April 26, 2018

Dear Friends in the UK,

It is always nice to “see” you. It is my honor and privilege to work with you and develop breakthrough treatments for Wolfram syndrome. Thank you so much for following my mission & vision. I would like to update you about our ongoing clinical trial.

Our first clinical trial of a re-purposed drug, dantrolene sodium, in patients with Wolfram syndrome is ongoing. We have been monitoring the safety, tolerability, and efficacy of dantrolene sodium in 19 patients who have qualified for the study. We have both male and female participants in pediatric and adult populations. You can find the information about the inclusion and exclusion criteria on the website https://wolframsyndrome.dom.wustl.edu/.

The planned duration of oral dantrolene sodium administration in this study is six months, with an optional extension phase up to 24 months. The planned overall duration of each patient’s participation in this study is nine months. For participants who continue in the optional extension phase, the planned overall duration is up to 27 months (screening, study drug dose maximization, outcome measure evaluation, and final safety follow-up).

All the participants are required to come to our clinic nine times in the first six months to determine the appropriate dose and ensure the safety. After the first six months, participants come to our clinic every six months up to 24 months. As of today, 19 patients have been taking dantrolene sodium for more than six months. In addition to safety and tolerability, we assess our participants’ visual acuity, remaining beta cell functions (i.e., their ability to produce insulin from their own pancreases), and neurological functions. Based on our initial analysis, our participants’ remaining beta cell functions improved by 37% after the 6-month treatment. Their visual acuity did not change. Please note that our clinical trial does not include a placebo arm and all the participants are taking dantrolene sodium. Thus, we should be careful about the interpretation of the results.

As our current trial is going well and we are achieving our milestones, I have started preparing for the next phase of this trial. I am considering the following possibilities:

1. A longer duration, multicenter trial with more participants.
2. Include the placebo arm. I understand that nobody wants to take the dummy drug for a long period of time, so I have been getting advice from medical officers conducting clinical trials for rare diseases on how to manage this.

In addition to dantrolene sodium, my research team has been looking into two new drugs for Wolfram syndrome. Unlike dantrolene sodium, these drugs are new, so we need to carefully collect more data from mouse models of Wolfram syndrome and healthy human subjects. To accelerate the pace of our study, I am creating humanized Wolfram mice and rats. These mice and rats carry human Wolfram syndrome gene mutations and quite useful for testing new

treatments. I am aware that we need to find a way to improve visual acuity. I have been developing a regenerative gene therapy for optic nerve degeneration using a novel neurotrophic factor in combination with gene transfer technology. A pre-clinical study in mice is ongoing, and I hope that this will be a breakthrough therapy for optic nerve degeneration in patients with Wolfram syndrome and other eye disorders that can lead to blindness.

In addition, I have been developing “genetic testing” for screening Wolfram syndrome and Wolfram-related diseases. I believe that Wolfram syndrome is an underdiagnosed disease. Using a single tube of blood, I would like to provide an accurate diagnosis. An accurate diagnosis serves as a basis for targeted therapy. An accurate diagnosis provides a sense of relief.

As always, please feel free to contact me with any questions or concerns (urano@wustl.edu). I would like to know what you think and how you feel. Thank you again for your support. Our potential is limitless. We have superpower to overcome this challenge.

With passion, hope, and gratitude,
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