11th International Wolfram Syndrome Symposium
Berkshire, England 2nd- 4th June 2026

Meeting Notes

Summary

These meeting notes have been developed to provide a helpful summary of the International Symposium for attendees, other professionals working in Wolfram Syndrome research and for the WS community of affected people and their families.

These notes include the following:

- Meeting agenda
- Abstracts provided by each researcher (where they can be shared)
- Points noted during the presentation (that does not represent a summary of the work – which has / will be published in peer reviewed journals).
- Meeting attendee list – with contact details (researcher version only).

Points to note:

Many of the researchers presented unpublished data and therefore only high-level summary points can be included in the notes. The willingness of researchers to share unpublished data highlights the extraordinary level of collaboration and trust among the WS research community.

Agenda: Day 1 (3rd June 2026)

(08:45-9:00) Welcome. Stephanie Gebel – CEO Snow Foundation & Tracy Lynch – CEO Wolfram Syndrome UK.

Gene-Editing and Precision Genomic Therapeutics

(9:00-9:45) Three Steps Toward a Cure for Wolfram Syndrome: From Drug Discovery to Base Editing. Fumihiko URANO, MD, PhD. Samuel E. Schechter Professor of Medicine. Director, Wolfram Syndrome Clinic at BJC HealthCare, Washington University School of Medicine, St. Louis, USA.

(9:50-10:20) Advancing Precision Genome Editing with Engineered Delivery Systems. Samagya Banskota, PhD. Boston University, Boston, USA.

(10:25-10:55) A Proof-of-Concept Study for Single-Nucleotide Base Editing to Prevent Vision Loss in a Wolfram Syndrome Mouse Model. Prof. Dr. Lies De Groef, Leuven Brain Institute, Dept. Of Biology, KU Leuven, Belgium.

Emerging Topics

(11:30-11:40) CISD2 in Wolfram Syndrome: A Short Update. Dr. Allen Kaasik, Department of Pharmacology, University of Tartu, ESTONIA

(11:45-11.55) Feasibility of Diabetes Technology in Wolfram Syndrome. Dr. Josie Elliott, Paediatrics Doctor and NIHR Academic Clinical Fellow, Department of Cancer and Genomic Sciences, University of Birmingham.

(12:00-12:20) WFS1E864K in Humans and Mice Causes Wolfram-Like Syndrome Optic Atrophy via Early Axonal Mitochondrial Dysfunction. Dr. Benjamin Delprat. MMDN, Université de Montpellier, EPHE, INSERM, Montpellier, France.

(12:25- 13.40) Lunch

Multisystem Pathophysiology and Disease Mechanisms in Wolfram Syndrome

(13:45-14:15) Network-Level MRI Biomarkers Suggest Sensory–Cerebellar Integration Failure in Wolfram Syndrome. Dr. Gema Esteban-Bueno & Juan Luis Fernández-Martínez. Primary Management Unit, Almeria Periphery-Almeria Health District, Andalusian Health Service. Spanish Association for Research and Support for Wolfram Syndrome, Almeria, Spain.

(14:20-14:50) Patient-Derived Hematopoietic Stem/Progenitor Cells (HSPCs) Gene Therapy to Protect β cells in Wolfram Syndrome. Raniero Chimienti, PhD - Diabetes Research Institute (DRI), Vita-Salute San Raffaele University, Milan, Italy.

(14:55-15:15) Mapping the WFS1 Interactome in Human Pancreatic β-cells. Dr. Mariana Igoillo Esteve & Dr Ane Olazagoitia Garmendia - ULB Center for Diabetes Research, Université Libre de Bruxelles.

Emerging and Repurposed Therapeutic Strategies

(15:50 – 16:35) Long-Term Neuro-Ophthalmological Outcomes in Brazilian Patients with Wolfram Syndrome Treated with Idebenone: A Comparative Cohort Study. Filipe Chicani, MD, PhD. Ophthalmologist with Neuro-ophthalmology, Retina, Cornea and Refractive Surgery Fellowships - Ophthalmology Departments of Federal University and State University of São Paulo (UNIFESP and USP), Brazil.

(16:40-17:25) Wolframin Regulates the Autophagy–NAD Axis: Therapeutic Implications for Wolfram Syndrome. Dr. Sovan Sarkar. Associate Professor | Department of Cancer and Genomic Sciences, University of Birmingham, UK.

(17:30-17:50) Modeling Wolfram Syndrome type 1 Using Patient-Derived iPSCs to Evaluate the in Vitro Effects of Tirzepatide on β-cell function. Dr. Giorgia Fulgini, Vita-Salute San Raffaele University, Milan, Italy.

(18.15) Dinner

Agenda: Day 2 (4th June 2026)

Clinical Trials and Translational Therapeutics

(9:00-9:20) TREATWOLFRAM: Post Hoc Analysis of a Trial of Sodium Valproate to Slow the Rate of Progression of Vision Loss in Wolfram Syndrome: Incorporation of an External Control Cohort into the Placebo Arm. Authors: Barrett T, Esteban-Bueno G, Dias R, Wright B, Orssaud C, Mlynarski W, Roubertie A, Wilson M, Yu-Wai-Man P, Lynch T, Lamb A, Barton D, Lugar H, Hershey T, Homer V.

(9:25-9:45) From Insights on Wolframin's Function to Gene Replacement Therapy for Visual Protection. Dr. Vania Broccoli, San Raffaele Research Hospital, Milan, Italy

(9:50-10:00) Slowing Wolfram Syndrome with GLP-1 Receptor Agonists: Real World Experience from an International Registry. Fumihiko URANO, MD, PhD. Samuel E. Schechter Professor of Medicine. Director, Wolfram Syndrome Clinic at BJC HealthCare. Washington University School of Medicine, St. Louis, USA.

(10:05-10:35) AMX0035 in Wolfram Syndrome: Program Progress and Emerging Insights. Dr. Jamie Timmons, MD. Senior VP, Medical Affairs, Amylyx Pharmaceuticals Inc.

Neurodegeneration and Circuit-Level Dysfunction

11:00-11:20) Early Axonal Pathology in WFS1 Deficiency Suggests a Broader Role for WFS1 in Neurodegeneration. Dr. Mario Plaas, University of Tartu, Estonia-Virtual Presentation**.**

(11:25-11:45) Hippocampal Dysfunction in a Murine Model of Wolfram Syndrome. Dr. Saumel Ahmadi, Department of Neurology, Washington University in St Louis, USA.

(11:50-12:10) Mechanistic insights into metabolic and synaptic dysfunction in WS1 neurons. Dr. Ghazal Ashrafi, Washington University School of Medicine, St. Louis, USA**.**

(12:15-12:25) Metabolomic Data of Patients with Wolfram Syndrome. C.Orssaud1; P. Reynier2,3; Cinzia Bocca2,3 and Mathieu Michel2,3 1- Ophthalmologic Functional Unit, OPHTARA Rare Disease Reference Center, HEGP, AP-HP, Paris, France2- Angers University, MITOVASC UMR, INSERM U-1083, CNRS 6015, Angers, France.

(12:25-12:45) Tackling the Pathophysiology of Wolfram Syndrome: Molecular Mechanisms and Clinical Relevance. Gabriel Siracusano PhD - Vita-Salute San Raffaele University, Diabetes Research Institute, Milan, Italy.

(12:50-13:20) First International Consensus Clinical Guidelines for Wolfram Syndrome: A Foundation for Care and Future Therapies. Dr. Josephine Elliott, Saumel Ahmadi, MD, Prof Patrick Yu Wai Man, Sarah Gladstone, MD, Tracy Lynch, Prof Timothy Barrett, and Fumihiko Urano, MD, on behalf of the International Wolfram Syndrome Clinical Guidelines Consortium.

(13:20-13:30) Call of Projects Update. Nolwen Le Floch – President of the French Wolfram Association.

(12:30- 1.30) Lunch and farewell

Day 1 (3rd June 2026)

1. Three Steps Toward a Cure for Wolfram Syndrome: From Drug Discovery to Base Editing. Fumihiko URANO, MD, PhD. Samuel E. Schechter Professor of Medicine. Director, Wolfram Syndrome Clinic at BJC HealthCare, Washington University School of Medicine, St. Louis, USA.

Abstract: Wolfram syndrome is a rare genetic disease that presents significant challenges for patients and their families. It typically begins in childhood with insulin-requiring diabetes and progressive optic nerve changes affecting vision, and over time, can involve broader neurological symptoms that increasingly affect daily life, with no disease-modifying treatments approved today. A major causative gene for Wolfram syndrome is WFS1, which encodes a protein essential for endoplasmic reticulum and mitochondrial function. We are pursuing a three-step strategy toward a cure: Step 1, oral medicines to slow progression; Step 2, base editing to halt progression and begin restoring function; and Step 3, regenerative therapy to restore tissues. In this talk, I will focus on the first two steps.

