

## TREATMENTS FOR WOLFRAM SYNDROME

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T-015862

### Technology Description

Dr. Fumihiko Urano at Washington University in St. Louis (WUSTL) and colleagues have developed therapeutic strategies to treat Wolfram syndrome. Wolfram syndrome is a rare, life-threatening, genetic disorder characterized by insulin-dependent diabetes mellitus, diabetes insipidus, optic nerve atrophy, and progressive neurodegeneration. The first symptom, diabetes mellitus, appears around age 6 with the additional associated conditions developing over the next two decades. Wolfram syndrome is an endoplasmic reticulum (ER) disorder that is caused by mutations in the WFS1 and CISD2 genes. These mutations cause dysregulation of calcium homeostasis and accumulation of misfolded WFS1 proteins which leads to ER stress and dysfunction. This, in turn, causes pancreatic beta cell death and neurodegeneration.

Despite this understanding, there are no therapeutics for Wolfram syndrome. Thus, there is a great need for treatments to delay, halt or reverse disease progression. Recently, Dr. Urano and colleagues have developed three technologies (WUSTL T-014512, WUSTL T-015666, and WUSTL T-015862) that could be used to treat Wolfram syndrome. A clinical trial to assess WUSTL T-014512 is currently ongoing, please see below for further information.

Additionally, these treatments may also have further utility. Wolfram syndrome is rare but its associated conditions are not. Thus, these treatment strategies may also have use for more prevalent ER stress and dysfunction-based disorders such as diabetes, retinal degeneration, and neurodegenerative diseases.

### **Dr. Urano's treatment approaches include the following technologies:**

**WUSTL T-014512:** This technology provides a small molecule therapeutic to treat Wolfram syndrome. Here, the inventors have repurposed dantrolene, an existing FDA-approved therapeutic that stabilizes ER calcium levels, for use in treating Wolfram syndrome.

**Stage of research-** The inventors have shown that dantrolene can suppress cell death and dysfunction in mouse models of Wolfram syndrome. Further, dantrolene can prevent cell death in neural progenitor cells derived from iPSCs of Wolfram syndrome patients.

**Clinical trial-** Dr. Urano is conducting a phase 1b/2 clinical trial to assess the safety, tolerability and efficacy of dantrolene sodium in treating pediatric and adult patients with Wolfram syndrome. In addition, the efficacy of dantrolene sodium on the cardinal manifestations of Wolfram syndrome, including visual acuity, remaining beta cell functions, and neurological functions will be assessed. The clinical trial is ongoing. It began in January 2017 and its estimated completion date is March 2021. Results are eagerly anticipated. For additional information see study [NCT02829268](#).

**WUSTL T-015666:** This technology provides a regenerative medicine approach to treating Wolfram syndrome. Work from Dr. Urano's lab has indicated that MANF (mesencephalic astrocyte-derived neurotrophic factor) and the MANF signaling cascade could be used to protect cells from ER stress-mediated cell death. Further, the inventors have identified the MANF receptor and it may also provide a useful therapeutic target. From this work, this technology was developed. It provides a strategy to treat Wolfram syndrome by delivering MANF to neurons, pancreatic beta cells and retinal ganglion to suppress neurodegeneration and improve beta cell mass.

**Stage of research-** The inventors have shown that administering recombinant MANF peptide and adeno-associated virus (AAV) expressing human MANF induces proliferation of residual beta cells in Wolfram mouse models. The inventors are also assessing the efficacy of recombinant MANF peptide and AAV on retinal degeneration in iPSC and mouse models of Wolfram syndrome.

**WUSTL T-015862:** This technology provides novel small molecule ER calcium stabilizers that, like dantrolene, target ER calcium transporters. These second-generation molecules are intended to be safer, more potent and have more bioavailability to the central nervous system.

**Stage of research-** The inventors have shown that these small molecules can prevent cell death in beta cell and iPSC models of Wolfram syndrome.

## Applications

- Treatment for Wolfram syndrome
- Potential to treat other ER stress disorders including
  - Diabetes
  - Neurodegenerative diseases
  - Retinal degeneration

## Key Advantages

- Solves an unmet need- provides therapeutic strategies to treat Wolfram syndrome and, potentially, other ER stress-related disorders
- Portfolio offers several therapeutic strategies
- New use for an existing product- dantrolene is an FDA approved molecule used to treat muscle spasms and malignant hyperthermia
- Second generation ER calcium stabilizers are:
  - Safer
  - More potent
  - More bioavailable to central nervous system and eyes

## Publications

- Abreu D, Urano F. [Current Landscape of Treatments for Wolfram Syndrome.](#) Trends Pharmacol Sci. 2019 Aug 13. pii: S0165-6147(19)30163-4. doi: 10.1016/j.tips.2019.07.011.
- Lu S, Kanekura K, Hara T, Mahadevan J, Spears LD, Oslowski CM, Martinez R, Yamazaki-Inoue M,

Toyoda M, Neilson A, Blanner P, Brown CM, Semenkovich CF, Marshall BA, Hershey T, Umezawa A, Greer PA, Urano F. [A calcium-dependent protease as a potential therapeutic target for Wolfram syndrome](#). Proc Natl Acad Sci U S A. 2014 Dec 9;111(49):E5292-301. doi: 10.1073/pnas.1421055111.

- Dryden, J. [Muscle relaxant may be viable treatment for rare form of diabetes](#). The Source- a Washington University in St. Louis publication, 2014 Nov 24.

## Patents

- WUSTL technology T-014512 [PCT patent application](#)
- WUSTL technology T-015862 [PCT patent application](#)

## Related Web Links

[Dr. Urano profile](#)

[Wolfram Syndrome International Registry and Clinical Study](#)