ST4TE Therapeutics

Next wave oral obesity therapeutics for improved quality and efficacy of weight reduction

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Anjali@state4tx.com

Experienced and committed founding team, advisors, and partners

*Team of **Metabolism Experts** and **Key Opinion Leaders***

Richard Kibbey, MD, PhD
Scientific Co-founder

Ralph H. Ensign Professor
Yale University School of Medicine

Matthew Merrins, PhD
Scientific Co-founder

Joseph F. Hoffman Professor
Cellular & Molecular Physiology

Ania Jastreboff, MD, PhD
Academic Co-founder

Harvey W. Cushing Professor
Director, Yale Obesity Research Center
Lead clinical investigator for multiple GLP-1 RA trials

Craig Thomas, PhD
Chemistry Collaborator

Senior Scientist, NCATS
>20 Years Kinase Med Chem

Development and Funding Partners

Recruiting Launch Team and Advisors

Anjali Kumar, PhD
Incoming CBO

20+ years of pharma R&D, business development, search & eval

Robert Williams, PhD
Lead Operator; Co-founder

Preclinical drug dev and startup operations

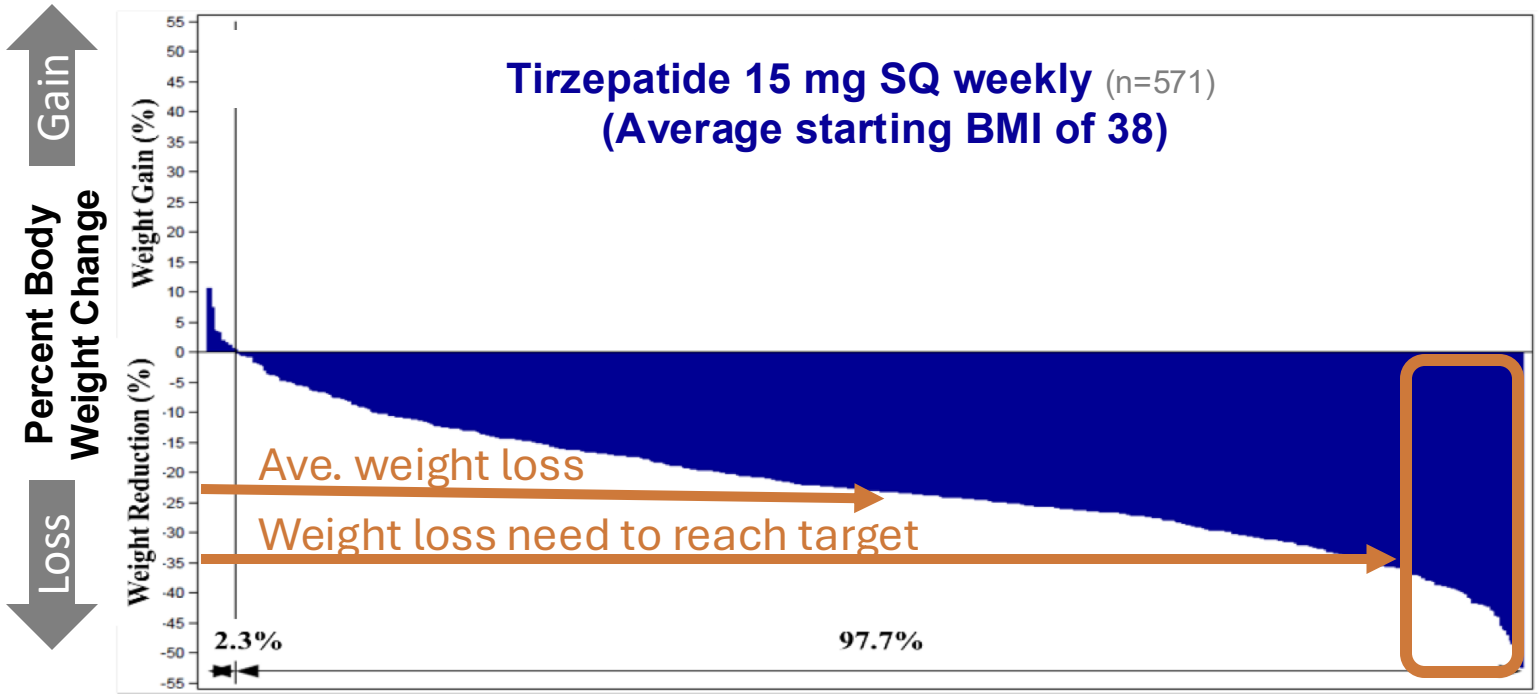
Unmet Need: Only ~10% reach their weight loss goal

