A Cure For Wolfram Three Steps 3.0

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REPLACE
damaged genes & tissues

PROTECT & REGROW
remaining tissues

STOP
progression

Mechanisms

Loss of function of WFS1

↓

Calcium Leakage from the endoplasmic reticulum to the cytosol (ER stress)

↓

Calpain 2 activation (enzyme)

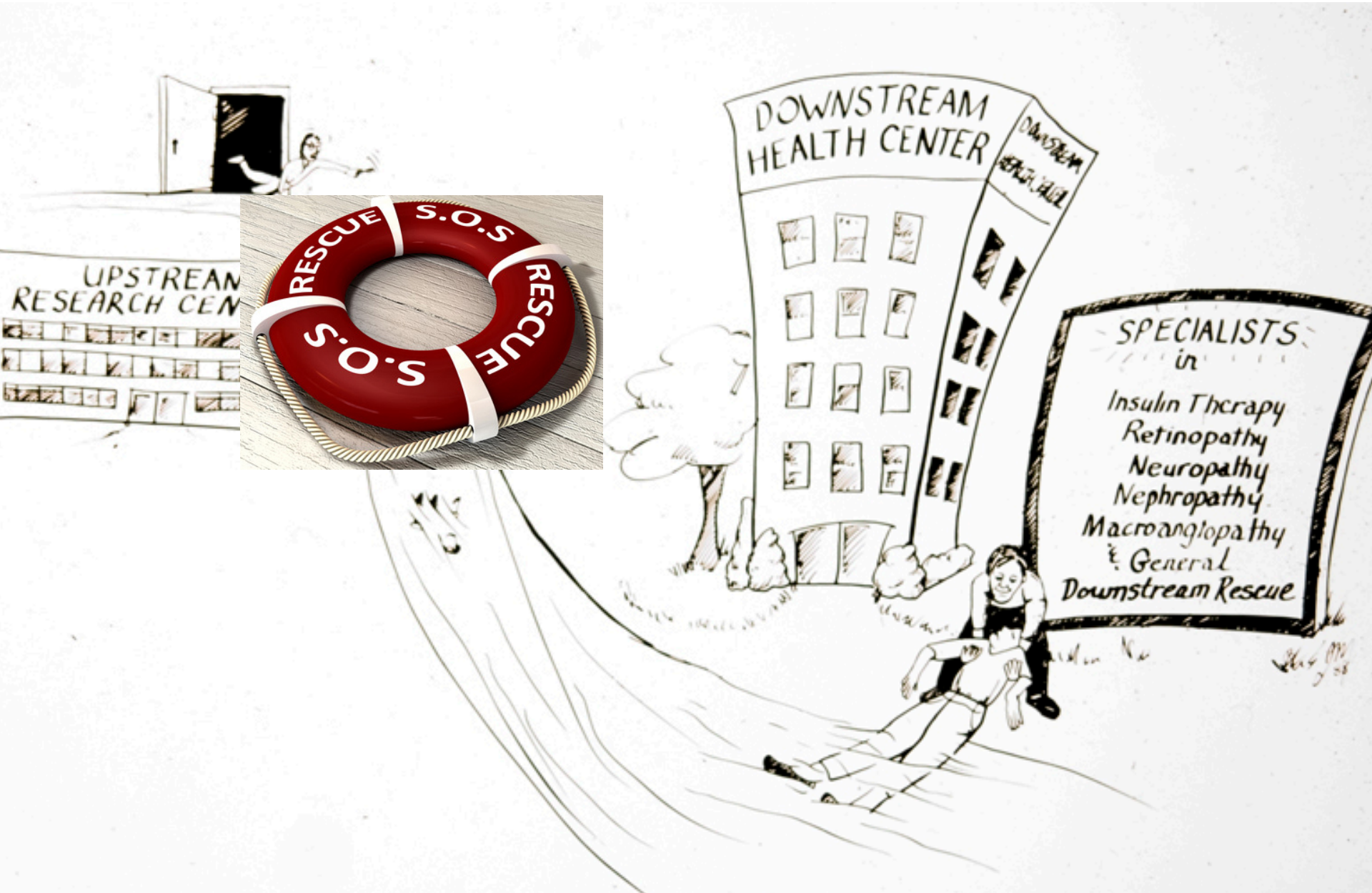
↓

Neuro/retinal degeneration

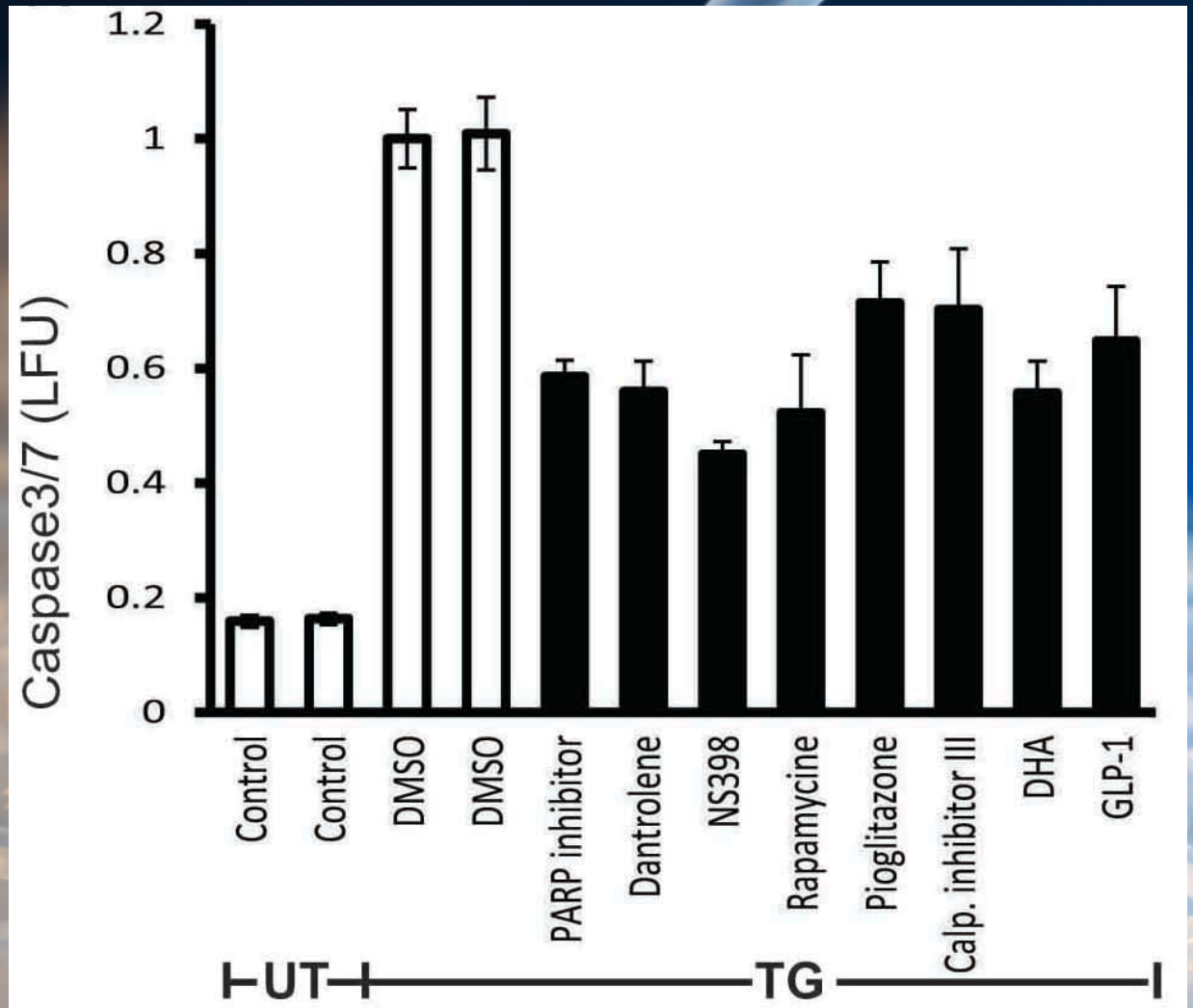
Beta cell death

Urano lab ref: Nature (2002); J Biol Chem (2006); Cell Metab (2006); J Clin Invest (2010); Proc Natl Acad Sci USA (2014); Science Sig (2015)