For Step 1, I will describe our drug discovery platform that combines structure-based in silico docking against AlphaFold models of canonical and mutant WFS1, including p.Arg558Cys (common in the Ashkenazi Jewish population) and a severe cohort frameshift variant, with functional testing of hits in patient iPSC-derived neurons, using readouts for cell viability and survival, endoplasmic reticulum functions, mitochondrial functions, and oxidative stress. This pipeline identified the combination of sodium phenylbutyrate (PBA) and taurursodiol (TUDCA; being tested in combination in the Amylyx trial) and is now nominating additional candidates.

For Step 2, I will present our in vivo adenine base-editing program targeting two clinically relevant variants: WFS1 p.Trp540* associated with severe manifestations and WFS1 p.Arg558Cys associated with milder manifestations, using dual AAV split base editors and engineered virus-like particles delivered to the eye, the central nervous system, and the pancreas. Correction efficiency, precision, and functional rescue are evaluated in patient iPSC-derived β cells, cortical neurons, and brain organoids, as well as in matched Wfs1 knock-in mice. Together, Steps 1 and 2 chart a path from slowing Wolfram syndrome today to stopping it and beginning to restore function tomorrow, with regenerative therapy in Step 3 as the longer-term goal.

Points noted:

- WS is a spectrum disorder where the type of variant determines the severity of the condition.
- A classification system has been developed for mild (both variants in frame), moderate (one variant in frame) and severe (neither in frame) WS manifestations, which includes ~95% of variants.
- There are also autosomal dominant WFS1 gene variants – Wolfram Related Syndrome (WRS).
- Step 1 is to target the molecular mechanisms of WS – a prototype endoplasmic reticulum (ER) disorder.

- Mutant forms of WFS1 alter the integrity of Mitochondria-Associated Membranes (MAM), reduce ER calcium levels, reduce ER mitochondria calcium transfer which leads to mitochondrial dysfunction and ER stress.
- Aim of step 1 is to develop medications to mitigate ER stress – one example is AMX-0035 (PBA+TUDCA).
- In published preclinical studies from 2023, AMX35 prevented beta cell death and increased insulin secretion in using pluripotent stem cell (iPSC) and mouse models.
- Following orphan drug designation and securing Investigational New Drug (IND) approval, a phase II clinical trial was conducted in a small number of US patients.
- The results of the clinical trial were published recently in May 2026 (link: https://www.jci.org/articles/view/198519).
- Compound screening studies are also being conducted to identify other potential drug candidates that can mitigate ER stress.
- Step2: Gene editing: the aim of gene editing is to correct the gene in target tissues.
- Base editing involves making only small changes and is therefore potentially much safer. It requires a base editor (enzyme) and a small piece of RNA. Note: The research involves somatic (non-reproductive cells) editing only; germline (reproductive cells) editing is not ethically approved.
- There are 2 main delivery methods for gene or base editing – AAV (viral Adeno-Associated Virus – which can be toxic) and eVLPs (engineered virus-like particles) [Note: there are also lipid nanoparticles]. Both approaches are currently being tested in WS cell and animal models.
- Studies are currently using Adenine base editing, but the base editor can introduce other mutations (bystander effects) – the aim is to reduce these effects as much as possible.
- 100% gene correction is not required – for example, 30%-40% gene correction improved glucose stimulated insulin secretion and calcium dynamics in iPSC models. The required correction level may not be the same in each cell type. Currently, achieving ~10% editing efficiency in brainstem, cerebellar regions and eye following intraventricular injections in neonatal mice.
- Base editing is also being explored in mouse and rat WS models. Different types of delivery systems and surgical techniques will be required.

2. Advancing Precision Genome Editing with Engineered Delivery Systems.
Samagya Banskota, PhD. Boston University, Boston, USA.

Gene editing technologies have opened new possibilities for treating rare genetic diseases at their root cause. However, the clinical impact of these therapies depends critically on the ability to deliver genome editing machinery safely, efficiently, and precisely to disease-relevant cells and tissues in vivo. While viral vectors have been important for the field, they also have limitations, including immune responses,

limited cargo capacity and manufacturing challenges. These challenges motivate the development of non-viral delivery systems for gene editing.

In my talk, I will describe our work engineering genetically encoded delivery systems for therapeutic gene editing. I will focus on virus-like particles, or VLPs, as programmable, non-replicating vehicles for delivering ribonucleoprotein cargos such as genome editors. Because VLPs can deliver editors transiently and without DNA, they offer an attractive approach for applications where long-term editor expression may create safety concerns.

I will discuss how we identified and addressed key barriers that limit VLP potency in vivo, including cargo release, cargo packaging and localization, and the stoichiometry of VLP components. By engineering solutions to these challenges, we developed engineered VLPs, or eVLPs, that can safely and effectively deliver genome editors to multiple tissues and organs in vivo.

Overall, this work shows how delivery engineering can help turn gene editing tools into therapies for rare diseases. It also highlights the broader potential of genetically encoded systems to overcome biological delivery barriers and expand the reach of genome editing medicines.

Points noted:

- The researcher presented unpublished data and therefore only high-level points can be shared.
- Gene editing techniques have advanced since their first publication in 2012. There are currently +200 clinical trials investigating gene therapies for a wide range of conditions, not just those that are defined as rare.
- The first gene therapy was approved in 2023 for Sickle Cell Disease (SCD), which uses CRISPR-CAS9. The uptake among patients has been quite low – finding patients and scaling up the complex treatment regimen has been challenging.
- How to make gene therapies scalable, accessible and equitable remains an important challenge.
- Another challenge is reaching the target cells – the gene editing package must be protected from degradation, target the desired cells, transverse the cell membranes and escape degradation (by endosomes).
- There are 2 modalities used to deliver gene therapies to target cells: i) Viral (Adeno-Associated Virus AAV) and ii) non-viral.
- AAVs offer high delivery of cargo (i.e. high transduction efficiency, specific tissue tropism (for AAV)) that can effectively escape endosomes. However, there is the risk of immune reactions and undesired long-lived exposure, which increases the risk of unintended modifications (the goal is to correct the gene and then disappear).
- Non-viral modality contains short-lived RNA cargo which has lower efficiency outside of the liver. Therefore, cargo preparation and delivery to the required target tissues is challenging.

- eVLPs Engineered Virus-Like Particles), 120-130nm in diameter, potentially offer the best of both modalities. eVLPs can easily enter target cells and contain protein cargo (not DNA or RNA), which is the most transient, reducing the risk of unintended modifications.
- Architectural engineering of the eVLPs can substantially improve their potency in vivo e.g. by improving the shuttling activity into the target cell nucleus.
- In the CNS, eVLPs do not diffuse well from the site of injection, but this can be improved with engineering techniques.
- In WS, one challenge is how to use gene editing to target the specific beta cells in the pancreas.
- This research group is collaborating with Dr Fumi Urano to test the functional effect of gene editing in WS patient-derived iPSCs (i.e. cell model).

3. A Proof-of-Concept Study for Single-Nucleotide Base Editing to Prevent Vision Loss in a Wolfram Syndrome Mouse Model. Prof. Dr. Lies De Groef, Leuven Brain Institute, Dept. Of Biology, KU Leuven, Belgium.

Abstract:

Purpose: Wolfram Syndrome (WS) is a rare autosomal recessive disorder (~1 in 770,000) caused primarily by *WFS1* mutations, leading to a.o. diabetes mellitus, diabetes insipidus, optic atrophy, neurodegeneration, and premature death. While diabetes is manageable, effective treatments for the neurodegenerative aspects are lacking. Base editing (BE) enables precise correction of point mutations and holds promise as a therapeutic strategy. Here, we characterize a novel *Wfs1Q670X* mouse model with emphasis on visual system pathology and aim to provide a proof-of-concept for BE targeting of retinal ganglion cells (RGCs) to prevent vision loss.

Methods: General health and survival were evaluated by longitudinal body weight monitoring and Kaplan–Meier survival analysis. The diabetic phenotype was assessed using intraperitoneal glucose tolerance testing (IPGTT). The visual phenotype was characterized through a behavioural assay (optomotor test), electroretinograms, and histological analysis. Adenine base editor (ABE) was delivered intravitreally at 2 months of age, prior to onset of visual deficits, using a dual AAV2/2 intein-split strategy to specifically target RGCs. Therapeutic efficacy was assessed through behavioural, electrophysiological, and histological readouts.

Results: *Wfs1Q670X* mice displayed a markedly reduced lifespan, with 37.5% of males and 12.5% of females deceased by 4 months of age. This sexual dimorphism correlated with an earlier onset and greater severity of diabetes in males, while females developed impaired glucose tolerance later. Unlike wild-type littermates, *Wfs1Q670X* mice did not gain weight with age. Visual decline was evident in both sexes from 4 months of age, with progressive reductions in contrast sensitivity and visual acuity. Electrophysiological analyses confirmed impaired RGC function and reduced photoreceptor responses. Despite these deficits, no significant RGC loss was detected. In addition, ER stress markers were elevated in the retina and optic nerve at 6 months, consistent with reported pathogenic mechanisms in WS. Finally, preliminary BE experiments demonstrated ~70% co-transduction efficiency of the dual AAV vectors in RGCs, establishing feasibility for functional rescue studies. ABE

significantly improved RGC and photoreceptor function at 4 and 6 months, representing 2 and 4 months post-treatment, respectively. Likewise, visual acuity was significantly better at 4 and 6 months of age.