NuSH therapies will require amplification to reach target, especially the next wave of orals

Heterogeneous and insufficient responses

Anticipating the next wave of oral meds

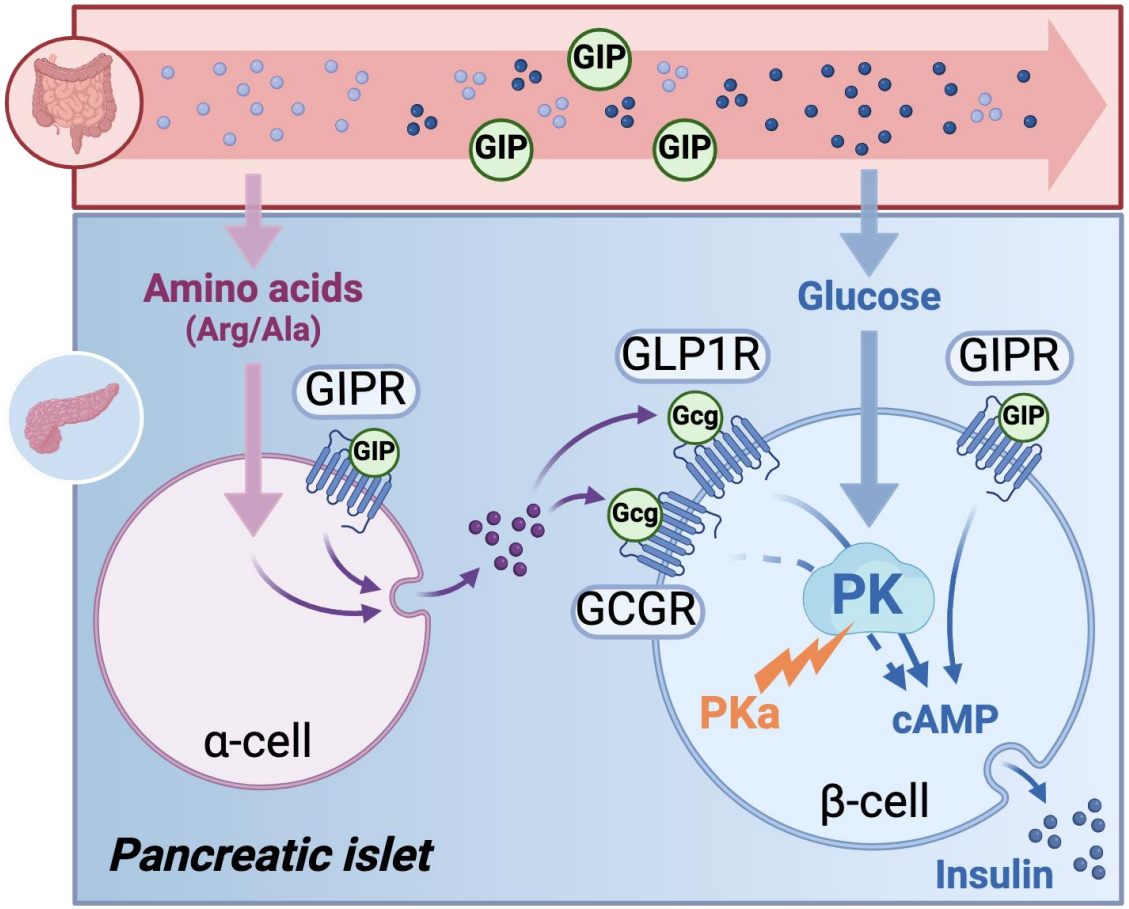
Limiting Muscle Loss



Jastreboff AM et al
Tirzepatide Once Weekly for the Treatment of Obesity. *N Engl J Med*. 2022.