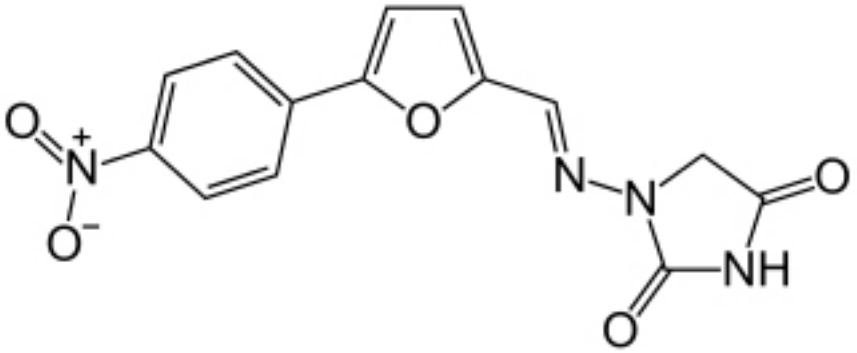
A DRUG targeting the UPSTREAM



Identify FDA-approved DRUGS that can prevent ER calcium depletion-mediated Cell Death



Dantrolene (FDA approved)



1. Targets ryanodine receptor in the ER

2. Spasticity (capsules)

Adults

25 mg once daily for seven days, then 25 mg t.i.d. for seven days,
50 mg t.i.d. for seven days, **100 mg t.i.d.**

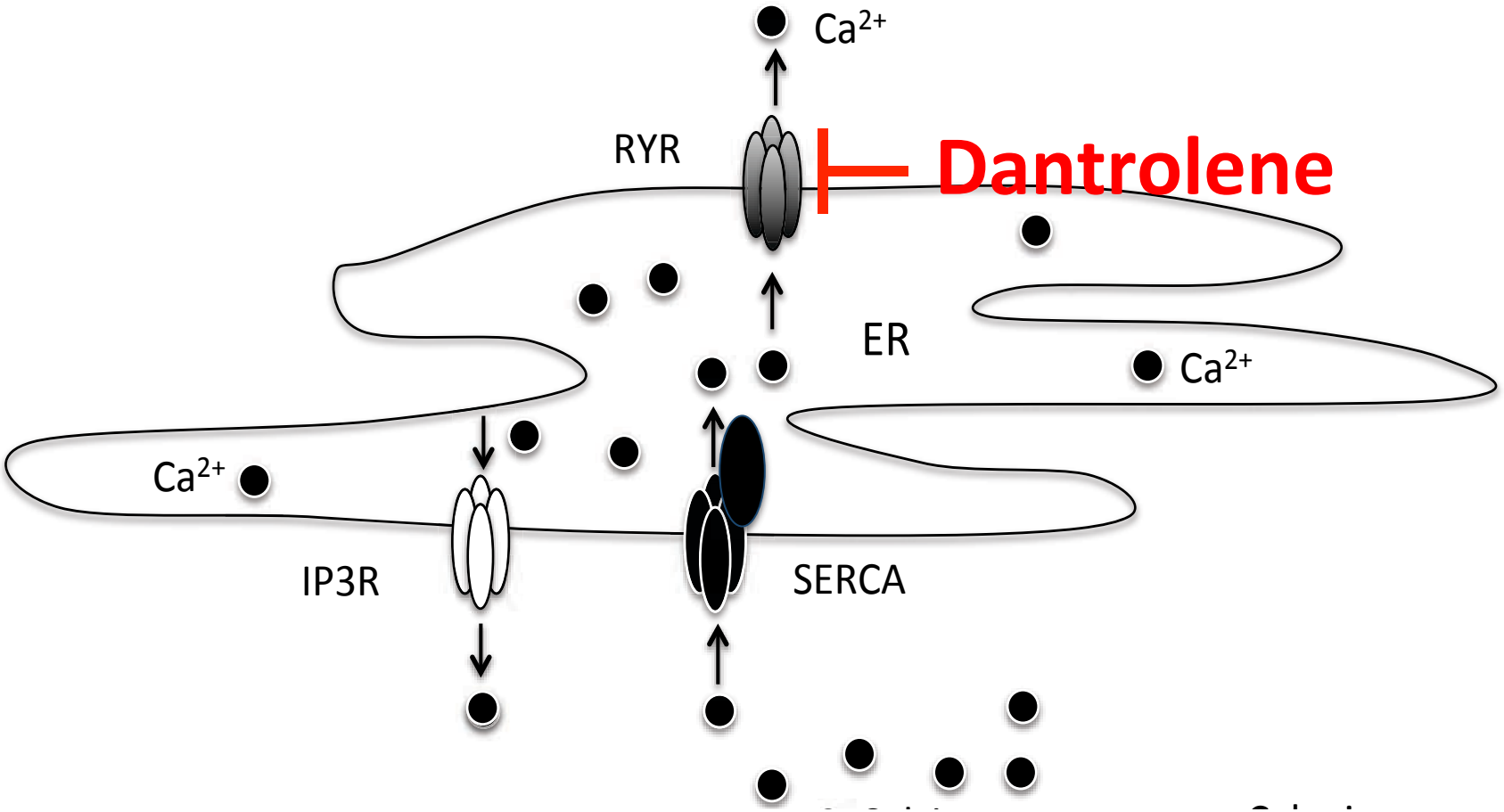
Children

0.5 mg/kg once daily for seven days, then 0.5 mg/kg t.i.d. for seven days
1 mg/kg t.i.d. for seven days, **2 mg/kg t.i.d.**