Conclusion: This novel *Wfs1Q670X* mouse model recapitulates key clinical features of WS, including diabetes, progressive visual dysfunction, and early mortality, making it a valuable model for mechanistic studies and therapeutic testing. The first results of this proof-of-concept study highlight the potential of ABE to efficiently target RGCs in vivo and correct the WS phenotype.

Points noted:

- The researcher presented unpublished data and therefore only high-level points can be shared.
- A novel WS knock-in (KI) mouse model (*Wfs1* Q670K) has been developed and registered with Mouse Genome Informatics (MGI), an international database resource, and therefore is available to other WS researchers.
- WS KI mice developed diabetes at 2 months of age (females a bit later), did not gain weight with age and displayed progressive visual decline from 4 months of age onwards with progressive decline in retinal ganglion cells (RGCs). Males had lower survival and poorer health status compared with females, although the cause of the gender differences is uncertain. Therefore, the researchers are working with females only.
- This WS KI mouse provides a valuable model for testing potential new therapies (including gene therapies) in WS.
- The researchers used this WS KI mouse model to conduct preliminary proof of concept base editing studies.
- Adenine Base Editing (ABE) was effective in WS-patient derived iPSC and differentiated neuronal cells in restoring WFS1 expression. Efficient transduction of RGCs with AAV2/2 vectors was achieved.
- ABE was able delay functional decline in WS KI mice, including retinal ganglion cell function and decline in visual acuity. The level of change seen in mice would be sufficient to give patients a noticeable improvement in vision. In humans, loss of visual acuity is typically noticed once around 25% of RGCs are lost, but they can still have reasonable vision when 60% are lost. A gain of 20-25% function would be considered clinically significant.
- Further research is needed to optimise ABE (e.g. additional control groups, determine based editing efficiencies, and mapping of off targets) and the delivery strategy. The aim is to develop a data package for 1st in human clinical trials.

4. CISD2 in Wolfram Syndrome: A Short Update. Dr. Allen Kaasik, Department of Pharmacology, University of Tartu, ESTONIA

The abstract will be available following publication of the data presented.

Points noted:

- The researcher presented unpublished data and therefore only high-level points can be shared.
- WS type 1 is caused by mutations in the WFS1 gene. The Wolframin protein (encoded by WFS1) is primarily found on membranes of endoplasmic reticulum (ER).
- WS type 2 is caused by mutations in the CISD2 gene.
- The protein encoded by CISD2 is also transmembrane protein but is much smaller than Wolframin and has a very different structure. It is located primarily in the membranes of the mitochondria and endoplasmic reticulum (ER).
- Both proteins are known to control calcium flux in mitochondria and ER.
- Studies show that the CISD2 overexpression protects *wfs1*- deficient neurons against axonal ATP loss and protects against NADH/NAD increase and excessive mitophagy.
- Evidence of co-immunoprecipitations between CISD2 and SERCA, RyR1, and WFS1 was also presented.
- Therefore, activation of CISD2 can compensate for WFS1 deficiencies. In addition, overexpression of CISD2 in WFS1 deficient neurons restores cytosolic calcium, mitochondrial dysfunction, ATP levels and axonal growth. However, the mechanisms are not yet understood.
- This research aimed to better understand the function of CISD2 - how CISD2 restores calcium flux and protects ATP levels; and whether CISD2 co-locates in the same complex or is directly associated with WFS1.

5. Feasibility of Diabetes Technology in Wolfram Syndrome. Dr. Josie Elliott, Paediatrics Doctor and NIHR Academic Clinical Fellow, Department of Cancer and Genomic Sciences, University of Birmingham.

No abstract provided.

Points noted:

- The researcher presented findings from an unpublished study on the use of continuous glucose monitors (CGM) and insulin pumps in WS patients, and therefore only high-level points can be shared.
- The study used a mixed methods approach – an online questionnaire and semi structured interviews (n=10; 3 parents, 7 WS affected people. All participants used CGMs).
- Type 1 Diabetes Mellitus (T1D) is an autoimmune disorder which requires the use of insulin therapy. WS is a neurodegenerative condition and although many patients are diagnosed with Diabetes Mellitus and require insulin, they

also experience other symptoms including Optic Atrophy which may impact their ability to use CGM and insulin pumps.

- Briefly, the study found that the HbA1c levels (a measure of glucose levels) in WS patients before and after use of CGMs or insulin pumps were not that different (not as much as expected).
- All patients using CGM would recommend this technology for other WS patients. The challenges experienced were mostly related to their vision loss e.g. with managing hypos / hypers (i.e. low and high blood sugar levels) or contacting the expert team for support.
- WS patients using insulin pumps found them easy to use and valued the freedom and independence that this technology gave them. They also had more stable glucose levels and needed much less insulin than is typically needed in T1D. Again, the challenges often related to vision loss – for example being unable to read the information on the pump or glucose meter, or to differentiate the colours in the patient information charts provided (CGM charts are currently colour coded red and green (should be in black and white for WS patients). Note: The Tandem t-slim pump can be controlled via a mobile phone with voiceover technology.
- Increasing the awareness among endocrinologists and other health professionals of Diabetes Mellitus in Wolfram Syndrome is needed.
- Increasing the usability of Diabetes Technology for VI individuals, including those with WS (e.g. being able to adjust font sizes, not using colours that are not visible for people with colour vision loss), would be very beneficial for these patients.
- The aim is to find out the usability of these technologies (CGM and Insulin pumps) for patients with WS and make them more accessible. This includes discussions with National Institute for Health and Care Excellence (NICE) to recommend changes (e.g. increase font sizes, remove the use of red/green colours on reports and the use of a different alarm for each type of event).
- A non-expert report of the study will be developed by the researchers and shared with WSUK for distribution among the WS community.

6. WFS1E864K in Humans and Mice Causes Wolfram-Like Syndrome Optic Atrophy via Early Axonal Mitochondrial Dysfunction. Dr. Benjamin Delprat. MMDN, Université de Montpellier, EPHE, INSERM, Montpellier, France.

Abstract: Wolfram-like syndrome, a rare dominant disorder caused by variants in the WFS1 gene, leads to progressive optic atrophy and severe visual impairment, but its underlying mechanisms remain unresolved, and no treatment is available. Here, we demonstrate that the WFS1E864K variant induces early and progressive optic nerve and retinal pathology in both humans and a genetically engineered mouse model. Two unrelated WFS1E864K carriers exhibited optic disc pallor, retinal nerve fibre layer thinning, and characteristic lamination of the outer plexiform layer. Mirroring these defects, Wfs1E864K mice showed early retinal ganglion cell dysfunction, inner retinal thinning, axonal loss, and demyelination. High-resolution imaging and

bioenergetic assays revealed that the Wfs1E864K variant impairs axonal mitochondrial structure, number, and metabolic activity, while transcriptomic profiling identified deregulation of genes linked to glial activation, lipid metabolism, axonal transport, and mitophagy. These convergent clinical, histological, and molecular findings establish axonal mitochondrial dysfunction as an initiating event in WFS1-related optic neuropathy and provide a tractable framework for therapeutic development in Wolfram spectrum disorders.

Points noted:

- The researcher presented unpublished data and therefore only high-level points can be shared.
- Optic atrophy is experienced by around 87% of patients with Wolfram related Syndrome (WRS / Wolfram-like Syndrome), which is usually autosomal dominant, but patients may also experience Diabetes Mellitus and/or deafness.
- Loss of retinal ganglion cells (RGC) is a key process in the progressive vision loss in Wolfram Syndrome. Outer plexiform layer lamination is characteristic in autosomal dominant Wolfram Syndrome.
- Studies were conducted using a WS mouse model which carries the E864K variant (homozygous), shared by 2 female patients (dominant negative) at their centre, who have a loss of RGCs in both eyes.
- Markers of retinal dysfunction and optic nerve damage were seen in both WRS mutant human cells and the mouse model and suggest inflammatory processing at the RCG level, and reduction in size and loss of myelination in the optic nerve.
- In the mouse model, there was a clear reduction in retinal ganglion cell function and inflammation of retina at level of RGC. Multiple changes were detected which included a reduction in cone cells beginning at P30, reduction in size of the optic nerve, reduction in number of axons within the optic nerve, a reduction in the medium and large axons and a decrease in myelination.
- Detrimental changes to mitochondria were also observed including in their structure, activity and transport, but no changes were detected in the mitochondrial ultrastructure in RGC soma.
- Defects in Mitochondria-Associated Membrane (MAM – which physical contact sites between the ER and mitochondria that regulate essential cellular processes such as calcium signalling and autophagy, among others) in RGC soma are also likely to be involved but it is unclear whether these are rescue processes or are pathogenic. It is also unclear why cone cells are affected but not rod cells.
- There may also be issues with mitochondria transport from the distal part of the optic nerve to the RGC soma. Lysosomal trafficking and protein aggregation may also be impacted.
- Additional studies are planned to further explore the cellular mechanisms that are involved in WRS.

