

May 29, 2021

Dear Friends in the UK,

Hello everyone. I pray you're in great spirits. Everyone in my research team has been vaccinated for COVID-19, and we are working very hard to develop novel treatments for Wolfram syndrome. Although our past has been harsh, our future looks brilliant now. I continue adhering to my three guiding principles: 1. Improve clinical care, 2. Raise awareness, and 3. Provide a cutting-edge treatment for Wolfram syndrome. Here are our updates.

### **An Upcoming Trial**

As I repeatedly mentioned in the past, a repurposed drug could be just a sticking plaster for Wolfram. So, we need a cutting-edge treatment designed explicitly for Wolfram syndrome. We have been focusing our efforts on developing AMX0035 to treat Wolfram syndrome with Amylyx in Cambridge, Massachusetts, in the US. AMX0035 targets endoplasmic reticulum stress (a molecular mechanism of Wolfram) and mitochondria dysfunction. A recent clinical trial of AMX0035 in patients with ALS, an adult-onset neurodegenerative disorder, was successful. Our pre-clinical data using induced pluripotent stem cells (iPSCs)-derived brain cells of Wolfram syndrome and Wolfram mice were positive. These considerations raise the possibility that AMX0035 is a promising medication for patients suffering from Wolfram syndrome. US FDA granted an orphan drug designation of AMX0035 for the treatment of Wolfram syndrome in October 2020. So, we are moving forward to a clinical trial.

Based on what I learned from Prof. Barrett's clinical trial in Europe, Dr. Hershey's research clinic in St. Louis, and our dantrolene trial in St. Louis, I designed a new trial protocol for AMX0035 with Dr. Patrick Yeramian and Dr. Jamie Timmons at Amylyx and Dr. Tamara Hershey at Washington University. Dr. Bess Marshall at Washington University kindly shared unpublished data with us, and Mrs. Hongjie Gu performed extensive statistical analyses to calculate the number of patients and duration of the study needed for the trial. Dr. Kent Leslie and Dr. Mabelle Manuel have been working with patients to create a patient advisory board for the trial. I have been discussing the fundraising strategy for the trial with Mr. Josh Cohen and Mr. Justin Klee, co-CEOs of Amylyx. Our trial protocol was submitted to the US FDA last week, and I sincerely hope that FDA will allow us to start a trial soon. The trial with AMX0035 is a significant development. Please stay tuned.

### **Regenerative Gene Therapy**

Our ultimate goal is to provide a cure by regenerative gene therapy. We have been trying to improve visual acuity and brain functions using viral vectors of a healthy Wolfram gene (WFS1) and a regenerative factor called MANF in rodent models of Wolfram and Wolfram iPSC-derived neurons and retinal ganglion cells. We are getting encouraging preliminary results. My goal is to start a trial in the next 3-7 years. It all depends on the fund and results of our pre-clinical studies.

### **Base Editing Gene Therapy**

We have been working with Dr. David Liu's team at Harvard University/Broad Institute and Dr. Catherine Verfaillie and Dr. Lieve Moons' teams at the Katholieke Universiteit Leuven to develop a novel gene therapy called Base Editing. This technology uses some components from CRISPR systems together with other enzymes to directly replace the abnormal WFS1 gene with the normal WFS1 gene. Our first set of experiments using iPSC from Wolfram patients was a success. We hope that we can bring this technology to our patients in the next 3-7 years.

### **Wolfram Genetics Clinic**

To improve the clinical care for patients with Wolfram syndrome and Wolfram-related disorders, I created a new genetics clinic at the Center for Advanced Medicine, Washington University Medical Center, in 2020. We offer genetic evaluations, education, and counseling for patients and family members of all ages with or suspected to have Wolfram syndrome or WFS1-related disorders. We also provide personalized management plans based on the type of your gene variants together with other specialists at our medical center, such as Dr. Marshall. Wolfram syndrome Research Alliance and the Snow Foundation have been referring patients to us (<https://wolframsyndrome.wustl.edu/>). We accept international patients. Please call +1-314-747-7300 to make an appointment.

I have been working super hard. I welcome any feedback or questions ([urano@wustl.edu](mailto:urano@wustl.edu)). We will work as one team and make a difference together. Thank you for your faith in my work.

Sincerely,  
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Attending physician at Barnes Jewish Hospital  
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