20/1/20

To: AILA (Italian Lafora Disease Association)

Dear friends at the AILA family,
I've been working on Lafora disease for 25 years. I started doing so during my Neurology training when I saw my first patient, and I could not stop, and as long as I can will not stop, trying to understand, and eliminate this disease.

Our current work proceeds along two fronts:

1) Understand why and how Lafora bodies form in the brain of patients with this disease. This is detailed biochemical and molecular biology work going deeper and deeper into mechanisms of glycogen formation and glycogen architecture. Along with colleagues we have made major advances in understanding this critical aspect of bioenergetics of the human brain. These advances will help understand the brain and how it stores and derives its energy for purposes well beyond Lafora disease. As such, our exceedingly unfortunate Lafora patients are teaching us a lot about our brains, which means ourselves, and this progress will have relevance to many other more common diseases, including neurodegenerative diseases of the brain, such as Alzheimer disease, and many common epilepsies. The progress in uncovering the basic mechanisms also is critical, because a clear understanding of pathogenesis is the surest way to a therapy.

2) While we explore the root mechanisms of Lafora disease to help patients of the future, we've urgently needed to help patients of today. As such, we've taken advantage of our discoveries of the disease genes to find treatments that do not require a comprehensive understanding of the pathology. This includes but is not limited to: antisense oligonucleotides (ASO) and Gene Replacement Therapy. The ASO work is now so advanced that we've essentially stopped the disease in its mouse model and are now preparing for a human clinical trial with an industry partner. I am so excited and hopeful that in one year or thereabouts Lafora patients will finally have a treatment to stop the disease. While the ASO therapy will be, we hope, a life-saver, it will not be easy for the patients, because they will need to receive lumbar puncture injections every three months lifelong. We would very much like to perfect a Gene Replacement Therapy approach, because in that case, once the missing gene is replaced, the patient is 'whole again', with a single injection. Currently, gene therapy approaches allow transfer of the correct gene to only approximately 20% of brain cells. Our very active research area now is to find ways to transfer the gene to closer to 100% of cells.

In summary, our research would greatly benefit from ongoing support from AILA and other sources in support of work towards a comprehensive understanding of the basis of the disease, and work towards improving the gene therapy technology to allow us correction of all or most of the brain.

Yours sincerely,

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