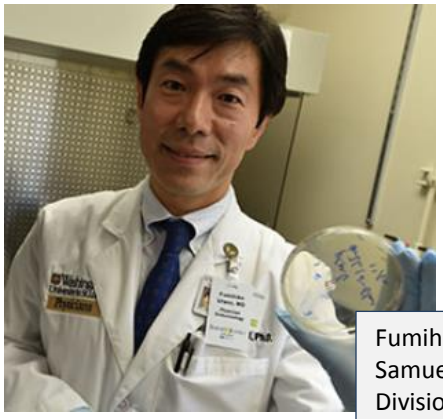


Fumihiko Urano MD, PhD
Samuel E. Schechter Professor of Medicine
Division of Endocrinology, Metabolism and Lipid Research

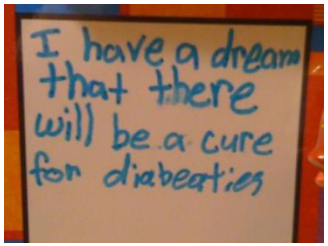
Wolfram Syndrome (WS) is a rare*, autosomal recessive disorder characterized by juvenile diabetes, optic nerve atrophy, deafness, and neurodegeneration. WS is often fatal by mid-adulthood due to multi-organ health complications. The goal of this work is to understand the molecular ER dysfunction mechanisms in WS, develop biomarkers to monitor progression and to identify patient-based therapeutics to identify actionable targets.
*1:500,000

Key Publications
March 2014
Dec 2014

Study Started

2011

June 2011
Awarded 2 year **Pilot funding from ICTS** to establish a yearly clinic for phenotypic characterization of children with WS and to collect and bank iPSCs from patients and family members to uncover biomarkers.



Study Completed

2013

FINDINGS:
Study results confirmed that WS has a pronounced impact on early brain development, accompanied with impairments in gait and balance. Identified ⬆ Calpain-2, a Ca+2 dependent protease implicated in ER –stress mediated and amyloid-mediated neuronal and beta cell death.

MECHANISM: Calcium Leakage to the cytosol

↓

Calpain 2 activation

↓

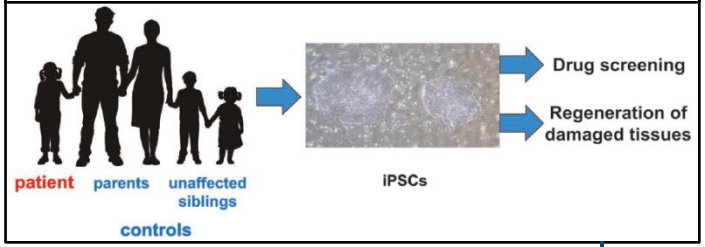
Cell Death

2014

Diabetes. 2014 Mar; 63(3): 844–846. PMCID: PMC3931391
Published online 2014 Feb 13. doi: 10.2337/db13-1809

Wolfram Syndrome iPS Cells: The First Human Cell Model of Endoplasmic Reticulum Disease

Fumihiko Urano



Proc Natl Acad Sci U S A. 2014 Dec 9; 111(49): E5292–E5301. PMCID: PMC4267371
Published online 2014 Nov 24. doi: 10.1073/pnas.1421055111
PNAS Plus
Medical Sciences

A calcium-dependent protease as a potential therapeutic target for Wolfram syndrome

Simin Lu,[a,b] Kohsuke Kanekura,[a] Takashi Hara,[a] Jana Mahadevan,[a] Larry D. Spears,[a] Christine M. Oslowski,[c] Rita Martinez,[d] Mayu Yamazaki-Inoue,[e] Masashi Toyoda,[e] Amber Neilson,[d] Patrick Blanner,[d] Cris M. Brown,[a] Clay F. Semenkovich,[a] Bess A. Marshall,[f] Tamara Hershey,[g] Akihiro Umezawa,[e] Peter A. Greer,[h] and Fumihiko Urano[a,i,1]

National Center for Advancing Translational Sciences

Ellie White Foundation For Rare Genetic Disorders

Snow Foundation For Wolfram Syndrome Research

National Institute of Diabetes and Digestive and Kidney Diseases

NCATS Drug Development Team (4/2015)

- Support for new screens for WS using known drugs, mechanism-based collection, diversity collection and improved assays
- Modification of structure of dantrolene and pioglitazone.

NCATS Global Rare Disease Registry (12/2015) WS International Registry joins seven inaugural members of GRDR.

FDA requests additional pre-clinical studies

FDA approves ODD #15-4745 for dantrolene sodium for "treatment of WS"

2015

Spring, 2016

Fall, 2016

Regulatory Support Center (RSC)

ICTS Regulatory Core assists in preparation of Orphan Drug Designation request for dantrolene sodium to FDA.

ICTS STAR (Special Translational Award Request) Funding for "Dose Escalation Studies for Dantrolene in Mouse and iPSC Models of WS"

Regulatory Support Center (RSC)

ICTS JIT award funding to prepare regulatory documents for "Phase 1b Clinical Trial for Dantrolene in Patients with Wolfram Syndrome"

FDA IND 133439 (Jan 2017) approval of dantrolene sodium in WS treatment

Dantrolene Clinical Trial

NCT02829268: 10/2016
Phase 1b Safety and Tolerability Trial in pediatric and adult WS patients

3 patients enrolled and taking dantrolene (Feb 2017)