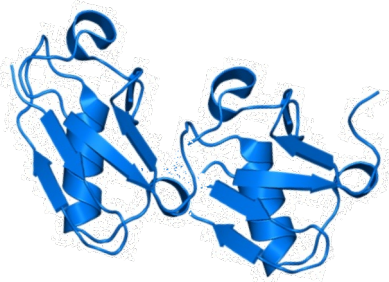
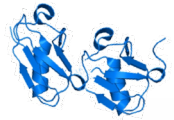


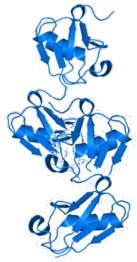


Combatting obesity through a novel mechanism

Jonathan S. Bogan, MD

Yale School of Medicine

Executive Summary



- ***Unique Investment Opportunity***
  - A new way to target obesity by blocking degradation of a proteolytic cleavage product.
  - The therapeutic effect is to burn calories in muscle and adipose tissues – distinct from other mechanisms.

- ***Multi-billion dollar market***
  - The global obesity market is estimated to reach $15.6B by 2024[1]

- ***Competitive Edge***
  - Novel target – ATE1 and associated proteins that degrade the TUG C-terminal cleavage product

- ***Large M&A potential and industry interest***
  - 18 M&A or IPO deals since January 2017[2]
  - Collaboration with major pharma to test specific downstream effectors of the pathway

- ***Development Plan***
  - Cell-based drug screen and secondary screen
  - Identify compounds could be used in a combination approach with currently approved diabetes drugs

1. Global View Research, 2. Pitchbook

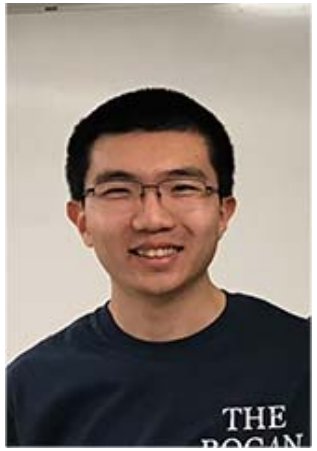
Experienced scientific and business leadership

Jonathan S. Bogan, MD

Associate Professor of Medicine and Cell Biology, Yale Univ. School of Medicine

Estifanos Habtemichael, PhD

Associate Research Scientist Dept. of Medicine Yale School of Medicine



Don Li, PhD

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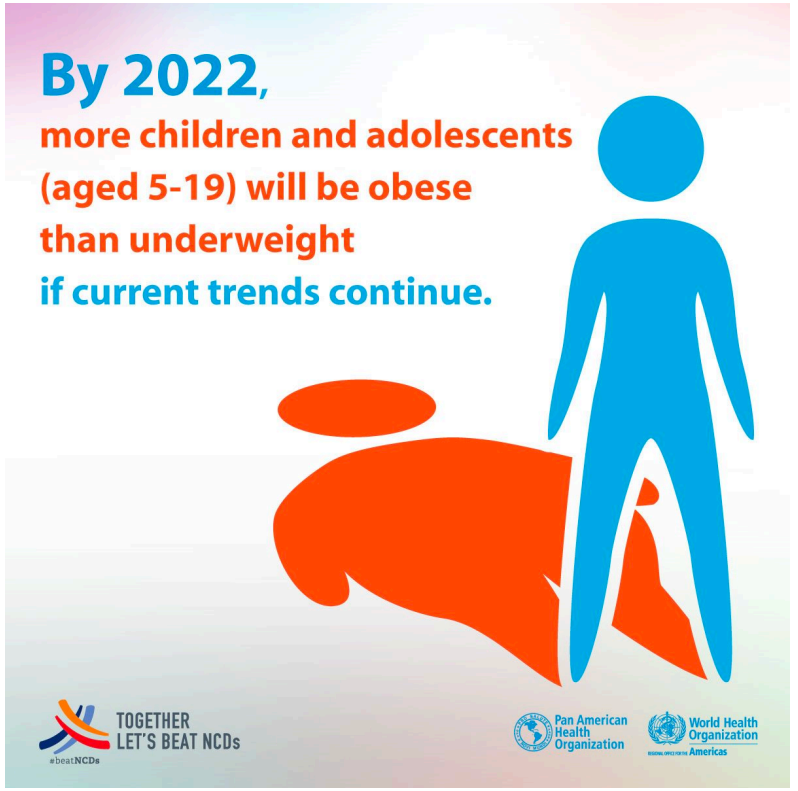
Obesity is a multi-billion dollar market