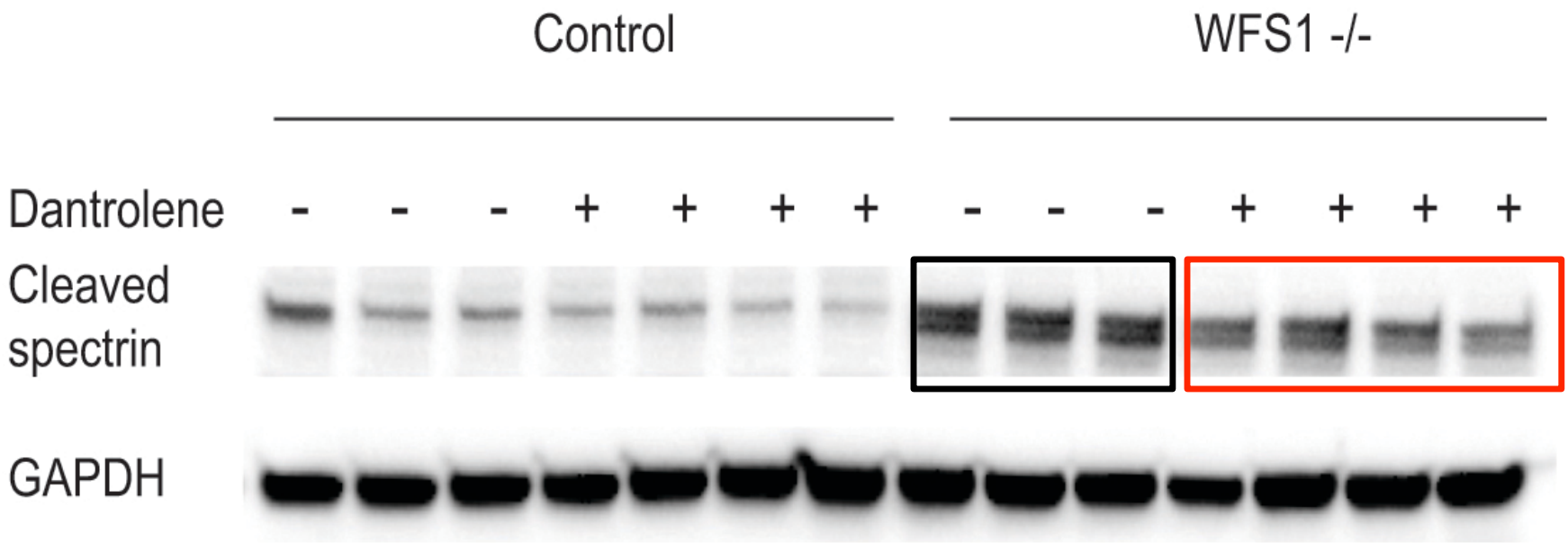
3. Malignant hyperthermia (intravenous)

1 mg/kg-10 mg/kg until symptoms subside.

Dantrolene targets ryanodine receptor localized to the endoplasmic reticulum



Dantrolene prevents calpain activation (cell death enzyme) in a Wolfram-neurdegeneration mouse model



i.p., q.d., 20 mg/kg, 4 weeks
(For Spasticity in children: 6 mg/kg/day)

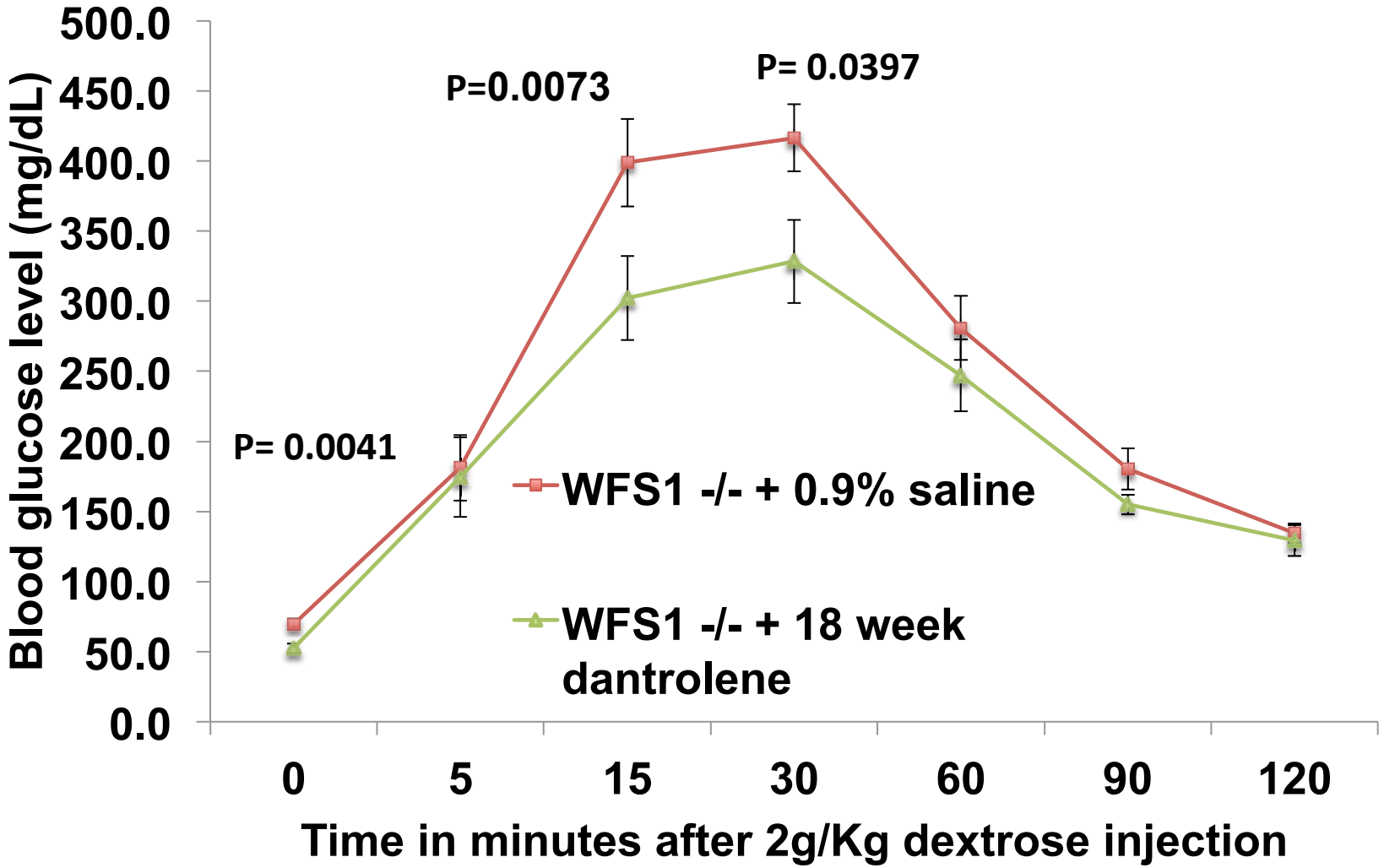
Dantrolene
in beta cell-specific WFS1 KO mice
(Wolfram-diabetes mouse model)

Group 1: 10 WFS1 beta cell-specific knockout male mice, 8 weeks of age, 6mg/kg of dantrolene, I.P. Injection for 5 days per week up to 18 weeks (10 mice).

