November 27, 2022

Dear Friends in the UK,

I hope you are well. I always feel your continued support and faith in me, which I appreciate. Here are my updates. We are making steady progress.

Upcoming clinical trial

We all know that we need novel treatments and therapeutic modalities for Wolfram syndrome, including oral and injectable medications. One of my strategies is to target the upstream disease mechanism and delay the progression of symptoms related to Wolfram syndrome, including optic nerve atrophy, neurodegeneration, and diabetes, using oral medication. I have been focusing on developing a new oral medication, AMX0035, to treat Wolfram syndrome in collaboration with Amylyx Pharmaceuticals in Cambridge, Massachusetts. AMX0035 targets endoplasmic reticulum stress and mitochondrial dysfunction (upstream molecular mechanisms of Wolfram syndrome). We have just published an article related to this project in a first-medical journal, and you should be able to read it at no cost (https://insight.jci.org/articles/view/156549).

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 to assess the efficacy of AMX0035 accurately based on the feedback from the US FDA and the patient board. We are working hard to start a trial in the next few months. Please stay tuned.

Gene Editing Therapy

The root cause of Wolfram syndrome is a pathogenic change in the WFS1 gene. Therefore, to correct these changes in the WFS1 gene are the best way to treat Wolfram syndrome. Instead of CRISPR, we have been using a next-generation gene editing technology, Base Editing, in collaboration with Dr. Catherine Verfaillie and Dr. Lieve Moons at Katholieke Universiteit Leuven in Belgium. Our preclinical study using iPSCs derived from Wolfram patients were successful. We plan to test this technology in our humanized mouse model of Wolfram syndrome.

In addition to Base Editing, we have been also testing Prime Editing to correct WFS1 gene pathogenic changes in Wolfram syndrome because of safety reasons. This is the newest version of gene editing, considered the best gene editing technology available to date. We have been collaborating with Dr. David Liu's team at Harvard/MIT on this project. Our ultimate goal is to use this therapeutic modality for our patients.

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

We have been trying to stop and reverse the progression of optic nerve atrophy by regenerative medicine. We have two strategies. The first strategy is to introduce a regenerative factor called MANF into eyes of Wolfram syndrome patients using a viral vector. MANF is a unique factor that

confers protection against ER stress and enhances proliferation of ER stressed cells. The second strategy is to inject mesenchymal stem cells into eyes of our patients. We can isolate mesenchymal stem cells from our fat cells and bone marrow. It has been shown that mesenchymal stem cell transplantation promotes retinal ganglion cell survival and regeneration in a rodent model of optic nerve damage. Preclinical studies using cell and rodent models of Wolfram testing MANF and mesenchymal stem cells for the treatment of optic nerve atrophy are ongoing. My goal is to start a regenerative therapy trial for optic nerve atrophy in the next 3-7 years.

Clinical service

To improve the clinical care for patients with Wolfram syndrome and WFS1-related disorders, including WFS1-related deafness and optic nerve atrophy, we have been running 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, Wolfram UK, 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. If you are a non-US patient, please call +1-314-273-3780 or send an email to WolframSyndrome@wustl.edu to make an appointment. US patients can call 314-362-3500 to make an appointment. Please make sure to tell a scheduler that you have Wolfram syndrome. Our medical center has been selected as a Rare Disease Center of Excellence (https://pediatricgeneticsgenomics.wustl.edu/clinical-care/nord-rare-disease-centers-of-excellence/), and we have excellent specialists.

Thank you for supporting Wolfram Syndrome UK. I plan to visit UK next year to meet with you. Let's keep on working as one team and make a difference together. See you soon!

Sincerely yours,
Fumi

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