7. Network-Level MRI Biomarkers Suggest Sensory–Cerebellar Integration Failure in Wolfram Syndrome. Dr. Gema Esteban-Bueno & Juan Luis Fernández-Martínez. Primary Management Unit, Almeria Periphery-Almeria Health District, Andalusian Health Service. Spanish Association for Research and Support for Wolfram Syndrome, Almeria, Spain.

Presentation summary:
Dr Gema Esteban Bueno presented preliminary unpublished work exploring the use of multimodal MRI in Wolfram syndrome. The study suggests that neurological involvement in Wolfram syndrome may reflect distributed brain network alterations rather than isolated focal degeneration. Multimodal MRI may help identify candidate imaging biomarkers for future patient stratification, longitudinal follow-up and clinical trial endpoint development. Further validation in larger and international cohorts will be needed.

8. Patient-Derived Hematopoietic Stem/Progenitor Cells (HSPCs) Gene Therapy to Protect β cells in Wolfram Syndrome. Raniero Chimienti, PhD - Diabetes Research Institute (DRI), Vita-Salute San Raffaele University, Milan, Italy.

Abstract: Wolfram syndrome type 1 (WS1) is a rare autosomal recessive neuroendocrine disorder caused by biallelic mutations in WFS1, classically characterized by early-onset diabetes and optic atrophy. While β cell vulnerability resulting from Wolframin deficiency and endoplasmic reticulum stress is a central feature of the disease, our recent findings suggest that WS1 also involves a previously underappreciated immunological component, with systemic inflammation, altered lymphocyte activation, and defective immune homeostasis potentially contributing to β cell damage.

Indeed, we found that Wolframin is expressed across multiple immune subsets in healthy individuals but is absent or defective in WS1 patient-derived immune cells. To investigate this pathogenic axis, we established a patient-derived stem cell platform by generating induced pluripotent stem cells (iPSCs) from 9 WS1 patients and 4 sex- and age-matched healthy donors (HD). These iPSC lines were used to derive CD34+ hematopoietic stem/progenitor cells (HSPCs) using an *in vitro* differentiation protocol, and we optimized conditions for their further differentiation into multiple hematopoietic lineages, including T lymphocytes, NK cells and monocytes. This integrated system was designed to recapitulate the immune abnormalities observed in patients and to enable the study of immune-β cell crosstalk in an autologous setting. Both patient-derived PBMCs (Peripheral Blood Mononuclear cells) and WS1-iPSC-derived HSPCs reproduced key features of WS1 immune dysregulation, including inflammatory activation and an altered immune subset balance, following their reconstitution in NSG mice, supporting the existence of a cell-intrinsic hematopoietic defect compared to HD-derived immune cells. In parallel, autologous WS1-iPSC-derived islets exhibited increased susceptibility to inflammatory injury, consistent with a pathogenic interaction between immune dysfunction and β cell stress.

To explore a therapeutic strategy, we corrected the WS1-derived HSPCs using a clinical-grade lentiviral vector encoding WFS1, restoring Wolframin expression while

preserving progenitor potential and multilineage differentiation. Together, these findings establish a patient-specific platform to model the hematopoietic contribution to WS1 and support HSPC gene therapy as a promising strategy to rebalance immune homeostasis and protect β cells in this syndrome.

Points noted:

- The researcher presented unpublished data; therefore, only high-level findings can be shared.
- The central research question being explored is: does the immune system contribute to Wolfram syndrome (WS) progression?
- Previous publications have reported that inflammation amplifies tissue damage and pancreatic beta-cell loss. Immune dysregulation and inflammation have also been observed in some patients with WS.
- One hypothesis is that stress in pancreatic islet cells increases the production of inflammatory cytokines. The resulting inflammation may be further amplified by the recruitment of immune cells, ultimately contributing to beta-cell death.
- In this research, cells derived from patients with WS exhibited a pro-inflammatory signature. Alterations in immune-cell subsets were identified in a small cohort of patients with WS, including impairment of natural killer (NK) cell effector subsets.
- In subsequent studies using a humanised mouse model of WS, similar alterations in immune-cell profiles were observed.
- Further studies investigated whether targeting patients' immune cells could reshape the inflammatory crosstalk with pancreatic islets. Re-establishment of wolframin expression in WFS1-deficient, patient-derived peripheral blood mononuclear cells (PBMCs) reduced immune-cell migration and islet infiltration. Wolframin re-expression may therefore prevent NK- and T-cell activation against WFS1-deficient islets, suggesting that restoring WFS1 expression in patients could limit immune-mediated damage to insulin-secreting cells.
- A WFS1-expressing lentiviral vector based on a clinical-grade backbone has been developed. Efficacy and toxicity studies are currently underway following the genetic correction of haematopoietic stem and progenitor cells (HSPCs) derived from patients with Wolfram syndrome.
- Future studies will evaluate whether immune-cell balance can be restored in the humanised mouse model through WFS1 correction and investigate how changes in immune-cell profiles contribute to endoplasmic reticulum stress and beta-cell damage.

9. Mapping the WFS1 Interactome in Human Pancreatic β-cells. Dr. Mariana Igoillo Esteve & Dr Ane Olazagoitia Garmendia - ULB Center for Diabetes Research, Université Libre de Bruxelles.

Abstract: Wolfram syndrome type 1 (WS1) is a rare neurodegenerative disorder caused by biallelic mutations in the WFS1 gene. Although WFS1 deficiency has been associated with endoplasmic reticulum (ER) stress, calcium dysregulation, and mitochondrial dysfunction, the precise molecular function of WFS1 remains poorly defined, limiting the development of mechanism-based therapeutic strategies.

Analysis of publicly available ER complexome profiling data indicates that WFS1 co-migrates with key components of the oligosaccharyltransferase (OST) complex, which mediates co- and post-translational protein N-glycosylation, an essential process for protein folding, stability, and cell signalling. These observations raise the hypothesis that WFS1 may associate with the OST machinery and indirectly modulate N-linked glycosylation. Building on this premise, the proposed project aims to: (1) systematically characterize the WFS1 interactome in human pancreatic β cells and neuronal cells using unbiased immunoprecipitation of endogenous WFS1 coupled to mass spectrometry, to assess the association with the OST complex and identify additional WFS1-associated proteins; (2) functionally evaluate selected candidates and determine the impact of WFS1 deficiency on OST complex stability and activity under basal and metabolic stress conditions, as well as on the expression or activity of additional putative partners; and (3) explore therapeutic opportunities through rational drug repositioning using integrative bioinformatic approaches, followed by functional validation in WFS1-deficient cellular models.

Preliminary unbiased immunoprecipitation experiments of endogenous WFS1 followed by mass spectrometry in the human β-cell line EndoC-βH1 recovered not only previously reported WFS1 partners, such as SERCA2 and SERCA3, but also low but reproducible amounts of several OST subunits, as well as a set of mitochondrial proteins involved in fatty-acid oxidation, redox regulation, and oxidative phosphorylation. While these findings do not establish direct physical interactions, they suggest a potential functional link between WFS1, protein N-glycosylation, and mitochondrial metabolic homeostasis that is currently under investigation.

Points noted:

- This is a new project for the researcher – which started 6 months ago. The researcher presented unpublished data and therefore only high-level points can be shared.
- The research aims to understand the function of WFS-1 inside cells and to explore the functional interactions of WFS-1 with a view to identifying new therapeutic opportunities for WS using repurposed drugs (i.e. existing medications currently available for other conditions / symptoms).
- Analysis of publicly available complexome profiling datasets derived from endoplasmic reticulum-enriched fractions in which, the molecular weight of each protein or protein complex is determined by mass spectrometry, revealed that WFS1 migrates with the B subunit of the oligosaccharyltransferse (OST) complex.
- The OST complex is an essential endoplasmic reticulum membrane-associated glycosylation complex composed of two sub-units OST-A and OST B, which are needed for the N-glycosylation of nearly all secretory and membrane proteins.
- Preliminary WFS1 immunoprecipitation studies coupled with mass spectrometry in a well-established human beta cell line, confirmed this potential association.

- The OST complex interacts with the SERCA2 pump (responsible for the movement of calcium from the cytoplasm into the ER). Impaired glycosylation inactivates SERCA2 leading to ER stress.
- Colocalisation of WSF-1 with other specific proteins does not confirm that WFS-1 physically interacts with the protein but suggests a potential functional link.
- These studies suggest that WFS-1 is linked with complexes involved in the N-glycosylation of proteins (which is required for essential cellular processes such as folding, stability and trafficking among others) and could become more involved in N-glycosylation during stress.
- A deficiency in WSF-1 could therefore potentially affect protein glycosylation.
- Future studies using other approaches and cell types are needed to validate the interaction found in this work.