The global obesity market is estimated to reach $15.6B by 2024[1]

World Health Organization

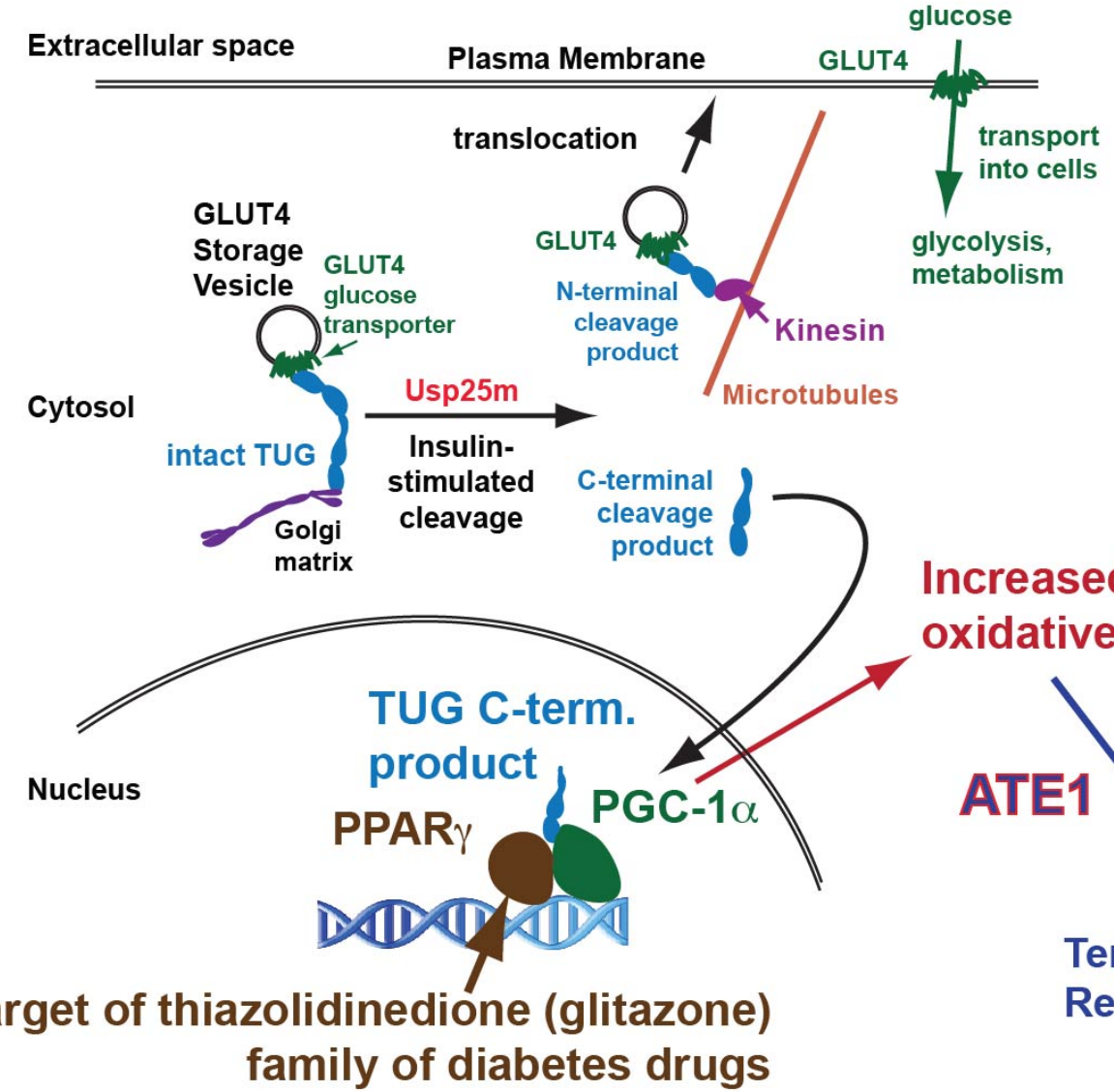
In the U.S. in 2015–2016, the prevalence of obesity was 39.8% in adults and 18.5% in youth (CDC).



