

September 11, 2020

Dear Friends in the UK,

I pray you and your family are safe and in good spirits. This year has been challenging for all of us, and I hope you will leverage this challenge further to upgrade your soul, kindness, and strength. Thank you for your emails in the last few months. Your kind words and encouragement keep me motivated and inspired.

My three guiding principles are: Improve clinical care, Raise awareness, and Provide a cutting-edge treatment for Wolfram syndrome. Here is our progress:

### **A Drug-Repurposing Clinical Trial**

Our drug-repurposing clinical trial of dantrolene sodium in patients with Wolfram syndrome has been almost concluded. Nineteen patients could successfully complete the required six-month phase, and many of them decided to stay on dantrolene sodium another 18 months. The results of this open-label clinical trial (all the participants took dantrolene sodium) show that dantrolene sodium is well tolerated by patients with Wolfram syndrome. Although the study was small, a select few patients seemed to have improvements in diabetes-related outcomes, which might correlate with a positive trend in other outcome measures, including visual acuity and brain functions. This study justifies further investigation into using dantrolene sodium and other new drugs targeting the same molecular pathway for the treatment of Wolfram syndrome.

### **Novel Drugs – A New Trial**

We are aware that a drug-repurposing is not the best approach to halt the progression of Wolfram syndrome. We need cutting-edge treatments designed explicitly for Wolfram syndrome. Based on the clinical trial data of dantrolene sodium in patients with Wolfram syndrome, we have been actively developing novel drugs targeting ER stress in collaboration with the drug development team at the National Institutes of Health (NIH)/National Center for Advancing Translational Sciences in the United States and a few biotech companies. We are currently focusing our efforts on developing AMX0035 with Amylyx in Cambridge, MA, to treat Wolfram syndrome. A recent clinical trial of AMX0035 in patients with ALS was a success. We are aiming at a multi-center international trial of AMX0035 for Wolfram syndrome as I have learned a lot from Dr. Barrett's clinical trial in Europe and Dr. Hershey's research clinic in St. Louis to design a trial. The trial with AMX0035 is a significant development, and I plan to keep you updated. We have also started working on ibudilast with Professor Ehrlich at Yale University and are establishing a collaboration with Mitochon Pharmaceuticals.

## **Regenerative Gene Therapy**

My current focus is to develop gene therapy for Wolfram syndrome. Our ultimate goal is to provide a cure using regenerative gene therapy. We have been trying to improve diabetes, visual acuity, and brain functions using viral vectors of a healthy Wolfram gene and a regenerative factor called MANF in mouse and rat models. We are getting encouraging preliminary results and have published two articles recently. We are currently testing two ways to deliver genes through intravitreal (for optic nerve) and intraventricular (for brain) injections.

## **Base Editing Gene Therapy**

In collaboration 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, we have been developing a novel gene therapy called Base Editing for Wolfram syndrome. This technology uses some components from CRISPR systems together with other enzymes to directly replace abnormal WFS1 gene with normal WFS1 gene. Although we are still at the early preclinical stage using cell models of Wolfram, we hope that we can bring this technology to our patients in the next 3-10 years. Eye Hope Foundation has been facilitating this important collaboration. Please stay tuned.

## **New Genetics Clinic**

To further improve the clinical care for patients with Wolfram syndrome and Wolfram-related disorders, I have created a new genetics clinic at Center for Advanced Medicine, Washington University Medical Center. 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/>).

As always, please feel free to contact me with any questions ([urano@wustl.edu](mailto:urano@wustl.edu)). I would like to know what you think and how you feel. Thank you again for your continued support and encouragement. I am thankful for everything Wolfram UK and friends in UK have done for patients, families, and researchers. We will go through this challenging period with unusual optimism and courage. I have no doubt better days are ahead. We will continue working as one team and change history together.

Sincerely,  
Fumi Urano, MD, PhD  
Samuel E. Schechter Professor of Medicine  
Barnes-Jewish Hospital  
Washington University School of Medicine

