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

**FINDINGS:**
Study results confirmed that WS has a pronounced impact on early brain development, accompanied with impairments in gait and balance. Identified \( \uparrow \) 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
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
- FDA requests additional pre-clinical studies
- FDA approves ODD #15-4745 for dantrolene sodium for “treatment of WS”

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”
- 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)