August 22, 2021

Dear Friends in the UK,

I pray you're in superb spirits. Our lab has been 100% functional and welcomed three new research team members lately. So, we are ready to accelerate our progress. 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

We just published the data of our drug-repurposing trial using dantrolene sodium in the Journal of Clinical Investigation Insight (https://insight.jci.org/articles/view/145188). This is an open-access article, and anyone can read it at no cost. Although the results were not what we had hoped, I learned a lot from this trial, which will help us design a new trial. As I repeatedly mentioned in the past, a repurposed drug could be just a band-aid for Wolfram. So, we need a new medication designed explicitly for Wolfram syndrome.

As you know, we have been focusing our efforts on developing AMX0035 for the treatment of 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 (https://www.nytimes.com/2020/10/16/health/ALS-treatment.html). Our pre-clinical data using induced pluripotent stem cells (iPSCs)-derived brain cells of Wolfram syndrome and Wolfram mice were positive, and we plan to publish the data soon. US FDA granted an orphan drug designation of AMX0035 for the treatment of Wolfram syndrome in October 2020. We submitted our clinical trial plan to the US FDA late May, 2021, and received their feedback late July, 2021. We are making steady progress to start this trial.

Our clinical trial of AMX0035 in patients with Wolfram syndrome has been designed based on Prof. Barrett's clinical trial design in Europe, Dr. Hershey's research clinic data in St. Louis, and our dantrolene trial design and data in St. Louis. I have been closely working 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 Bess Marshall at Washington University kindly shared unpublished data with us, and Mrs.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. Machelle Manuel at Amylyx have been working with patients to create a patient advisory board for the trial. Ms. Allison Lusis has been assigned to this important project as a lead for the regulatory affairs. My nurse coordinator, Mrs. Stacy Hurst, RN, and lab manager, Mrs. Cris Brown, are ready to conduct this at our medical center. I have been discussing the fundraising strategy for the trial with Mr. Josh Cohen and Mr. Justin Klee, co-CEOs of Amylyx. I have also identified potential grant support from the National Institutes of Health (NIH) and discussed this with a few NIH officers. I will keep on doing my best to start this trial as soon as possible.

Regenerative Gene Therapy

I am aware that we need a strategy to regenerate damaged tissues in patients with Wolfram syndrome, and my tool to accomplish this goal is to develop 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. Our new preliminary results are encouraging. 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

The best way to treat genetic disorders is gene-editing or base-editing-based therapy for sure. We have been working with Dr. David Liu's team (Dr. Gregory Newby) 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 using 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. We have been getting positive results using iPSCs from Wolfram patients. I 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, the Snow Foundation, and the Ellie White Foundation have been referring patients to us (https://wolframsyndrome.wustl.edu/). We accept international patients via our international patient care office. Please call +1-314-273-3780 to make an appointment. US patients can call +1-314-747-7300 to make an appointment.

I have been doing my best to save our patients. I welcome any feedback or questions (urano@wustl.edu). We will work as one team and make a difference together. Thank you for your faith in my work.

Sincerely,
Fumi Urano, MD, PhD
Samuel E. Schechter Professor of Medicine
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