10. Long-Term Neuro-Ophthalmological Outcomes in Brazilian Patients with Wolfram Syndrome Treated with Idebenone: A Comparative Cohort Study.

Filipe Chicani, MD, PhD. Ophthalmologist with Neuro-ophthalmology, Retina, Cornea and Refractive Surgery Fellowships - Ophthalmology Departments of Federal University and State University of São Paulo (UNIFESP and USP), Brazil.

Abstract: **Background:** Wolfram syndrome (DIDMOAD) is a rare inherited neurodegenerative disorder characterized by diabetes mellitus, optic atrophy, diabetes insipidus, and deafness, with additional neurologic and psychiatric manifestations in some patients. There is currently no definitive treatment. Because mitochondrial dysfunction and endoplasmic reticulum stress may contribute to disease pathogenesis, Idebenone has been considered a potential therapeutic option for visual impairment.

Purpose: To compare long-term neuro-ophthalmological outcomes in Brazilian patients with Wolfram syndrome treated with Idebenone versus patients followed without clinical treatment.

Methods: Fifteen Brazilian patients with Wolfram syndrome were followed for a mean of 56 months (range, 12-114 months) and underwent biannual neuro-ophthalmological evaluations, including clinical history, best-corrected visual acuity, colour vision, pupillary reflexes, Humphrey visual fields, fundoscopy, retinography, optical coherence tomography (OCT), and laboratory safety monitoring (liver function tests). Patients were divided into a treated group receiving Idebenone (n=10) and an untreated group (n=5). In the treated group, mean treatment duration was 83 months (range, 50-143), mean age at treatment initiation was 19.2 years (range, 12-30), and 7/10 patients were male. In the untreated group, mean follow-up was 33 months (range, 12-55), mean age at baseline was 22.8 years (range, 13-31), and 3/5 patients were female. Three treated patients were excluded from outcome analysis because of confounding clinical events (subcapsular cataract with juvenile glaucoma in one eye, irregular treatment exposure, and ischemic/haemorrhagic stroke).

Results: Among the 7 treated patients included in the final analysis, visual acuity was stable or improved in 4 and worsened in 3. Visual fields were stable or improved in 4 and worsened in 3. OCT retinal nerve fibre layer measurements were stable or

improved in 6 and worsened in 1. No clinical or laboratory adverse effects related to Idebenone were reported. In the untreated group (n=5), visual acuity worsened in all patients; visual fields worsened in 3 patients and could not be reliably performed in 2 because of severe visual loss; OCT retinal nerve fibre layer measurements worsened in 3 patients, improved in 1, and were unavailable for comparison in 1.

Conclusions: In this longitudinal observational cohort, Idebenone was well tolerated and was associated with relative stabilization of visual function and OCT findings in a subset of treated patients, whereas untreated patients generally showed progressive visual decline. These findings support further investigation in larger, randomized, multicentre studies.

Points noted:

- The researcher presented unpublished data and therefore only high-level points can be shared.
- 300 million people have a rare condition – 72% have a genetic origin and 75% affect children. Patients have ~10 visits before their diagnosis and to date 6-8,000 rare diseases have been identified.
- Idebenone is a co-enzyme Q derivative that helps to restore energy production at a cellular level.
- This study assessed the long-term outcomes of treatment with Idebenone in a small number of WS patients in Brazil (n=15; 10 treated, 5 not treated). As this was an observational study (i.e. patients are followed over time, but they are not assigned by researchers to a specific treatment or control group), the Idebenone-treated and non-treated groups were not the same. Patients were followed over a number of years (mean duration = 56 months), and their visual acuity was assessed over time using a range of different measures.
- This study represents the longest follow-up of WS patients reported in the literature.
- Consistent with previous findings, Idebenone was well tolerated and was associated with some stabilization of vision function in sub-set of treated patients.
- As a next step, the results of the study will be published and suggest that a multi-centre double blind clinical study in WS patients is warranted.

11. Wolframin Regulates the Autophagy–NAD Axis: Therapeutic Implications for Wolfram Syndrome. Dr. Sovan Sarkar. Associate Professor | Department of Cancer and Genomic Sciences, University of Birmingham, UK.

No abstract provided.

Points noted:

- The researcher presented unpublished data and therefore only high-level points can be shared.

- This research is focused on autophagy which is a critical process for the clearance and recycling of “rubbish” inside cells. Autophagy plays a critical role in many areas including cell housekeeping, stabilizing energy and metabolic processes (homeostasis), ageing, and diseases such as neurodegeneration through the removal of mutant proteins.
- In two landmark papers published in 2006 [Hara et al. (Nature, April 2006); Komatsu et al. (Nature, April 2006)], loss of autophagy was shown to cause neurodegeneration in normal mice. In a more recent paper, re-activation of autophagy in mice with autophagy depletion enabled neurons to recover and reduced neurodegeneration. These findings highlight the critical role of autophagy in neurodegeneration.
- The overall aim of this research is to target the defective autophagy in WS (and other neurodegenerative diseases) and identify repurposed drugs that could represent potential new therapeutic interventions in this condition.
- One goal is to identify the cellular mechanisms underlying defective autophagy in WS that mediate neuronal cell death. Depletion of NAD (nicotinamide adenine dinucleotide - an essential co-enzyme, which plays a central role in cell metabolism) was found to cause cell death during loss of autophagy.
- NAD deficit was found in WS patient-derived neurons, whilst NAD boosters were shown rescue disease phenotypes (e.g. cell death).
- Brain organoids have also been developed to explore how brain development and autophagy are affected in WS.
- This research shows that one mechanism that impairs autophagy in neurodegeneration is through the depletion of NAD. Therefore, NAD boosters could therefore represent potential therapeutic candidates for future clinical trials in WS.

12. **Modeling Wolfram Syndrome type 1 Using Patient-Derived iPSCs to Evaluate the in Vitro Effects of Tirzepatide on β-cell function.** Dr. Giorgia Fulgini, Vita-Salute San Raffaele University, Milan, Italy.

Abstract: **Background and Rationale**

Within a precision-medicine project on Wolfram Syndrome type 1 (WS1), 10 paediatric and adult patients were enrolled in a clinical trial evaluating tirzepatide, a dual GIP/GLP-1 receptor agonist, as a potential disease-modifying treatment. In parallel, we generated patient-derived iPSCs, differentiated them into β-like cells, and treated them in vitro with tirzepatide to assess patient specific β-cell functional and molecular responses.

Materials and Methods

iPSCs were generated from the 10 WS1 patients by Sendai virus-based reprogramming and validated for identity, genomic integrity, viral clearance, pluripotency, trilineage differentiation, and tested for mycoplasma contamination. Validated clones were differentiated into insulin-producing cells using a multistage pancreatic differentiation protocol. Tirzepatide effects were assessed after acute, up to 4 hours, and chronic, 7 days, exposure by glucose-stimulated insulin secretion in dynamic perfusion, ER–mitochondria interaction analysis, and bulk RNA sequencing.

Results

All 10 WS1 iPSC lines were successfully generated, validated, and differentiated into insulin producing cells, although with marked patient-specific variability in β-cell marker expression and secretory function. Acute tirzepatide exposure showed a trend toward enhanced glucose-stimulated insulin secretion, less evident after chronic treatment. Bulk RNA sequencing identified an early transcriptional response, with 54 differentially expressed genes after acute exposure and partial normalization after prolonged treatment. Gene Ontology analysis revealed enrichment of processes linked to cellular senescence, stress-response pathways, intracellular signalling, and organelle homeostasis. Tirzepatide-treated cells also showed changes in ER–mitochondria contact sites, supporting a potential effect on organelle crosstalk.

Conclusions

This study establishes a patient-derived iPSC platform to model β-cell dysfunction in WS1 and assess in vitro responses to tirzepatide. The data reveal heterogeneous β-cell functional responses, transient modulation of senescence- and stress-related pathways, and changes in ER–mitochondria interactions. These results are being analysed in relation to clinical response, to validate iPSC derived β-like cells as a disease-modelling and drug-screening platform and to investigate mechanisms underlying tirzepatide action in WS1 β cells.

Points noted:

- The researcher presented unpublished data and therefore only high-level points can be shared.
- Tirzepatide is a dual GLP-1 and GIP agonist (i.e. activates two pathways). It is a once-weekly injection prescribed for Type-2 Diabetes Mellitus and obesity.
- 10 WS type-1 patients have previously been enrolled in a clinical trial in Italy to investigate whether Tirzepatide can increase the natural production of insulin.
- In this study, iPSC lines were generated from each of the 10 patients involved in the Tirzepatide clinical study and met all the required quality criteria. These new iPSC lines are now available to the scientific community for future WS research.
- Each iPSC line was differentiated into insulin-producing cells and the effects of acute treatment with Tirzepatide were investigated to explore the cellular mechanisms involved.
- The WS patient derived insulin-producing cells showed a variable response to acute Tirzepatide treatment (e.g. in level of insulin secretion). The relationship between the response to Tirzepatide treatment and level of mutation in the WFS1 gene has not yet been explored.
- The cellular mechanisms involved in the response to Tirzepatide will be further explored in future studies.

