HRA meeting: Enhancing the role of nonprofits in accelerating therapeutic development

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DISCLOSURE:

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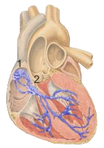
The Problem

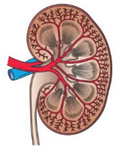
Diabetes is a major global and national health problem

Currently affects 529 million people worldwide

It inflicts significant human suffering & represents a serious economic burden

People with diabetes are 2-times more likely to have heart disease or stroke than those without





Additional complications include kidney disease, nerve damage, blindness, and amputations as well as increased risk of developing MASLD
(Metabolic dysfunction–Associated Steatotic Liver Disease, aka NAFLD)

Despite advances in diabetes technology and a record number of approved therapeutic options only ~25% of people with diabetes requiring insulin achieve target blood sugar control

Diabetes Ther
https://doi.org/10.1007/s13300-023-01399-0

ORIGINAL RESEARCH

Gaps Remain for Achieving HbA1c Targets for People with Type 1 or Type 2 Diabetes Using Insulin: Results from NHANES 2009–2020

Received: January 31, 2023 / Accepted: March 21, 2023

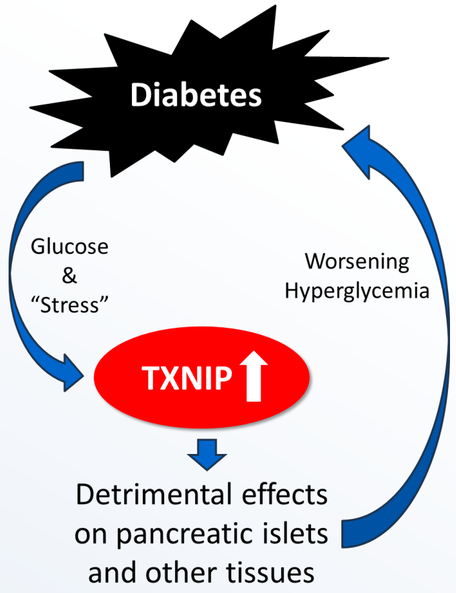
The most expensive chronic condition in the USA @ $413 Billion annually

Medical expenses are ~ 2.6 x higher in people with diabetes than those without

A New Target to Address It

Thioredoxin-interacting protein (TXNIP):

- **Oxidative stress protein**
- **Well conserved across species**
- **Identified as top glucose-induced gene in human islets**
- **Is increased in diabetes (T1D & T2D)**
- **Promotes inflammation**
- **Has detrimental effects on cell function and survival**



Thioredoxin-Interacting Protein Is Stimulated by Glucose through a Carbohydrate Response Element and Induces β-Cell Apoptosis

Alexandra H. Minn, Christian Hafele, and Anath Shalev

ORIGINAL ARTICLE

Thioredoxin-Interacting Protein

A Critical Link Between Glucose Toxicity and β-Cell Apoptosis

Junqin Chen,[1] Geetu Saxena,[1] Imran N. Mungrue,[2] Aldons J. Lusis,[2] and Anath Shalev[1]

Thioredoxin-interacting protein deficiency induces Akt/Bcl-xL signaling and pancreatic beta-cell mass and protects against diabetes

Junqin Chen,* Simon T. Hui,‡ Francesca M. Couto,* Imran N. Mungrue,§ Dawn B. Davis,*,† Alan D. Attie,† Aldons J. Lusis,§ Roger A. Davis,‡ and Anath Shalev*,1

Alpha Cell Thioredoxin-interacting Protein Deletion Improves Diabetes-associated Hyperglycemia and Hyperglucagonemia

Brian Lu, Junqin Chen, Guanlan Xu, Truman B. Grayson, Gu Jing, SeongHo Jo, and Anath Shalev