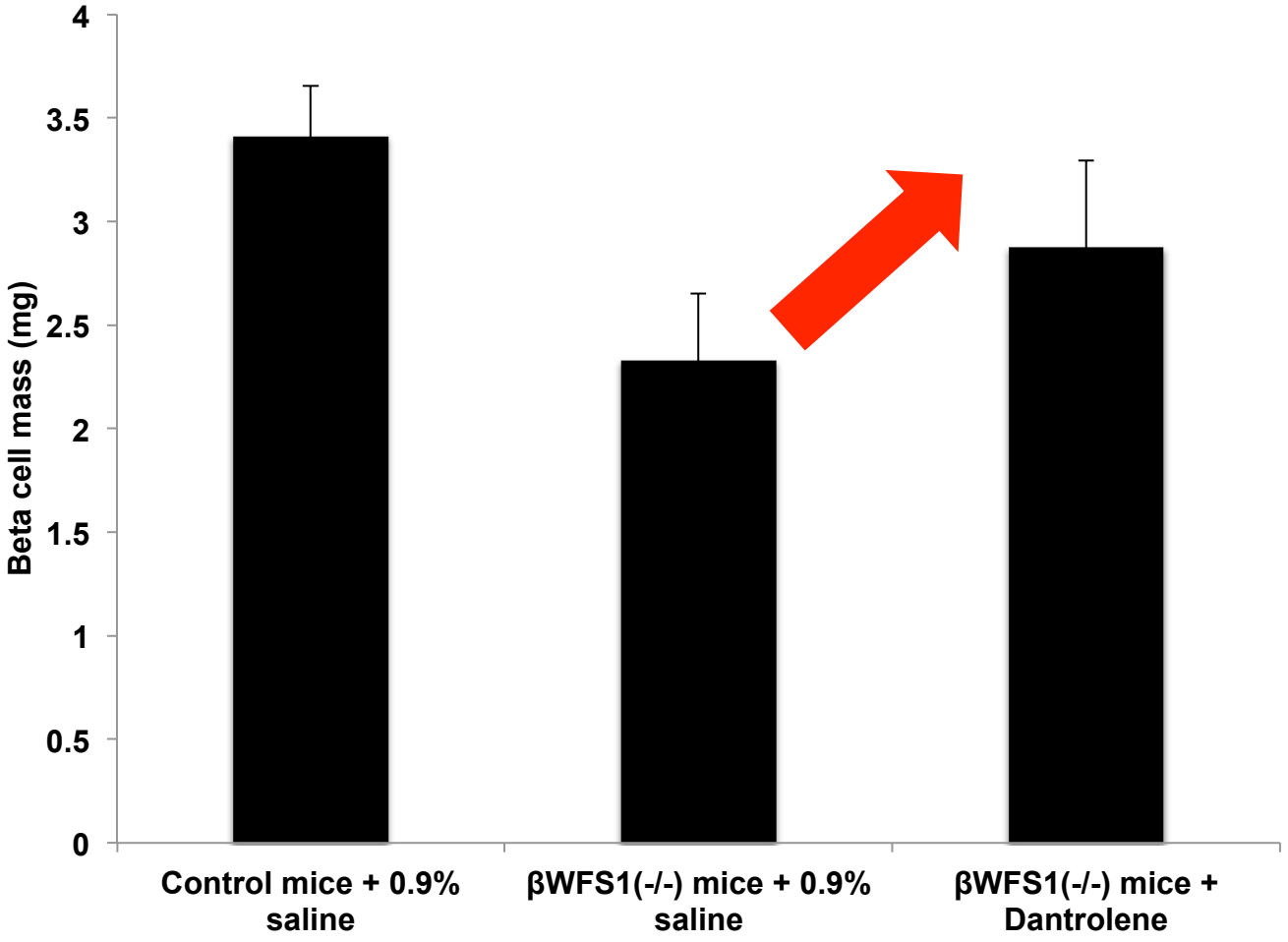
Group 2: 10 WFS1 beta cell-specific knockout male mice, 8 weeks of age with 0.9% saline (10 mice).

Group 3: 10 Littermate control male mice, 8 weeks of age with 0.9% saline (10 mice).

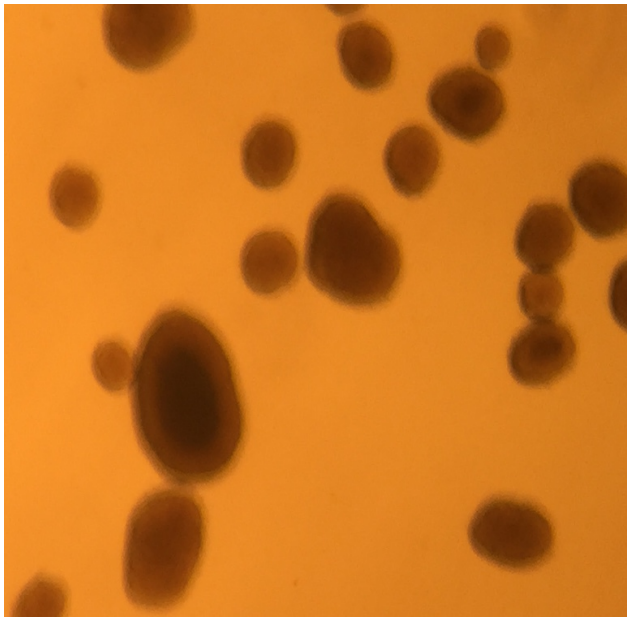
18-week treatment with dantrolene



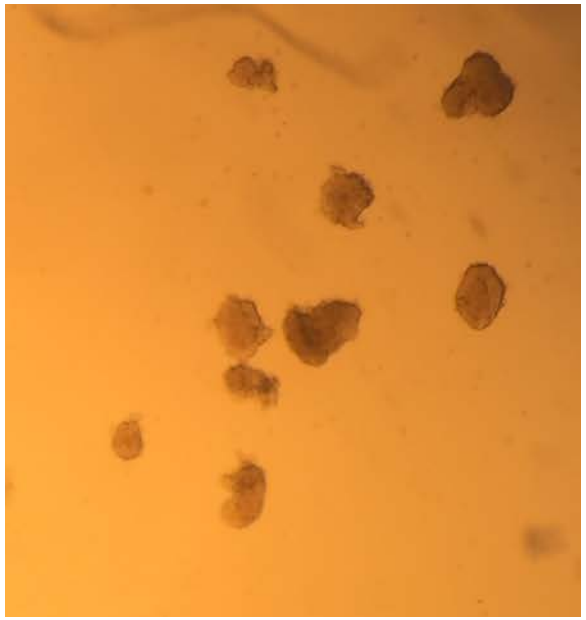
Beta cell mass is preserved in dantrolene-treated WFS1 KO mice



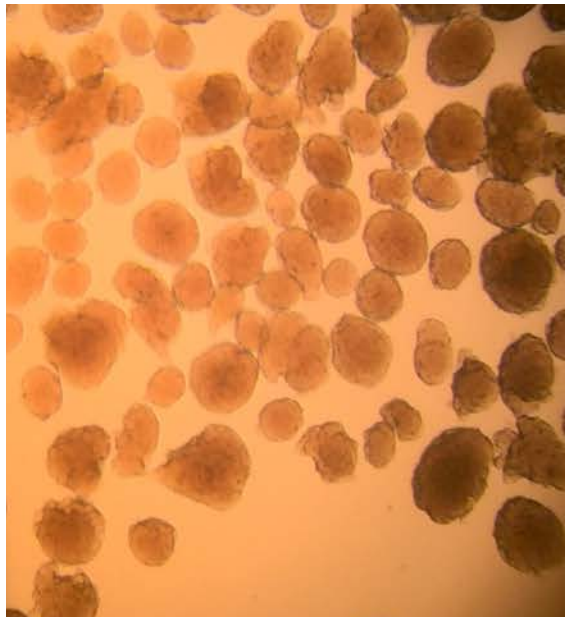
Bright field microscopy image of islets from Wolfram mice treated with dantrolene