World Health Organization

1. Global View Research

A novel mechanism for insulin action in muscle and fat
A novel target to treat obesity



The translocated proteins coordinate glucose uptake, blood pressure, and lipid metabolism.

The nuclear protein complex increases body heat.

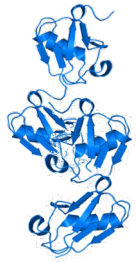
Increased expression of genes to promote oxidative metabolism and thermogenesis

ATE1

Degradation of the TUG C-terminal cleavage product and of bound PGC-1α

Termination of effects on gene expression
Reduced oxidation of metabolic substrates

How we plan to target this pathway



- **The TUG C-terminal cleavage product:**
  - **prolongs the half-life of PGC-1α**
  - **stabilizes its interaction with PPARγ**

- **Degradation of the TUG C-terminal product:**
  - **is controlled by a specific mechanism**
  - **requires ATE1, a druggable enzyme**

- **We plan a cell-based screen to identify compounds that stabilize the TUG C-terminus.**
  - **a dual-fluorescent reporter will provide an internal control**
  - **cells will express relevant ATE1 isoforms**

- **Secondary screens will measure:**
  - **effects on cellular respiration**
  - **effects on ATE1 activity toward the TUG product in vitro**

- **Effects of identified compounds may be enhanced by concurrent PPARγ agonist treatment.**

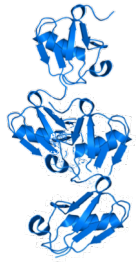
Competitive Advantage & Commercial Interest

Advantages of targeting this TUG-C/PGC-1α/PPARγ pathway over other possible therapeutic approaches:

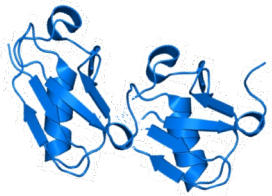
	Stabilizing the TUG C-terminal product	Enhancing brown adipose tissue	Targeting the regulation of appetite	Wasting calories in urine/feces	Bariatric surgery
Capitalizes on the large mass of skeletal muscle	✓	x	x	x	x
Counters a "vicious cycle" that promotes obesity	✓	?	?	x	✓
Circumvents compensatory mechanisms controlling energy balance	✓	?	✓	x	✓
No surgical complications or micronutrient deficits	✓	✓	✓	✓	x

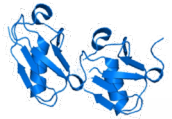
Commercial Validation: ongoing collaboration with large pharma for secreted protein effectors of pathway.
Clinical Development: Human SNP in PPARγ modulates TUG-C binding; additional pharmacogenetic markers.

Blavatnik Development Plan for IP Generation



Step 1	***Step 2***	***Step 3***
Develop a ratiometric, dual-fluorescence reporter to use in a high-throughput screen for compounds that stabilize the TUG C-terminal cleavage product. Clone and express relevant ATE1 isoforms in target cells for screen.	High-Throughput Screen for compounds using WuXi or Charles River Laboratories as CRO	Validate compounds biochemically in muscle and adipose cells. Perform a secondary screen measuring effects on cellular oxygen consumption. Time permitting: Assess selected compounds for effects to inhibit ATE1 activity toward the TUG product in vitro. This may help with optimization of lead compounds.
$ 100,000	$ 100,000	$ 100,000





Discovery

- Novel enzymatic target regulating energy expenditure
- *In vivo* validation of the relevance of TUG-C
- *In vivo* validation of ATE1 as a target
- Assays for screening TUG-C preservation