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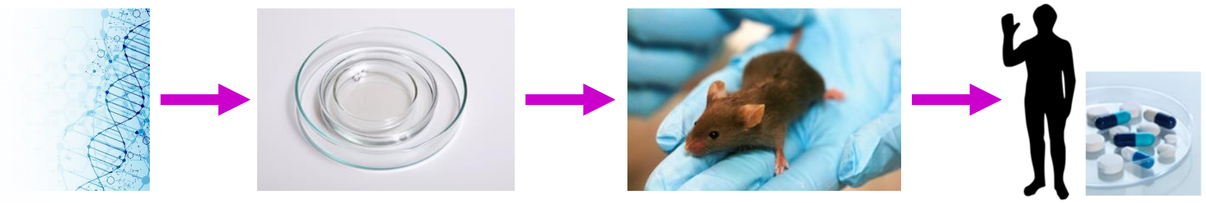
TXNIP is a key detrimental factor in this vicious cycle

Target Rationale: Pre-Clinical & Clinical

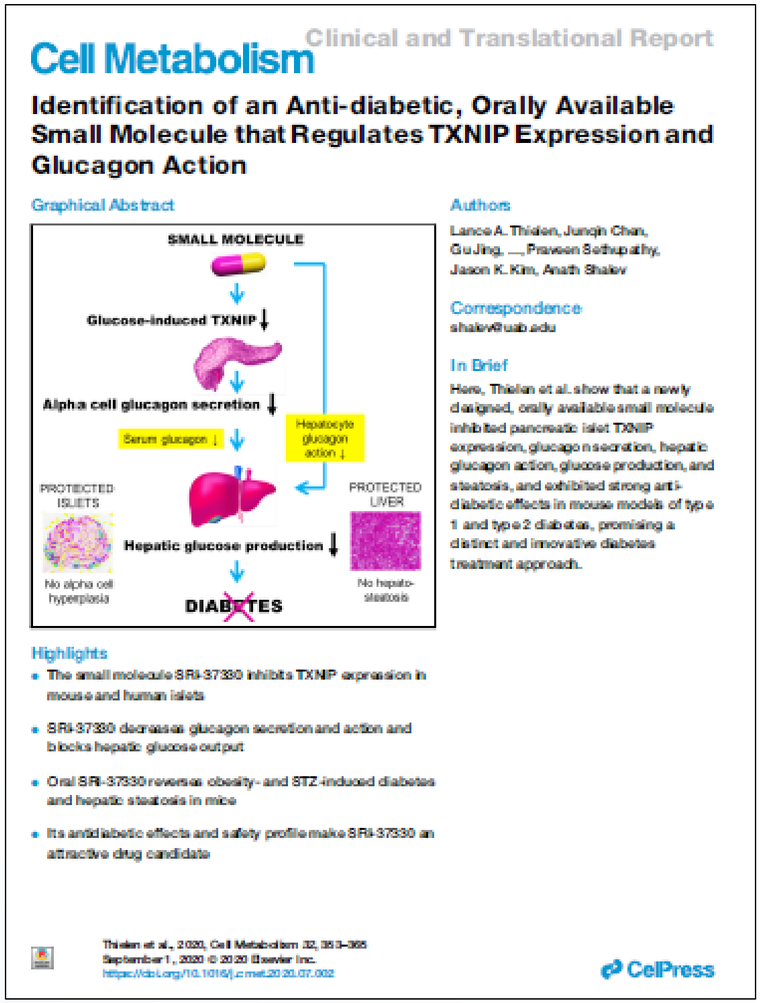


- **Genetic TXNIP deletion protects** multiple mouse models **against diabetes** (without causing any adverse effects). *(Chen…Shalev, FASEB 2008)*
- Non-specific pharmacological **inhibition of TXNIP with repurposed verapamil** (calcium channel blocking anti-hypertensive) **improves diabetes in mice and humans with T1D and T2D.** *(Xu…Shalev, Diabetes 2012; Ovalle…Shalev, Nature Medicine 2018; Xu…Shalev, Nature Communications 2022; Forlenza…the CLVer Study Group, JAMA, 2023)* BUT, limitation due to cardiovascular side effects.
- Specific **inhibition of TXNIP with new chemical entity TIX100** (small molecule, no calcium channel blockade) **improves diabetes in mouse models of T1D and T2D.**

→Targeting TXNIP is a **novel, disease-modifying approach** for the treatment of diabetes.