Control mice

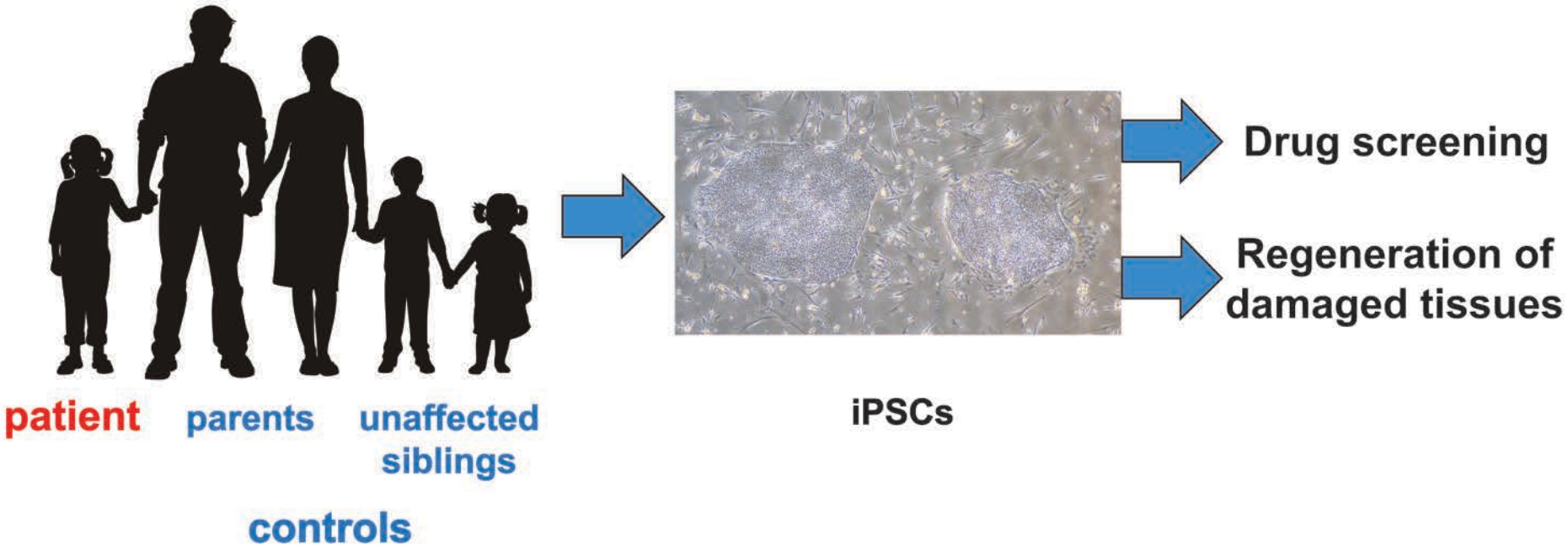


β-WFS1 -/- mice
Tx: saline



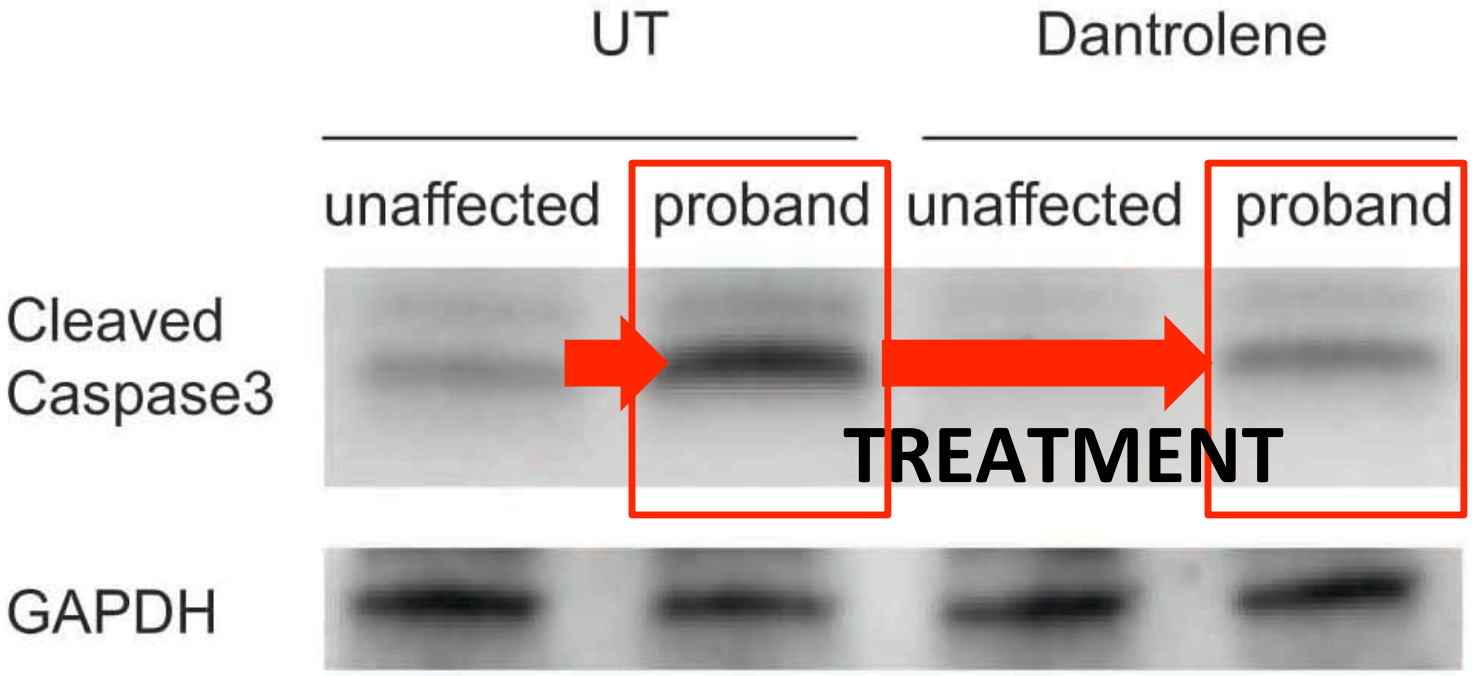
β-WFS1 -/- mice
Tx: dantrolene

Induced Pluripotent Stem Cells from Wolfram patients

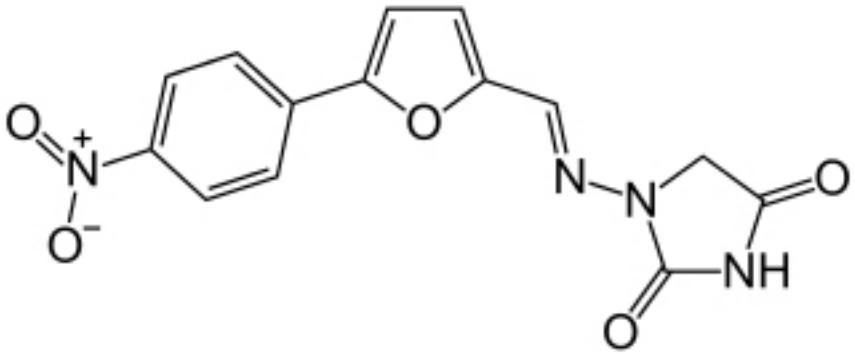


Urano F. *Diabetes* (2014)

