, the reward is huge, because it is potentially a cure. This is where we are, and we would not be anywhere near here without your help. I feel very good to say this is where WE are. I feel we have come here together, each of you and all members of our team in the lab. I wish you all a good new year. Please do not hesitate to ask me anything anytime.

Berge