February 28, 2022

Dear Friends in the UK,

Hello,

It is always nice to “see” you. As I write this message to you, I am feeing your support, trust, and faith in me. I keep on doing my best to provide the best clinical care and develop safe and effective treatments for patients with Wolfram syndrome. Here are my updates, and I feel hopeful.

Upcoming clinical trial

In the past, I looked for existing drugs that could be beneficial for patients with Wolfram syndrome. This effort led to a few clinical trials, but a repurposed drug could be just a band-aid for Wolfram, and we need a new medication for Wolfram syndrome. I have been focusing my efforts on developing a new drug, AMX0035, for the treatment of Wolfram syndrome in collaboration with Amylyx Pharmaceuticals in Cambridge, Massachusetts. They have been collaborative and generous. AMX0035 targets endoplasmic reticulum stress (a molecular mechanism of Wolfram) and mitochondrial 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 study using cell and rodent models of Wolfram syndrome was positive. We have deposited the data to the public server (https://www.biorxiv.org/content/10.1101/2021.11.07.467657v1) and plan to publish it in a medical research journal soon.

US FDA granted an orphan drug designation of AMX0035 for the treatment of Wolfram syndrome in late 2020. We submitted our clinical trial plan to the US FDA and received their feedback in the late summer of 2021. We have examined our longitudinal study data and dantrolene clinical trial data extensively and have created an innovative clinical trial 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 hope to start a trial late summer of 2022. Please stay tuned.

Regenerative Gene Therapy for Optic Nerve Atrophy

My strategy is to stop/delay the progression of Wolfram syndrome using oral medications and restore functions of retinal ganglion cells, brain cells, and insulin-producing cells by regenerative gene 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. Our preliminary results are encouraging. Dr. Venu Gurrum has recently joined my lab to accelerate the progress of this project. He is an expert in gene therapy for inherited optic nerve atrophy. My goal is to start a gene therapy trial in the next 3-7 years.

Gene-editing and Base-editing Therapy

The best way to treat genetic disorders is gene-editing or base-editing-based therapy. We have been working with Dr. David Liu's team at Harvard University/Broad Institute and Dr. Catherine Verfaillie's team 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 are making steady progress, and I hope that we can bring this technology to our patients in the next 3-7 years.

Genotype-Phenotype relationship and a new drug target

We are pleased to announce that Dr. Saumel Ahmadi, a pediatric neurology resident at Washington University Medical Center, is joining my research team and will be developing a new method to study the genotype-phenotype relationship in Wolfram syndrome. He will also use the same method for identifying new drug targets for the treatment of Wolfram syndrome.

Clinical service

To improve the clinical care for patients with Wolfram syndrome and Wolfram-related disorders, I have been running the WFS1 clinic at the Center for Advanced Medicine, Washington University Medical Center. This clinic has been incredibly 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 my clinic, which I really 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 based on the type of gene variants our patients have in collaboration with other specialists at our medical center. 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 (this is a new number) 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. February 28th is Rare Disease Day this year, and Every day is Rare Disease Day, Wolfram syndrome day, for me. Let's work as one team and make a difference together.

Sincerely yours,
Fumi

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