Dantrolene prevents apoptosis in Wolfram iPSC-derived neuronal cells



Dantrolene



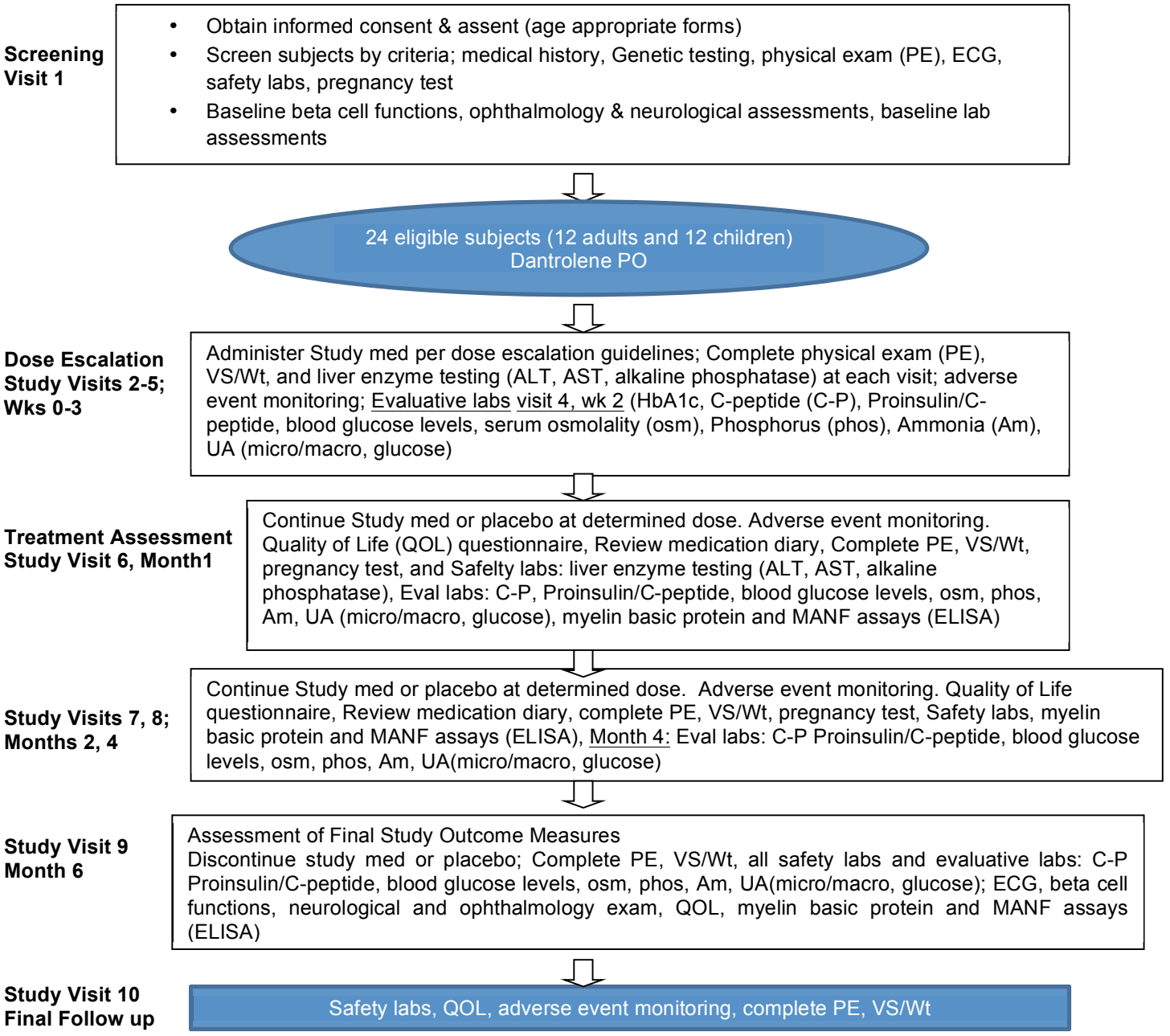
1. **Preclinical studies in the Wolfram neurodegeneration mouse model**
2. **Orphan drug designation (Approved by FDA, 2016)**
3. **Safety studies in patients with Wolfram syndrome**

A Proof of Concept Clinical Trial

ClinicalTrials.gov Identifier: NCT02829268

- An open label and ascending dose study in children and adult patients
- To assess the safety and tolerability of dantrolene administered orally at upper end of therapeutic dose range for 6 months.
- Primary endpoint
  - Safety and Tolerability (Liver enzymes)
- Secondary endpoints
  - Beta cell function (C-peptide, mixed meal challenge test)
  - Balance test
  - Visual acuity
  - QOL, WURS, ER stress

FIGURE: CLINICAL TRIAL DIAGRAM



Dose escalation in the first four weeks

Screening

Adult patients

Visit #2: 25 mg once daily for seven days, then

Visit #3: 25 mg t.i.d. for seven days

Visit #4: 50 mg t.i.d. for seven days

Visit #5: 100 mg t.i.d.

Pediatric patients

Visit #2: 0.5 mg/kg once daily for seven days, then

Visit #3: 0.5 mg/kg t.i.d. for seven days

Visit #4: 1 mg/kg t.i.d. for seven days

Visit #5: 2 mg/kg t.i.d.

- **Duration: 6-9 months (Screening, Dose escalation, 6 month treatment, and follow-up)**
- **24 patients (12 adults, 12 children)**
- **Primary endpoint**
  - **Safety (liver enzymes, lab test, physical exams)**
  - **Tolerability (Dose escalation over 4 weeks)**
- **Secondary endpoints**
  - **Beta cell function (baseline C peptide, Mixed meal boost test)**
  - **Balance test (Mini-BESTest)**
  - **Visual acuity**
  - **QOL, WURS, Serum biomarkers (MANF, MBP)**

Anticipated Timeline

- **February 2016: Orphan Drug Designation Approved by the US FDA**
- **June 2016: A clinical trial protocol submitted to the WashU Institutional Review Board (IRB)**

- Fall 2016: IRB approval
- Winter 2016: Screening and Recruitment of Patients
- Spring-Summer 2017: Commencement of the trial

Funding: **Snow Foundation and Ellie White Foundation**

National Institutes of Health (pending)

Private Foundations, such as JDRF (pending)