De-Risking TIX100

- ✓ Strong, **peer-reviewed preclinical data** *(Thielen…Shalev, CellMet)*
- ✓ TIX100 specifically **targets TXNIP (approach that has successfully been translated to humans with T1D and independently validated)** → Phase 2/3 verapamil trials *(Ovalle…Shalev, Nature Medicine 2018, CLVer trial JAMA 2023)*
- ✓ TIX100 is a lot **more potent, effective and specific** in inhibiting TXNIP than verapamil AND has **additional benefits** (counters hyperglucagonemia and excessive glucose production by liver)
- ✓ 7 sets of **animal models and human islet studies indicate TIX100 efficacy**
- ✓ TIX100 has **multiple indications** with very **large markets (T1D, T2D, MASLD** = metabolic dysfunction–associated steatotic liver disease, aka NAFLD = non-alcoholic fatty liver)


Cell Metabolism
Clinical and Translational Report

Identification of an Anti-diabetic, Orally Available Small Molecule that Regulates TXNIP Expression and Glucagon Action

Graphical Abstract

Authors
Lance A. Thielen, Junqin Chan, Gu Jing, …, Praveen Sethupathy, Jason K. Kim, Anath Shalev

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In Brief

Here, Thielen et al. show that a newly designed, orally available small molecule inhibited pancreatic islet TXNIP expression, glucagon secretion, hepatic glucagon action, glucose production, and steatosis, and exhibited strong anti-diabetic effects in mouse models of type 1 and type 2 diabetes, promising a distinct and innovative diabetes treatment approach.

Highlights

- The small molecule SRI-37330 inhibits TXNIP expression in mouse and human islets
- SRI-37330 decreases glucagon secretion and action and blocks hepatic glucose output
- Oral SRI-37330 reverses obesity- and STZ-induced diabetes and hepatic steatosis in mice
- Its antidiabetic effects and safety profile make SRI-37330 an attractive drug candidate

Thielen et al., 2020, Cell Metabolism 32, 353–365
September 1, 2020 © 2020 Elsevier Inc.
https://doi.org/10.1016/j.cmet.2020.07.002

CellPress

Start-Up: Initial Focus T1D

Unmet need

There are no oral medications for T1D approved. To stay alive, individuals with T1D require multiple daily insulin injections and/or continuous insulin infusion.

Paradigm shift

Based on the recognized role of beta cells in the pathogenesis of T1D, it is no longer considered a pure autoimmune disease

Type 1 diabetes mellitus as a disease of the β-cell (do not blame the immune system?)

Bart O. Roep[1,2]✉, Sofia Thomaidou[3], René van Tienhoven[1] and Arnaud Zaldumbide[3]

TIXiMED's edge

Until very recently, pharmacological interventions for T1D were focused entirely on immuno-suppression/modulation leaving the issue of beta cell pathology unaddressed. TIX100 can fill this gap.

ROI

The lower number of patients and the shorter length of trials required for a novel T1D drug as opposed to T2D allows for a faster and better return on investment.

Moving TIX100 into Humans

- **Chemistry, Manufacturing and Control (CMC):** Scale up and optimization of TIX100 manufacturing: >2kg of medical grade, >99% pure (GMP) TIX100 clinical trial material successfully manufactured.

curia

- **Drug Product Development & Production:**
  - Capsule production: ~4000 capsules successfully produced

Piramal Pharma Solutions

- **Toxicology & Pharmacokinetics:** IND-enabling studies:
  - Rat & Dog dose range finding (DRF) studies (3d & 7d)
  - GLP 28-Day Rat & Dog studies
  - Safety Pharmacology

sequani NON CLINICAL

康龙化成 PHARMARON

- **Regulatory: FDA cleared TIX100 for human trials → IND active**
  - Clinical CRO contracted
  - Drug product available → ready to start

Kinexum