

February 2021

Dear Friends in the UK,

I wish and pray that 2021 is a year of splendid health and big success for you. Despite all the uncertainty, troubles, and challenges on our planet, I have focused my mind and efforts on helping and saving our patients with Wolfram syndrome and WFS1-related disorders. I have been adhering to my three guiding principles: 1. Improve clinical care, 2. Raise awareness, and 3. Provide a cutting-edge treatment for Wolfram syndrome.

I wanted to write this blog for you because we have exciting updates.

A Drug-Repurposing Clinical Trial of Dantrolene Sodium

Nineteen patients completed the required six-month phase, and many of them decided to stay on dantrolene sodium another 18 months. You can find the results of this open-label clinical trial here - <https://www.medrxiv.org/content/10.1101/2020.10.07.20208694v1>. In short, the results show that patients with Wolfram syndrome were well tolerated with dantrolene sodium. 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. Dantrolene sodium appears to have multiple targets in addition to the endoplasmic reticulum, a therapeutic target of Wolfram syndrome. Thus, we need second-generation dantrolene, which would be a more specific regulator for the endoplasmic reticulum. Because dantrolene sodium is not a specific regulator, we probably need to increase the dose of dantrolene to make it more effective, especially for patients who have severe manifestations. However, dantrolene sodium may cause liver damage if we increase the dose. We may still use it for patients who have milder symptoms, and this should be investigated further.

An Upcoming Trial

A repurposed drug could be just a sticking plaster for Wolfram. So, as you can imagine, we need cutting-edge treatments designed explicitly for Wolfram syndrome. We are currently focusing our efforts on developing AMX0035 with Amylyx in Cambridge, MA, USA, to treat Wolfram syndrome. The targets of AMX0035 are the endoplasmic reticulum and mitochondria. A recent clinical trial of AMX0035 in patients with ALS was a success, and pre-clinical data using induced pluripotent stem cells (iPSCs)-derived brain cells of Wolfram syndrome was positive. Thus, US FDA has granted an orphan drug designation of AMX0035 for the treatment of Wolfram syndrome. I have learned a lot from Prof. Barrett's clinical trial in Europe and Dr. Hershey's research clinic in St. Louis to design a new trial for AMX0035, and we are aiming at a multi-center international trial of AMX0035 for Wolfram syndrome. 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 diabetes, visual acuity, and brain functions using viral vectors of a healthy Wolfram gene (WFS1) and a regenerative factor called MANF in mouse and rat models. We are getting encouraging preliminary results and have published two articles recently.

<https://www.nature.com/articles/s41374-020-0436-1>

<https://www.ncbi.nlm.nih.gov/pmc/articles/PMC7233417/>

We are currently testing the efficacy of AAV-MANF on optic nerve atrophy in rodent models of Wolfram. We hope to update you on this soon.

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 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. We are getting encouraging pre-clinical data using iPSC models.

New Genetics Clinic is up and running.

To improve the clinical care for patients with Wolfram syndrome and Wolfram-related disorders, I created a new genetics clinic at the Centre for Advanced Medicine, Washington University Medical Centre. 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 centre, 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.

As always, please feel free to contact me with any questions (urano@wustl.edu). I would like to know what you think and how you feel. Thank you for your faith in my work. We will work as one team and make a difference together.

Sincerely,

Fumi Urano, MD, PhD

Samuel E. Schechter Professor of Medicine

Attending physician at Barnes Jewish Hospital

Washington University School of Medicine