November 29, 2021

Dear Friends in the UK,

We live in a time of tumult. Many are wary of all the negativity, but I am incredibly positive and energetic and committed to making a difference. Our lab is 100% functional, and we are making steady progress. Here is a summary of our research progress.

RESEARCH ACTIVITIES

A Drug-Repurposing Clinical Trial

Our drug-repurposing clinical trial of dantrolene sodium in patients with Wolfram syndrome was concluded. This was the first-ever clinical trial in paediatric and adult Wolfram syndrome patients with an open-label phase Ib/IIa trial design. Although the study was small, a select few patients seemed to have improvements in diabetes-related outcomes, which might correlate with a positive trend in other outcome measures, including visual acuity and brain functions. The results of this study were published in the Journal of Clinical Investigation Insight, in August this year and is available for anyone (https://insight.jci.org/articles/view/145188). This study justifies further investigation into using a next-generation dantrolene sodium and other new drugs targeting the endoplasmic reticulum stress (a molecular mechanism of Wolfram syndrome) for the treatment of Wolfram syndrome.

Novel Drugs

A repurposed drug could be just a band-aid for Wolfram, and we need a cutting-edge treatment designed explicitly 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. 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 were 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 October 2020. We submitted our clinical trial plan to the US FDA in May and received their feedback in July 2021. We are revising our trial protocol to ensure the safety of our patients and assess the efficacy of AMX0035 accurately. I spend certain amount of time every single day on this project with medical officers at Amylyx and my colleagues at Washington University. We hope to start this new clinical trial in Spring/Summer of 2022.

Regenerative Gene Therapy

I am aware that we need a strategy to regenerate damaged tissues in patients with Wolfram syndrome, and my tool to accomplish this goal is a regenerative gene therapy. We have been trying to improve visual acuity and brain functions 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. 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 a 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, Belgium, 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.

CLINICAL ACTIVITIES

To improve the clinical care for patients with Wolfram syndrome and Wolfram-related disorders, I created a new genetics clinic at the Centre for Advanced Medicine, Washington University Medical Centre, in October 2020. 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 personalised management plans based on the type of gene variants our patients have in collaboration with other specialists at our medical centre. We accept international patients via our international patient care office. 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 centre has been selected as a Rare Disease Centre of Excellence, and we have excellent specialists.

Thank you for supporting Wolfram UK. We will work as one team and make a difference together.

Sincerely yours,

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