FDA-approved drugs

Stop the progression

Novel drugs

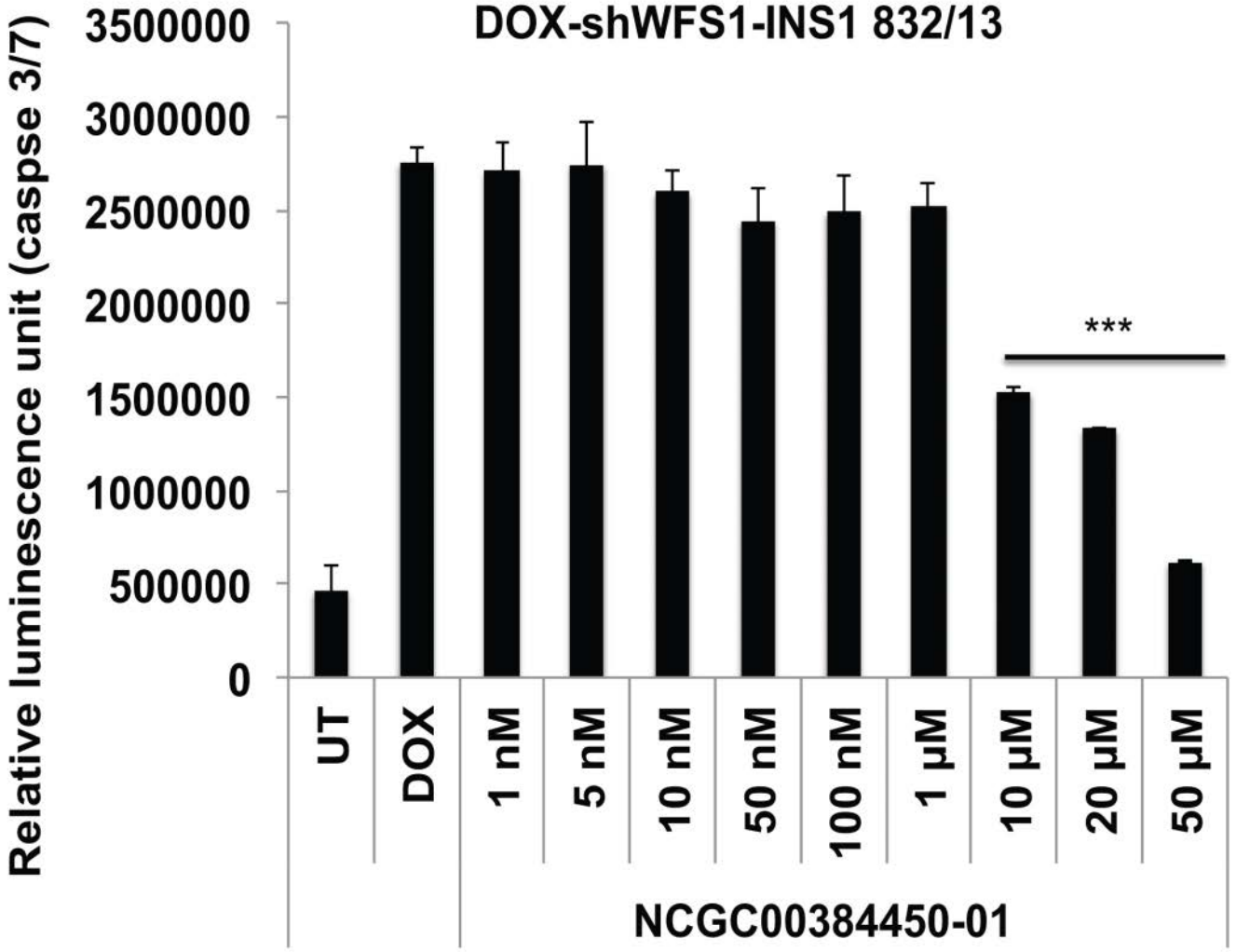
Identify novel drugs that can prevent WFS1 gene depletion-mediated Cell Death

Washington University-National Center for Advancing Translational Sciences (NCATS)/NIH Joint Diagnostic and Therapeutic Development (2014-present)

The Therapeutics for Rare and Neglected Diseases (TRND) program at NCATS

- Aims to encourage and speed the development of new treatments for rare and neglected diseases.
- Optimization and pre-clinical testing of therapies, with the goal to generate sufficient-quality data to support successful Investigational New Drug applications to the Food and Drug Administration and first-in-human studies in limited circumstances.

NCGC00384450-01 prevents WFS1-depletion-mediated beta cell death



New Drug Candidates designed for the treatment of Wolfram syndrome

1. **Medicinal chemistry**
2. **Pharmacokinetics and toxicity studies**
3. **Preclinical studies in cell and animal models for the Investigational New Drug (IND) application**

Anticipated Timeline

- **2014-2015: Screening of drugs**
- **2015: Testing in cell models of Wolfram**
- **2015-2016: Identification of two lead drug candidates**
- **2016: Toxicity and PK studies of two drug candidates**

- 2016-2017: Testing of two lead drug candidates in mouse models
- 2016-2017: Further modification of two lead drug candidates
- 2017-2018: Toxicity and PK studies of modified candidates
- 2018-2020: Further animal studies and human studies

A Cure For Wolfram
Three Steps 3.0

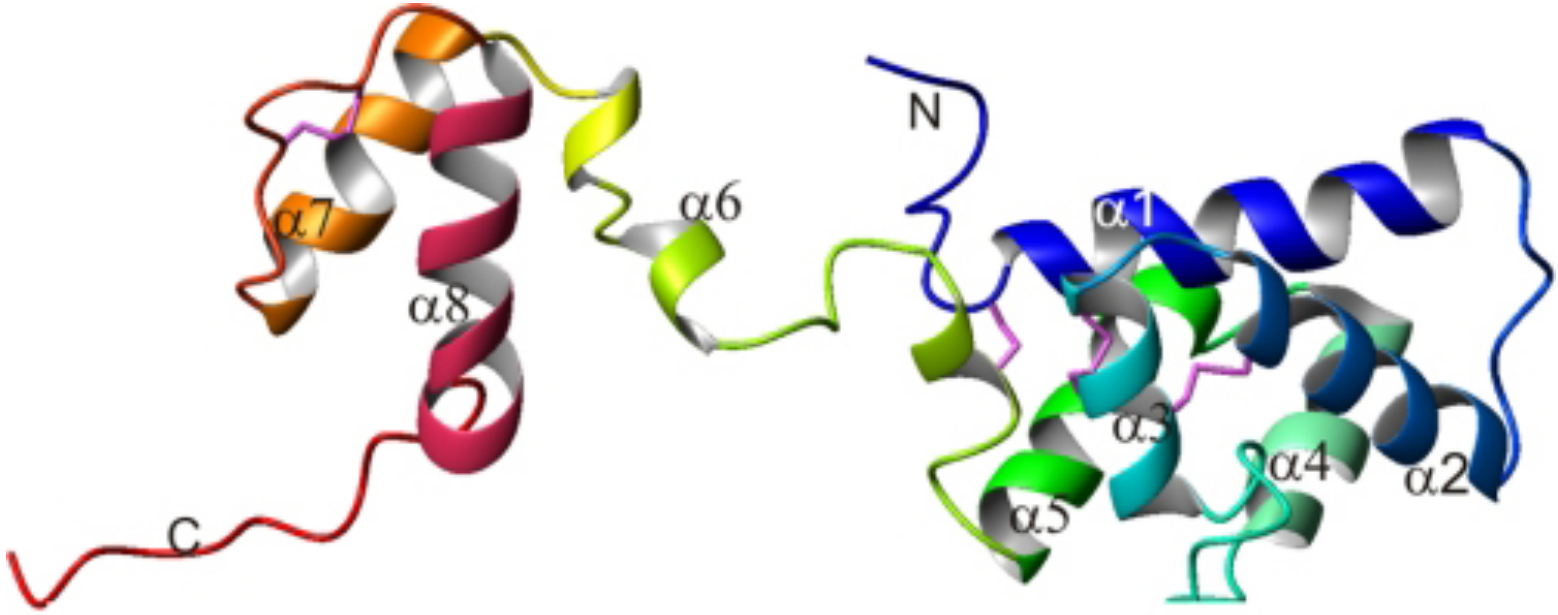
REPLACE
damaged genes &
tissues

PROTECT & REGROW
remaining tissues

STOP
progression

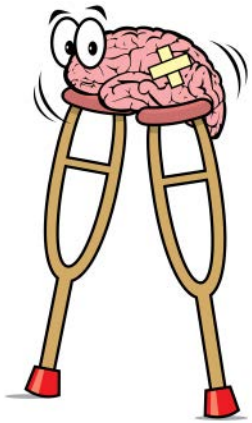
REGENERATION FACTORS
Produced in our body

