

May 30, 2022

Dear Friends in the UK,

I'd like to begin by thanking all of you for your support, trust, and faith in me. I work very, very hard to provide the best clinical care and develop safe and effective treatments for patients with Wolfram syndrome. Here are my updates. I trust you read them with hope and credulity.

Upcoming clinical trial

As all of us know, we need new treatments and therapeutic modalities for Wolfram syndrome, including oral medications, gene therapy, and regenerative therapy. I have been focusing my efforts on developing a new drug, AMX0035, to treat Wolfram syndrome in collaboration with Amylyx Pharmaceuticals in Cambridge, Massachusetts. AMX0035 targets endoplasmic reticulum stress (a molecular mechanism of Wolfram) and mitochondrial dysfunction. Our pre-clinical study using cell and rodent models of Wolfram syndrome was a success, and we have deposited the data to the public server (<https://www.biorxiv.org/content/10.1101/2021.11.07.467657v1>). In addition, we conducted additional studies using cells from our patients, and the data will be published in a medical research journal soon.

US FDA granted an orphan drug designation of AMX0035 to treat Wolfram syndrome in late 2020. We designed a clinical trial plan based on the longitudinal study data and dantrolene clinical trial data. We have been carefully crafting our protocol to ensure the safety of our patients and assess the efficacy of AMX0035 accurately. I spend a certain amount of time every single day on this project with medical officers at Amylyx and my colleagues at Washington University. We have been communicating with US FDA and plan to start a trial later this year. The official announcement will come from Amylyx. Please stay tuned.

Regenerative Therapy for Optic Nerve Atrophy – Gene Therapy and Stem Cell Transplantation

My strategy is two-fold. First, I want to stop/delay the progression of Wolfram syndrome using oral medications. I will then restore functions of retinal ganglion cells, brain cells, and insulin-producing cells by regenerative therapy. Our first target is **vision**. We have been trying to improve visual acuity using viral vectors expressing a healthy Wolfram gene (WFS1) and a regenerative factor called MANF in cell and rodent models of Wolfram syndrome. We also plan to test stem cell transplantation to improve vision in rodent models of Wolfram syndrome. My goal is to start a regenerative therapy trial in the next 3-7 years.

Prime Editing Therapy

Correct gene mutations are the best way to treat genetic disorders, including Wolfram syndrome. Instead of CRISPR or base-editing, we have started using Prime Editing to correct WFS1 gene mutations in Wolfram syndrome. This is a newer version of gene editing, considered the best gene editing technology available to date. We can now test the technology in high-quality Wolfram syndrome iPSC-derived retinal ganglion cells. We are doing our best to make rapid progress in this project.

Clinical service

To improve the clinical care for patients with Wolfram syndrome and Wolfram-related disorders, we run the WFS1 clinic at the Center for Advanced Medicine, Washington University Medical Center. This clinic has been successful, and I see patients from different states and countries almost every week. The Snow Foundation, the Ellie White Foundation, the Unravel Wolfram Syndrome, and the FB groups related to Wolfram syndrome have referred patients to our clinic, which I appreciate. We offer genetic evaluations, education, and counseling for patients and family members of all ages with or suspected to have Wolfram syndrome and WFS1-related disorders. We also provide personalized management plans with other specialists at our medical center and beyond. We accept international patients via our international patient care office. We also accept out-of-state patients. To make an appointment, please call +1-314-273-3780. US patients can call 314-362-3500 to make an appointment. Our medical center has been selected as a Rare Disease Center of Excellence, and we have excellent specialists.

Thank you for supporting Wolfram Syndrome UK. Let's work as one team and make a difference together.

Sincerely yours,
Fumi

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