Clinical Development

- Human SNP in PPARγ modulates TUG-C binding
- Additional pharmacogenetic markers

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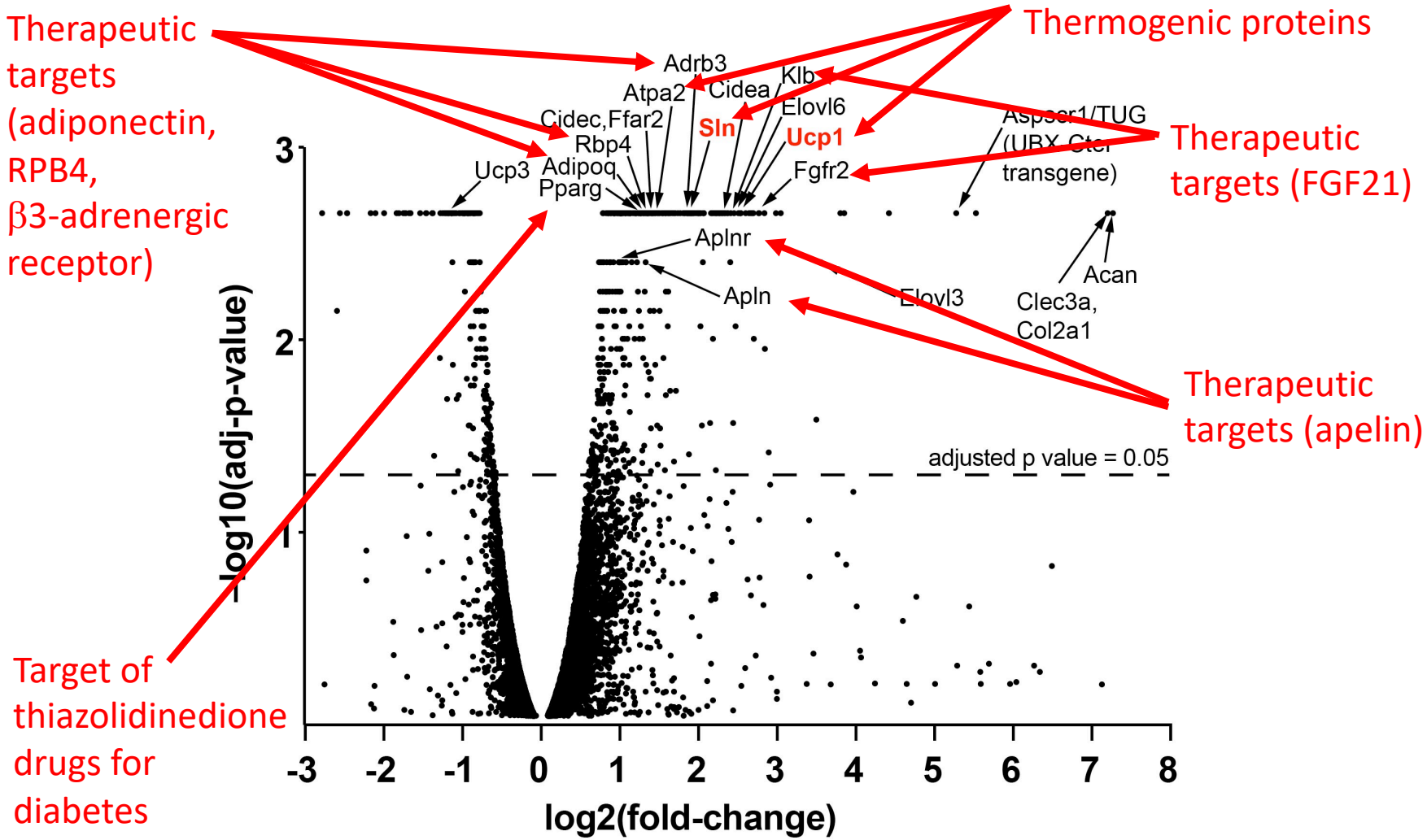
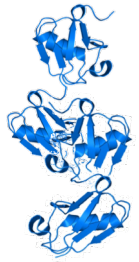
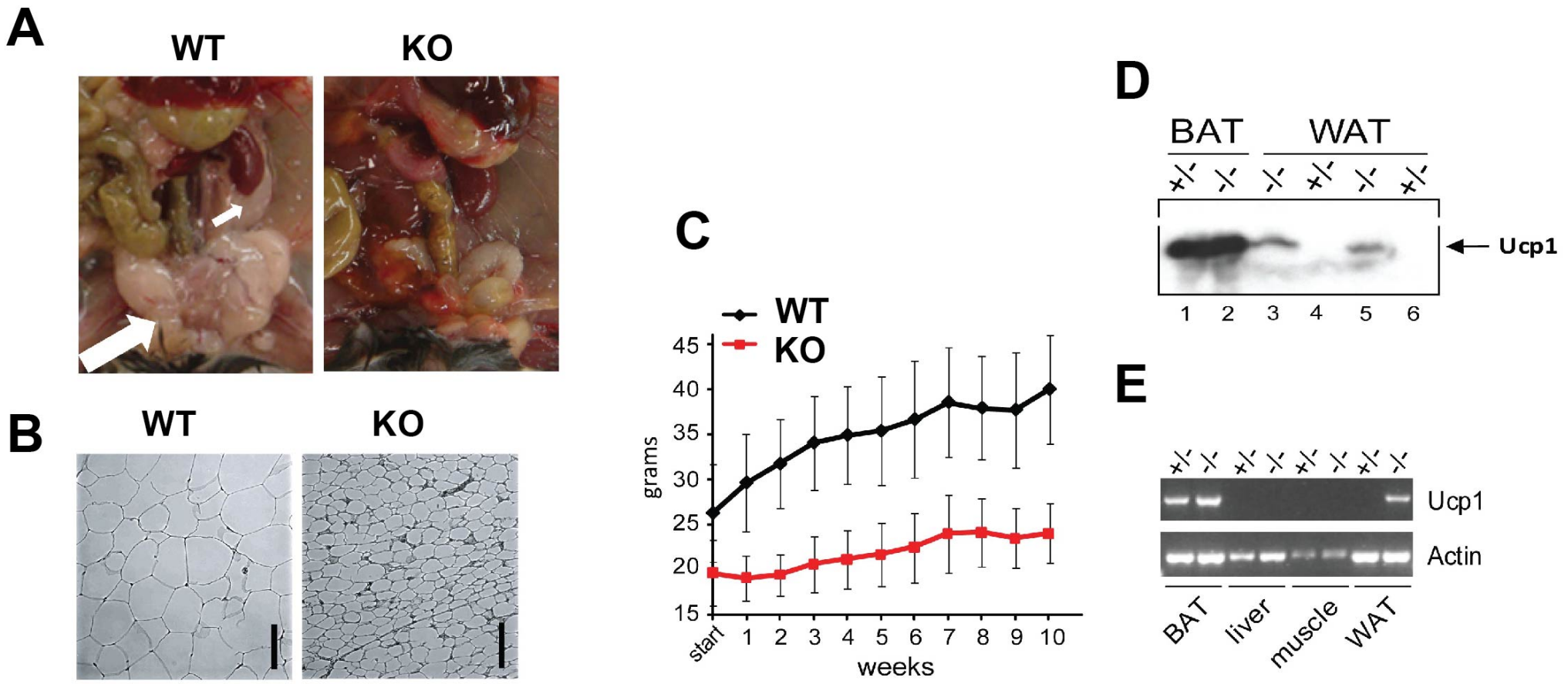
Supplemental Data

Key data: the TUG C-terminal product induces a broad program of gene expression to increase thermogenesis in muscle



Blocking the degradation of TUG-C results in fat loss, reduced weight gain on an obesogenic diet, and induction of Ucp1 in white adipose tissue





Inducible whole-body KO of OCR7575 results in dramatic loss of abdominal fat in ~1 month (A, B), reduced weight gain on HFD (C), and induction of Ucp1 protein (D) and mRNA (E) in white adipose tissue. This work was done by a third party having no knowledge of the mechanism of action.