MANF: Regeneration Factor



Produced in our body

MANF-based treatment



Neuronal damage

Retinal degeneration

Diabetes

MANF-like drugs

MANF Receptor agonists

Anticipated Timeline

- **2016-2018: Generation of MANF-like drugs (receptor modulators)**

- 2018-2020: Preclinical studies in cell and animal models
- 2020-: Preclinical to First-in-Human Studies

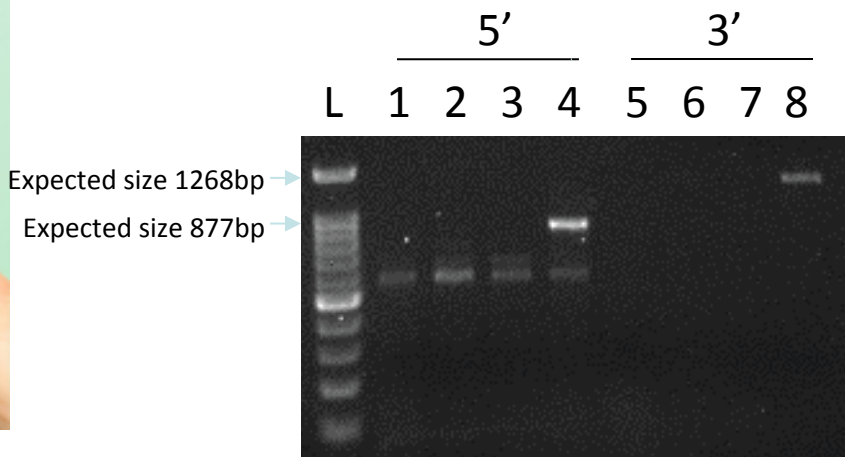
A Cure For Wolfram Three Steps 3.0

REPLACE
damaged genes & tissues

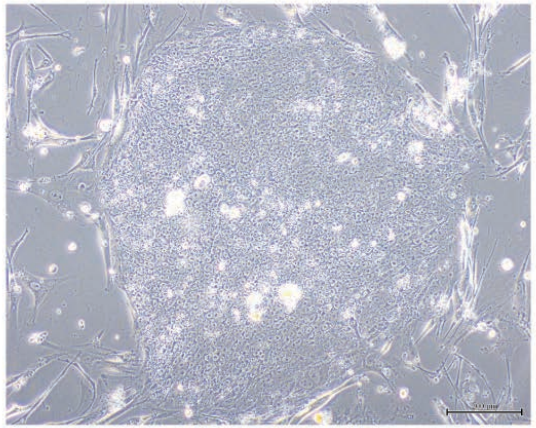
PROTECT & REGROW
remaining tissues

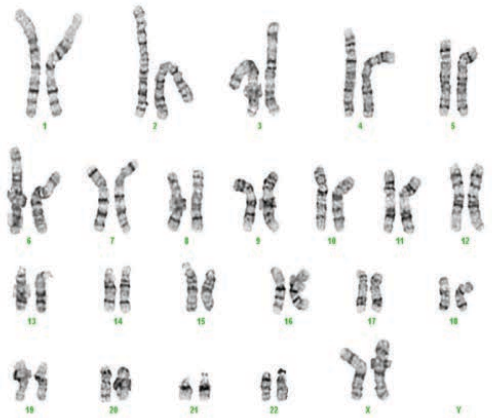
STOP
progression

Replace disease-causing DNA with the healthy one (CRISPR/CAS9)

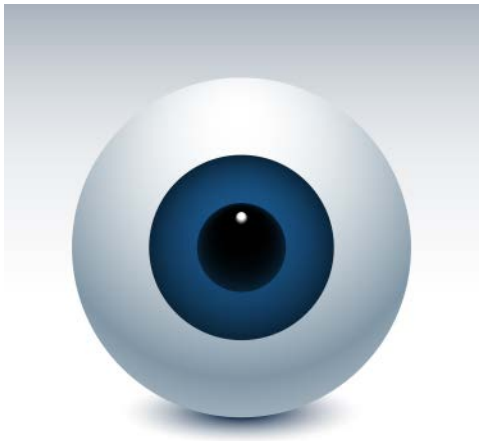


Brain Cells and Eye cells from skin cells

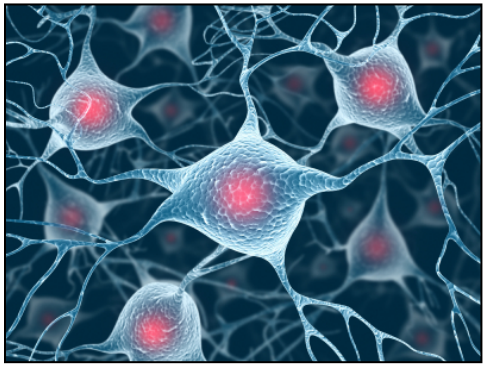




iPS Cells



EYE



BRAIN

Anticipated Timeline

- **2016-2020: Early stage preclinical studies**

- After 2021: Preclinical to First-in-Human Studies

Washington University

Wolfram Etiology
Cris Brown
Mai Kanekura
Simin Lu
Damien Abreu
Kohsuke Kanekura
Jana Mahadevan
Stephen Stone
Amy Clark
Takuya Yagi
Takashi & Mariko Hara

Wolfram syndrome registry
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Amber Neilson
Jeff Millman

ER Disease Center
Kelly Moley
Bradley Evanoff
Karen Seibert
Jonathan Heusel
Catherine Cottrell
Hussam Al Kateb

Type 1 Diabetes
Emil Unanue
Jean Schaffer

Optic Nerve Atrophy
Raj Apte

Neurodegeneration
Timothy Miller
David Holtzman
Matthew Harms
Celeste Karch
Valeria Cavalli
Robert Schmidt
David Wozniak

Regenerative Medicine
Lila Solnica-Krezel
[illegible]

Nephrotic Syndrome
Ying Maggie Chen

Calcium
David Piston
Zeno Lavagnino
Larry Spears
Clay Semenkovich

Autophagy
Abhinav Diwan

U Birmingham
Timothy Barrett

NIH/NCATS
Francis Collins
Ajit Jadhav
David Maloney
Anton Simeonov
Bandon Harvey
Mark Henderson
Petra Kaufmann