Day 2 (4th June 2026)

13. TREATWOLFRAM: Post Hoc Analysis of a Trial of Sodium Valproate to Slow the Rate of Progression of Vision Loss in Wolfram Syndrome: Incorporation of an External Control Cohort into the Placebo Arm. Authors: Barrett T, Esteban-Bueno G, Dias R, Wright B, Orssaud C, Mlynarski W, Roubertie A, Wilson M, Yu-Wai-Man P, Lynch T, Lamb A, Barton D, Lugar H, Hershey T, Homer V.

Introduction: TREATWOLFRAM (NCT03717909) was a multi-centre international randomised placebo-controlled trial evaluating whether repurposed sodium valproate slowed the rate of vision loss (the primary outcome) in patients with Wolfram syndrome. Although no significant difference was observed between the treatment and placebo arms for the primary outcome, notable baseline imbalances were present: the placebo group were younger, had better vision at baseline, and shorter duration of optic atrophy. Consequently, it remains possible that a true treatment effect may have been obscured by these imbalances. To address this, we aimed to augment the internal placebo arm with natural history data from an external cohort curated by Washington University (the I-TRACK study) to construct comparator populations better aligned with the treated cohort.

Methods: The TREATWOLFRAM trial enrolled 63 participants (children > 6 years and adults), with genetically confirmed Wolfram syndrome, randomised 2:1 to sodium valproate or matched placebo. The I-TRACK study was a prospective observational (non-intervention) cohort study of child and adult patients with Wolfram syndrome and their unaffected siblings. I-TRACK enrolled 127 participants, of whom 50 had Wolfram syndrome. Follow-up of the I-TRACK cohort overlapped with the TREATWOLFRAM trial (2019-2024).

Results: The I-TRACK cohort was used to construct several alternative control populations: a) exclusively internal controls; b) exclusively external controls; c) mixture models incorporating both internal placebo and weighted external data; and d) a synthetic control arm derived from modelling approaches. These comparator populations were designed to improve baseline alignment with the treated cohort and to assess the robustness of treatment effect estimates under different assumptions regarding exchangeability and borrowing. All external-control analyses were conducted post-hoc, designed to complement the protocol-specified analyses and not to replace or reclassify them. Consistent with ICH E9 and agency guidance, findings will be presented with explicit caveats regarding generalisability, residual confounding, and the exploratory nature of the work.

Conclusions: This work outlines approaches for the incorporation of external data and demonstrates how synthetic control arms could be used in future clinical trials in Wolfram syndrome.

Points noted:

- The researcher presented unpublished data and therefore only high-level points can be shared.
- Sodium Valproate (SV) is a licensed medication for epilepsy and is neuroprotector. The primary outcome of the TREATWOLFRAM trial visual

acuity – a patient relevant outcome. i.e. could SV slow visual decline in WS patients?

- 63 patients were recruited across 4 countries France Poland, Spain, UK 42 were randomised to receive SV while 21 received placebo (i.e. “fake / dummy” treatment).
- Statistical analysis revealed that the placebo patients were younger and at baseline had better vision and shorter duration of optic atrophy and had less advanced Diabetes Mellitus, with shorter insulin treatment. During the study, the SV treated group experienced slightly slower progression in their vision, which was below statistical significance (i.e. the researchers could not conclude that the SV treated group was different from the placebo).
- Dr Tammy Hershey (Washington University, St Louis, USA), is leading a long-term observational study of 50 WS patients – (i.e. helps to understand the natural history of WS). The timeline of this study (2010 to 2023) overlaps with TREATWOLFRAM study period.
- 4 different control populations were created and compared with the TREATWOLFRAM data – i) internal control (main trial analysis), ii) mix model (best matched control cohort), iii) external contract (external control data only) and synthetic control (modelling to create an own control for each patient).
- Although there was a trend towards effectiveness, the statistical significance requirements were not met. Therefore, there was no statistically significant difference between the SV-treated group and the placebo group.
- This work outlines how synthetic WS control groups can be created using a natural history dataset of WS patients and compared with WS patient clinical trial data. This type of approach could be used to help to reduce / limit the placebo group needed in future WS clinic trials.
- This dataset will be made available to the WS research community

14. From Insights on Wolframin's Function to Gene Replacement Therapy for Visual Protection. Dr. Vania Broccoli, San Raffaele Research Hospital, Milan, Italy.

No abstract provided.

Points noted:

- The researcher presented unpublished data and therefore only high-level points can be shared.
- WFS1 gene impacts many different processes. To develop a WFS1 gene therapy – i) need to confirm WFS1 reverses the observed cellular dysfunction, ii) identify which cells to target iii) validate the gene therapy iv) evaluate using in vivo (animal models).
- In WFS1 deficient glial cells, ER stress can be normalised through 3 pathways after WFS1 gene re-expression. The glial cells were also activated with inflammatory markers.
- Using animal models developed by other WS research groups, inactivation of RGCs resulted in dramatic loss of vision.

- The researchers subsequently focused on developing an AAV gene therapy promoter and protocol for each cell type – i.e. RGCs and glial cells.
- When gene therapy was used to rescue both RGCs and glial cells, the effects on WFS1 expression were additive. In addition, no harmful effects were seen in the retina. Therefore, this work supports the further development of this gene therapy approach for visual symptoms.
- The next step is to publish the work in a scientific peer-reviewed journal.
- The researchers are also preparing an IND package for FDA, but need significant investment (~$4.5M USD) to progress to clinical trials.

15. Slowing Wolfram Syndrome with GLP-1 Receptor Agonists: Real World Experience from an International Registry. Fumihiko URANO, MD, PhD. Samuel E. Schechter Professor of Medicine. Director, Wolfram Syndrome Clinic at BJC HealthCare. Washington University School of Medicine, St. Louis, USA.

Abstract: Wolfram syndrome is a rare genetic disease that presents significant challenges for patients and their families. It typically begins in childhood with insulin-requiring diabetes and progressive optic nerve changes affecting vision, and over time, can involve broader neurological symptoms that increasingly affect daily life, with no disease-modifying treatments approved today. A major causative gene for Wolfram syndrome is WFS1, which encodes a protein essential for endoplasmic reticulum and mitochondrial function.

We are pursuing a three-step strategy toward a cure: Step 1, oral medicines to slow progression; Step 2, base editing to halt progression and begin restoring function; and Step 3, regenerative therapy to restore tissues. In this talk, I will focus on real-world clinical experience within Step 1 with glucagon-like peptide-1 receptor agonists (GLP-1 RAs).

GLP-1 RAs are well-established medicines for type 2 diabetes that, in preclinical and human cell models of Wolfram syndrome, also enhance glucose-dependent insulin secretion, preserve β-cell function, attenuate endoplasmic reticulum stress, and exert neuroprotective effects, all of mechanistic relevance to Wolfram syndrome. To understand how this class is performing in everyday practice, we conducted a retrospective cohort study of 84 individuals with genetically confirmed Wolfram syndrome and insulin-dependent diabetes mellitus enrolled in the Washington University Wolfram Syndrome International Registry and Clinical Study, examining prevalence of GLP-1 RA use, rationale for initiation, glycemic and visual outcomes, side effects, and reasons for discontinuation.

Approximately one-third of eligible participants had received a GLP-1 RA, most commonly semaglutide or liraglutide, with dulaglutide and Tirzepatide also represented. The most frequent rationale for initiation was glycemic improvement, alongside physician recommendation and interest in potential benefits for vision and neurological function. Across the cohort, hemoglobin A1c and body mass index did not change significantly, and visual acuity declined over two years in line with the

natural history of the disease. Gastrointestinal side effects were common and contributed to frequent discontinuations.

These observations show that GLP-1 RAs have been adopted in a meaningful proportion of Wolfram syndrome patients, illustrate the practical considerations that shape their everyday use, and provide a foundation for future prospective trials of GLP-1 RAs as part of Step 1 in our three-step strategy toward a cure.

Points noted:

- Step 1 is to develop oral medications to slow the progression of WS by reducing ER stress.
- iPSC lines from +50 WS patients are now available. Compound screening using iPSC lines to identify potential therapeutic candidates that could reduce ER stress in WS is being conducted.
- GLP-1 receptor antagonists (GLP-1RA e.g. Liraglutide and semaglutide) could be beneficial for WS patients in treating Diabetes Mellitus and for its neuroprotective effects.
- A retrospective chart review study (i.e. study of existing patient medical records; n = 84) found that 30 WS patients were receiving a GLP-1 RA (mean age = 27 years) and 50 were taking insulin (mean age = 29 years, with similar age of onset).
- GLP-1RA were initiated most frequently to control Diabetes Mellitus and for their neuroprotective effects, including vision. The commonest use was Semaglutide or Liraglutide, but Dulaglutide and Tirzepatide were also prescribed. There were more patients with milder form of disease in the GLP-1 treated group.
- In the GLP-1 group comparison of pre- and post- 1-year treatment, identified no significant changes in control of Diabetes Mellitus (HbA1c) or BMI while vision declined in line with previous WS natural history studies (i.e. the reduction in visual acuity was between 0.59 and 0.7 LogMAR).
- Gastrointestinal side effects were common (as has been widely reported with the use of this class of products), resulting in discontinuations.
- This was a small sample of retrospective data and therefore the treated and untreated groups were not the exactly the same (i.e. as would be intended in a clinic trial).
- Further analysis to compare GLP-1 receptor agonists with insulin treatment, and to compare the different GLP-1 products is on-going / planned.

