August 28, 2022

Dear Friends in the UK,

You are my heroes. When I am stressed and tired, I go to emails and social media posts from our patients and families. These emails and posts give me a reason to keep on going. I always appreciate your continued support and faith in me. Here are my updates.

Upcoming clinical trial

We need new treatments and therapeutic modalities for Wolfram syndrome, including oral and injectable medications for optic nerve atrophy and neurological issues. 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 and mitochondrial dysfunction (molecular mechanisms of Wolfram syndrome). The results of our pre-clinical studies using iPS cells from our patients of Wolfram syndrome were encouraging, and we have deposited the data to the public server (https://www.biorxiv.org/content/10.1101/2021.11.07.467657v1).

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 based on the feedback from the US FDA and the patient board. We are working very hard to start a trial this year. Please stay tuned.

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

Our current focus is 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.

Prime 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 started using Prime Editing to correct WFS1 gene pathogenic changes in Wolfram syndrome because of safety reasons. 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 iPS cells and iPSC-derived retinal ganglion cells. We have created rodent models that have pathogenic changes in the Wfs1 gene, humanized Wolfram mice and rats, to test this technology. Our ultimate goal is to use this therapeutic modality for our patients.

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, 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 or send an email to WolframSyndrome@wustl.edu. US patients can call 314-362-3500 to make an appointment. 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 am always impressed by their hard work and dedication, and Mrs. Tracy Lynch, Mr. Paul Lynch, and other staff members, such as Mr. Alan Nye, are my heroes. I plan to visit UK soon to meet with you. Let’s keep on working as one team and make a difference together. Thank you again!

Sincerely yours,
Fumi

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