February 27th, 2023

Dear Friends in the UK,

As spring approaches, I wanted to take a moment to thank you for your continued support and faith in me. Your encouragement has meant so much, and I am truly grateful for it. I would like to provide you with a quick update on my progress. I am happy to report that we are making steady strides and moving in the right direction.

Upcoming clinical trial

There is a pressing need for new treatments and therapeutic modalities for Wolfram syndrome, including oral and injectable medications. One promising strategy is to target the upstream disease mechanisms and delay the progression of symptoms associated with Wolfram syndrome, such as optic nerve atrophy, neurodegeneration, and diabetes, using oral medication.

To this end, we have been focusing on developing a new oral medication, AMX0035, in collaboration with Amylyx Pharmaceuticals in Cambridge, Massachusetts. AMX0035 targets endoplasmic reticulum stress and mitochondrial dysfunction, which are upstream molecular mechanisms of Wolfram syndrome. We recently published an article related to this project in a leading medical journal, which is available to read for free at this link: https://insight.jci.org/articles/view/156549.

The US FDA granted an orphan drug designation for AMX0035 to treat Wolfram syndrome in late 2020. Based on longitudinal study data and dantrolene clinical trial data, we have designed a clinical trial plan and have been carefully crafting our protocol to ensure the safety of our patients and to accurately assess the efficacy of AMX0035. We are excited to announce that our trial protocol has been approved by the US FDA and the Washington University Medical Center Institutional Review Board. With this approval, we are now one step closer to starting our clinical trial for the treatment of Wolfram syndrome. Following completion of the site initiation requirements, we plan to initiate the trial within the next month. We have worked tirelessly to ensure that our trial is conducted with the utmost care and efficacy, incorporating feedback from the US FDA and the patient board.

We will continue to provide updates on our progress and look forward to advancing the field of Wolfram syndrome treatment.

Gene Editing Therapy

Wolfram syndrome is caused by pathogenic changes in the WFS1 gene. The most effective way to treat this condition is to correct these changes in the gene. Instead of CRISPR, our team has been collaborating with Dr. Catherine Verfaillie and Dr. Lieve Moons at Katholieke Universiteit Leuven in Belgium to use the next-generation gene editing technology, Base Editing. Our preclinical study using iPSCs derived from Wolfram patients has been successful, and we plan to test this technology in our humanized mouse model of Wolfram syndrome.

For safety reasons, we have also been testing Prime Editing to correct WFS1 gene pathogenic changes in Wolfram syndrome. This is considered the best gene editing technology available to date, and we have been collaborating with Dr. David Liu's team at Harvard/MIT on this project. Our goal is to use this therapeutic modality to treat our patients.

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

We are investigating regenerative therapy as a means to halt and potentially reverse the progression of optic nerve atrophy. We have developed two strategies for this purpose.

The first involves the introduction of a regenerative factor called MANF into the eyes of patients with Wolfram syndrome using a viral vector. MANF is a unique factor that offers protection against ER stress and enhances the proliferation of ER-stressed cells.

The second strategy involves the injection of mesenchymal stem cells into the eyes of patients. We can isolate these cells from adipose tissue and bone marrow. Studies have shown that mesenchymal stem cell transplantation promotes retinal ganglion cell survival and regeneration in rodent models of optic nerve damage.

Ongoing preclinical studies are testing both the MANF and mesenchymal stem cell approaches in cell and rodent models of Wolfram syndrome, to evaluate their efficacy in treating optic nerve atrophy. Our goal is to launch a clinical trial for regenerative therapy in optic nerve atrophy within the next 3-7 years.

Clinical service

To improve clinical care for patients with Wolfram syndrome and related disorders, including WFS1-related deafness and optic nerve atrophy, we established the WFS1 clinic at the Center for Advanced Medicine, Washington University Medical Center. This clinic has been highly successful, with patients coming from different states and countries almost every week. We are grateful to the Snow Foundation, the Ellie White Foundation, Unravel Wolfram Syndrome, Wolfram UK, and Facebook groups related to Wolfram syndrome for referring patients to us.

We provide genetic evaluations, education, and counseling to patients and family members of all ages who have, or are suspected to have, Wolfram syndrome and WFS1-related disorders. We also offer personalized management plans in collaboration with other specialists at our medical center and beyond. We welcome international patients through our international patient care office and out-of-state patients. Non-US patients can schedule an appointment by calling +1-314-273-3780 or sending an email to WolframSyndrome@wustl.edu. US patients can call 314-362-3500 and let the scheduler know that they have Wolfram syndrome.

Washington University Medical Center has been recognized as a Rare Disease Center of Excellence (https://pediatricgeneticsgenomics.wustl.edu/clinical-care/nord-rare-disease-centers-of-excellence/) with excellent specialists who are committed to providing exceptional care to our patients.

Thank you for your support of Wolfram UK. I'm excited to announce that I plan to visit the UK this September to meet with you in person. Let's continue to work together as a unified team and make a real difference. I can't wait to see you soon!

Sincerely yours,
Fumi

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