16. AMX0035 in Wolfram Syndrome: Program Progress and Emerging Insights.

Dr. Jamie Timmons, MD. Senior VP, Medical Affairs, Amylyx Pharmaceuticals Inc.

Abstract: Amylyx Pharmaceuticals will provide an update on the ongoing development of AMX0035 as a potential therapy for Wolfram syndrome. The session will offer an overview of the company's work in this area and describe the current direction of the program. The presentation will reflect Amylyx's continued focus on advancing therapeutic options and supporting the Wolfram syndrome community.

Points noted:

- The 24- and 48-week results from the Phase 2 HELIOS trial of AMX0035 in Wolfram syndrome were published in an open access journal in May 2026, (link to publication: https://www.jci.org/articles/view/198519
- An update on the 96-week results was included in the presentation and is available on the Amylyx website (Our Science/Publications/Scroll down to "AMX0035 in Wolfram Syndrome: Program Progress and Emerging Insights" presentation.)
- AMX0035 – is a combination of PB and TURSO (sodium phenylbutyrate and taurursodiol), which were shown in to reduce ER stress and mitochondrial dysfunction in WS pre-clinical studies.
- The HELIOS study is a small (12 WS patients), single country (i.e. USA), open label WS Phase 2 clinical trial. Included WS patients were +17 years, with functionally recessive mutations in WFS-1 and a minimum level of residual function of beta cells. Included patients used insulin to control their Diabetes Mellitus but did not take GLP-1s at least during the initial 48-week study period (patients were able to take GLP-1 therapy during the extension period i.e. 48 to 96 weeks).
- The primary endpoint was the change in baseline C-peptide levels at weeks 24, 48 and 96, as measured by a 240 min Mixed Meal Tolerance Test (MMTT). In addition, a range of secondary exploratory endpoints were included relating to i) beta cell function and Diabetes Mellitus control, ii) vision, iii) patient reported outcomes and iv) physician reported outcomes.
- The results were evaluated in two groups –i) intent to treat (includes all 12 recruited patients) and ii) per protocol (11 patients – 1 patient with 1 confirmed mutation of WFS-1 and 1 non-confirmed mutation was excluded from this group).
- The 96-week data showed a continued response in the primary endpoint, with a 14% increase in C-peptide levels from baseline in the per-protocol treated group. For secondary endpoints (e.g. HbA1c levels, visual acuity), responses were either improved compared to baseline or suggested stability compared with the progression seen in natural history studies. Patient reported outcomes were no change or improved / very improved, while physicians reported no worsening.
- AMX0035 was well tolerated over the 96-weeks with mild GI adverse effects reported in some patients. 1 severe adverse event was reported, but this is unlikely to be due to the study treatment. Importantly, no new safety signals were identified.
- Overall, the 1-year timepoint provided the best response (Primary endpoint at 48 weeks: 52% increase in C-peptide secretion from baseline in the per-protocol treated group).

- The limitations are the small number of patients and the open label design.
- These finding support the continued investigation of AMX0035 in Phase III studies. Therefore, Amylyx is currently developing the design for the Phase III trial. The design of the trial, including how many participants, will inform how many sites and which countries will participate in the study.
- The heterogeneity of the WS patient population makes it more challenging to develop the best clinical trial design, define the patient inclusion criteria (i.e. which patients to study) and select the most appropriate endpoints to study the disease burden.
- Amylyx is interested is reducing the number of placebo-treated patients and developing a more robust control group using the available WS natural history data, however it is important to understand how regulatory authorities (e.g. FDA, EMA, MAA) view this type of approach. At the moment, Amylyx is assuming that they will need to require the inclusion of some placebo-treated patients in the Phase III study.
- Amylyx is intending to take the time to develop the best Phase III WS clinical trial protocol, so the study can progress as quickly as possible when it launches. There is a lot of excitement about the WS Phase III study in the company.

17. Early Axonal Pathology in WFS1 Deficiency Suggests a Broader Role for WFS1 in Neurodegeneration. Dr. Mario Plaas, University of Tartu, Estonia-Virtual Presentation

Abstract: Wolfram syndrome type 1 (WS1) is a rare neurodegenerative disorder caused by pathogenic variants in *WFS1*, which encodes an endoplasmic reticulum (ER) transmembrane protein. *WFS1* has been primarily linked to calcium (Ca^{2+}) homeostasis, mitochondrial function, and ER stress responses. However, the intracellular and tissue-level pathological changes caused by *Wfs1* loss, particularly in neuronal tissue, remain poorly understood.

In our previous work, we demonstrated that loss of *Wfs1* function disrupts the balance between GABA and glutamate, leading to degenerative changes in parvalbumin-positive (PV+) interneurons and the surrounding perineuronal net. Notably, these alterations occur despite the absence of detectable *WFS1* expression in PV+ interneurons, suggesting indirect or circuit-level mechanisms of pathology.

In this presentation, we provide the first evidence that the role of *WFS1* in the development of neurodegenerative pathology may be substantially broader than previously assumed. We show for the first time that the brains of *Wfs1* loss-of-function rats contain distinct axonal aggregates that are already detectable at 3 months of age, with features reminiscent of axonal pathology described in Alzheimer's disease. Importantly, these aggregates increase markedly with age,

indicating progressive axonal and/or axonal cytoskeletal damage, which may result in protein accumulation and impaired transport of proteins and neurotransmitters.

The exact nature of these aggregates remains unclear. They may represent either a pathological process or a cellular rescue response. Nevertheless, our findings identify early and progressive axonal pathology as a previously unrecognized feature of *WFS1* deficiency and suggest that *WFS1* may have a broader role in neurodegenerative disease mechanisms than currently appreciated.

As the researcher presented unpublished data no further high-level points can be shared.

18. Hippocampal Dysfunction in a Murine Model of Wolfram Syndrome. Dr. Saumel Ahmadi, Department of Neurology, Washington University in St Louis, USA.

Abstract: Wolfram syndrome (WS) is a rare neurogenetic condition characterized by diabetes, sensorineural hearing loss, optic nerve atrophy, and progressive neurodegeneration. WS is caused by variants in *WFS1* gene. It is a prototype endoplasmic reticulum (ER) stress disorder, and the mechanisms causing neuro-phenotype in WS are not well studied. Hence, we explored the neurodegenerative phenotype in a patient-relevant murine model of WS. We used a mouse strain bearing human disease relevant *WFS1 (*p.W542*) variant on both alleles. We performed gross morphological assessment, behavioural assessment, performed *ex vivo* hippocampal multielectrode array (MEA) assay for measurement of cellular and neuronal network activity, *in vivo* intracranial electroencephalography (EEG) for assessment of seizure and non-seizure electrophysiology phenotypes, as well as immunohistochemistry. We found that our murine model of WS had reduced life expectancy. We also found a strong expression of WFS1 protein in the hippocampus, which led us to hypothesize that the neuropsychiatric changes in WS could be due to hippocampal dysfunction. This was supported by hippocampal cellular hyperexcitability and neuronal network dysfunction. However, similar to WS patients, WS mice do not have unprovoked seizures. Behaviourally, mice did have a robust reduction in fear conditioning. In conclusion, murine model of WS recapitulates human phenotypes of absence of seizures, intact motor function, and psychiatric changes. This discovery opens potential for repurposing drugs which affect neuronal excitability, for WS.

Funding: KL2 career development award KL2TR002346; Uplifting Athletes Young investigator award; Eunice Kennedy Shriver National Institute of Child Health & Human Development of the National Institutes of Health grant P50 HD103525 to the Intellectual and Developmental Disabilities Research Centre at Washington University; National Institutes of Health grant P30 DK020579.

Points noted:

- The researcher presented unpublished data and therefore only high-level points can be shared.

- Sleep disorders, memory loss and temperature dysfunction are some of the psychiatric symptoms of progressive neurodegeneration in WS.
- The hippocampus and cerebellum are two densely connected areas of the brain.
- In this study, a WFS-1 mouse model showed shorter lifespan, with females living longer.
- The strongest presence of WFS-1 protein was found in the hippocampus– suggesting that this region of the brain could be involved early in the neurodegeneration process in WS.
- Further studies using this WFS-1 mouse model identified dysfunction in neuronal firing. However, similar to WS patients, seizures were not detected. (NB: Seizures are not a recognised characteristic of WS).
- These findings highlight the central importance of the neuronal activity of the hippocampus in WS, which could offer a new therapeutic target in this condition.

19. Mechanistic insights into metabolic and synaptic dysfunction in WS1 neurons. Dr. Ghazal Ashrafi, Washington University School of Medicine, St. Louis, USA.

No abstract provided.

Points noted:

- The researcher presented unpublished data and therefore only high-level points can be shared.
- Synaptic communication across neurons is highly energy consuming. The human brain contains 100 billion neurons with 100 trillion synapses. It is therefore highly-energy intensive with no energy reserves. Although the brain represents only ~2% of body weight, it uses ~20% of total body energy.
- Mitochondrial and synaptic dysfunction leads to neurodegeneration and neuropsychiatric changes and symptoms.
- Neuronal presynaptic terminals are particularly susceptible to neurodegeneration.
- WFS1 interacts with IP3 receptors, which interact with VDAC (Voltage Dependent Anion Channel) to support calcium handling and mitochondrial metabolism.
- Studies in WS-induced neurons, generated from WS patient-derived iPSCs (provided by Dr Fumi Urano), identified mitochondrial changes, including alterations in morphology, calcium release, protein composition. Further studies identified impaired synapse formation and maturation in these WS-induced neurons cells, and also impaired vesicle release (i.e. release of neurotransmitters a central process in neural communication).
- The next step is to explore whether these changes to the mitochondria and synapses can be rescued by WFS1.

20. Metabolomic Data of Patients with Wolfram Syndrome. C.Orssaud1; P. Reynier2,3; Cinzia Bocca2,3 and Mathieu Michel2,3 1-Ophthalmologic Functional Unit, OPHTARA Rare Disease Reference Center, HEGP, AP-HP, Paris, France2- Angers University, MITOVASC UMR, INSERM U-1083, CNRS 6015, Angers, France.

No abstract provided.

Points noted:

- The researcher presented unpublished data and therefore only high-level points can be shared.
- The aim of this research was to analyse the level and type of metabolites from WS patients and compare them with controls to increase the understanding of the pathophysiology of this condition.
- Blood samples were taken from 28 WS patients and 30 controls and the levels of a range of targeted and non-targeted metabolites (n=630) were compared.
- Significant differences were detected in some of targeted and non-targeted metabolites – this includes metabolites related to MAM (Mitochondria Associated Membranes), which are altered in WS.
- The researchers are currently preparing a manuscript for publication in a scientific peer-reviewed journal and are conducting further analysis to better understand and explain the reasons for the metabolite variations.

21. Tackling the Pathophysiology of Wolfram Syndrome: Molecular Mechanisms and Clinical Relevance. Gabriel Siracusano PhD - Vita-Salute San Raffaele University, Diabetes Research Institute, Milan, Italy.

Abstract: Wolfram syndrome type 1 (WS1) is caused by pathogenic WFS1 variants and is recognized as a multisystem disorder in which β-cell failure and neurodegeneration coexists with broader cellular dysfunction. To define the molecular basis of disease, we investigated the effects of the c.316-1G>A and c.757A>T WFS1 mutations in pancreatic β-cells differentiated from patient-derived induced pluripotent stem cells (iPSCs). WS1 β-cells displayed defective insulin granule maturation, altered Ca2+ handling, enhanced autophagic activity, and increased susceptibility to inflammation-induced apoptosis, highlighting convergent stress pathways that may contribute to progressive β-cell loss. Notably, treatment with the GLP-1 receptor agonist liraglutide ameliorated these alterations and restored key β-cell functions.

We extended this analysis to the immunological compartment from WS1 patients carrying different classes of WFS1 mutations. We identified immune dysregulations associated with a systemic pro inflammatory signature, supporting the idea that WFS1 deficiency affects not only endocrine and neuronal cells but also immune homeostasis. We further explored how the immune dysfunctions may relate to clinical manifestations and disease heterogeneity.

Together, these findings provide a broader view of WS1 pathophysiology, linking mutation-specific cellular defects to clinically relevant inflammatory mechanisms. This integrated perspective may help uncover actionable targets and guide the development of more personalized therapeutic strategies for WS1.

Points noted:

- The researcher presented unpublished data and therefore only high-level points can be shared.
- Studies in WS pancreatic islets, generated using WS patient-derived iPSCs, found impaired insulin processing, altered calcium handling, changes in autophagy; and inflammation-induced beta cell death.
- An WFS1 variant disrupting an acceptor splice site highlighted the impact of alternative splicing on beta cell apoptosis in a patient with WS. The Wolframin mutation did not appear to affect pancreatic islet differentiation.
- RGS4 gene, a negative inhibitor of insulin secretion, was upregulated.
- Treatment with Liraglutide, a GLP-1 receptor agonist, restored these abnormal processes and protected against inflammation-induced cell death.
- The researchers conducted further studies to investigate the potential role of the immune system in these pro-inflammatory processes in WS, and whether targeting the immune response could help slow disease progression.
- The results suggest that immunological mechanisms may be involved in the pro-inflammatory response seen in WS and therefore may represent a new target for therapeutic intervention.
- The researchers will prepare a manuscript for publication in a scientific peer-reviewed journal and further explore the immunological mechanisms involved including disease heterogeneity (i.e. differences between people with WS).

22. First International Consensus Clinical Guidelines for Wolfram Syndrome: A Foundation for Care and Future Therapies. Dr. Josephine Elliott, Saumel Ahmadi, MD, Prof Patrick Yu Wai Man, Sarah Gladstone, MD, Tracy Lynch, Prof Timothy Barrett, and Fumihiko Urano, MD, on behalf of the International Wolfram Syndrome Clinical Guidelines Consortium.

Abstract: Wolfram syndrome is a rare genetic disease that presents significant challenges for patients and their families. It typically begins in childhood with insulin-requiring diabetes and progressive optic nerve changes affecting vision, and over time, can involve broader neurological symptoms that increasingly affect daily life. There are no disease-modifying treatments approved today, and until now, no international clinical guidelines have existed, leaving diagnostic and management practices to vary substantially between centres. A shared standard of care is essential, both to ensure that diagnosis, monitoring, and management are consistent for patients worldwide, and to allow new therapies to be evaluated and integrated reliably as they emerge. In this talk, we will present the first international consensus clinical guidelines for Wolfram syndrome.

The guidelines were developed by an international steering committee co-chaired by Timothy Barrett (University of Birmingham, UK) and Fumihiko Urano (Washington University in St. Louis, USA), together with the International Wolfram Syndrome Clinical Guidelines Consortium. The committee performed a systematic review of more than 350 peer-reviewed publications and drafted consensus statements across six clinical domains: diagnosis and general management; neuro-ophthalmology; neurology; endocrinology; urology and gastroenterology; and psychiatry and cognition. A panel of more than 50 international specialists from North America, Europe, Latin America, and Asia evaluated the statements through a modified three-round Delphi process, with consensus defined as 80% or greater agreement. Structured feedback from patients and families was incorporated through international advocacy organisations including the Snow Foundation and Wolfram Syndrome UK.

All 36 final consensus statements reached the predefined threshold of 80% or greater agreement, spanning diagnosis and genetic testing, multidisciplinary care organisation, neuro-ophthalmology, neurology, endocrinology, urology and gastroenterology, and psychiatry. The guidelines also propose a unified Wolfram Spectrum Disorders framework that distinguishes childhood-onset and adult-onset WFS1-Wolfram syndrome, WFS1-related disorders, and CISD2-Wolfram syndrome, supporting accurate classification and tailored care.

These are the first international consensus clinical guidelines for Wolfram syndrome and provide actionable recommendations for clinicians worldwide. Implementation should be accompanied by prospective audit to expand the evidence base and inform future iterations. By aligning clinical practice across centres, the guidelines create the foundation on which our broader three-step research strategy, from oral medicines to base editing to regenerative therapy, can be brought to patients.

Points noted:

- The first international consensus clinical guidelines for WS have been developed to provide recommendations for the diagnosis and management of WS patients worldwide.
- The guidelines were developed with input from physicians across 12 diverse specialties, as well as patients and family members, to understand the factors they would want to be included and to provide feedback on draft guideline statements. Three rounds of review and feedback were conducted to develop the final guidelines.
- The steering committee included representatives from patient organisations with lived experience of WS (Wolfram Syndrome UK and The Snow Foundation) in addition to WS clinical experts.
- The next step is to publish the guidelines in a scientific peer-reviewed journal and disseminate them to clinicians worldwide.
- A patient-friendly format will also be made available, so those affected by WS and their families can access the guidelines.

23. Call of Projects Update. Nolwen Le Floch – President of the French Wolfram Association

Points noted:

- The speaker thanked the research community for their expertise and participation in the symposium.
- The French Wolfram Association and Foundation for Rare Diseases, France will issue a joint call for WS research projects later this year.
- The next WS International Research Symposium will be held in France in summer 2027. The exact dates will be confirmed as soon as possible.

Gina Isherwood, PhD Wolfram Syndrome UK, June 2026