NuSH = Nutrient-Stimulated Hormone

GLP-1 signaling depends on an activated Pyruvate Kinase

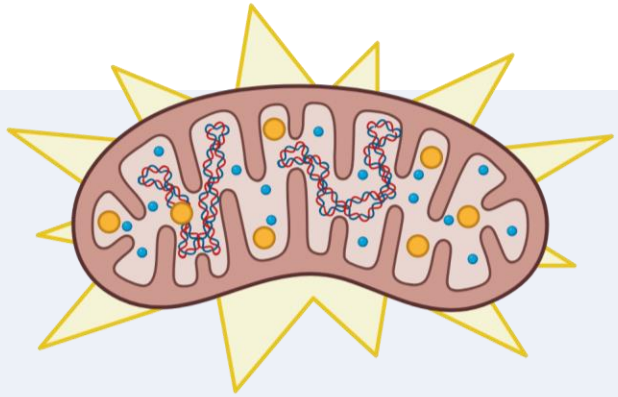


Pyruvate Kinase activation in vivo

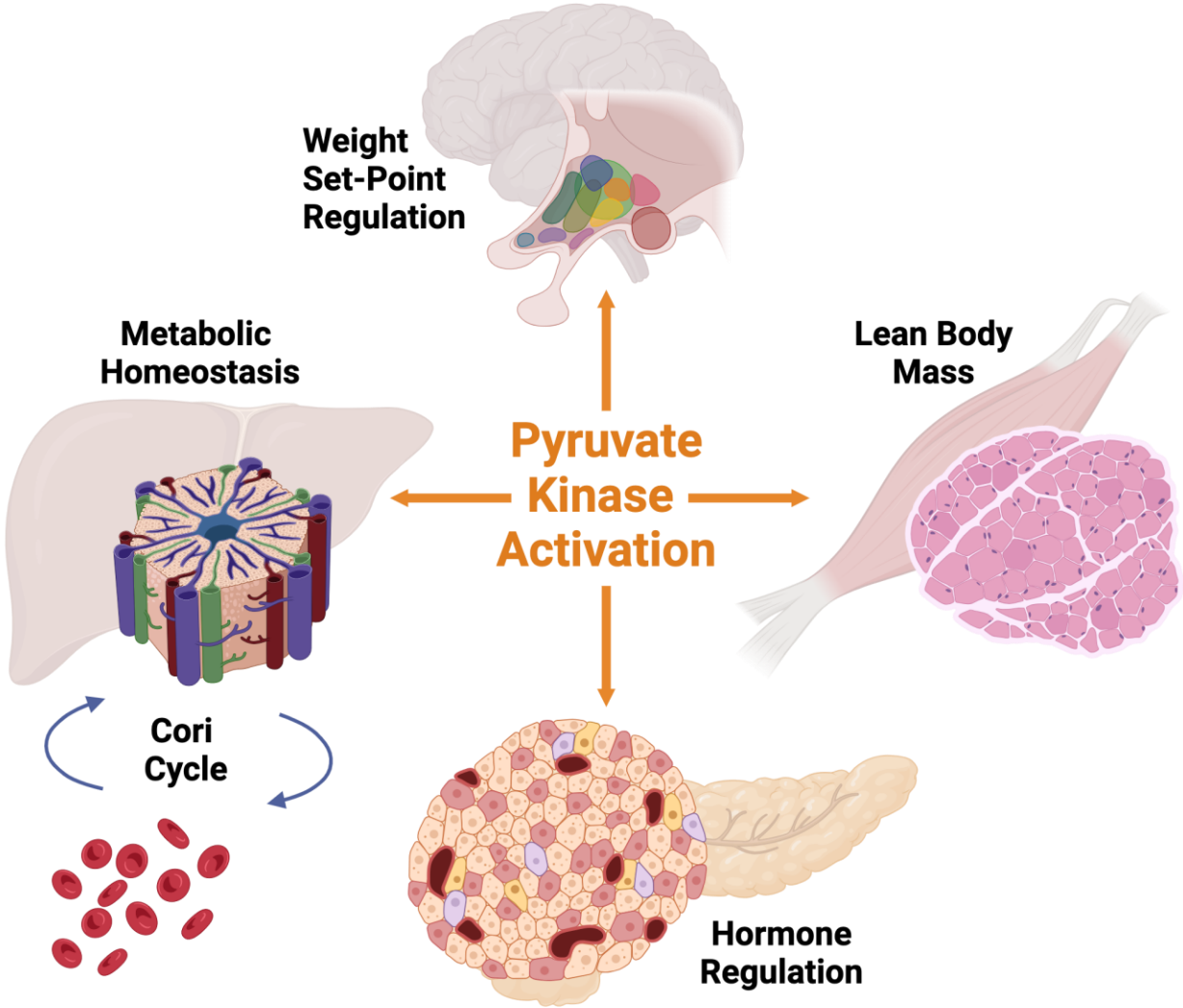
- Integrates metabolism with GLP-1 signaling
- Improves pancreatic islet function and health
- Decreases blood glucose and lipids
- Decreases hepatic lipids
- Improve glucose tolerance
- **Synergizes with GLP-1**

We are translating our understanding of islet PK activation to obesity-relevant tissues

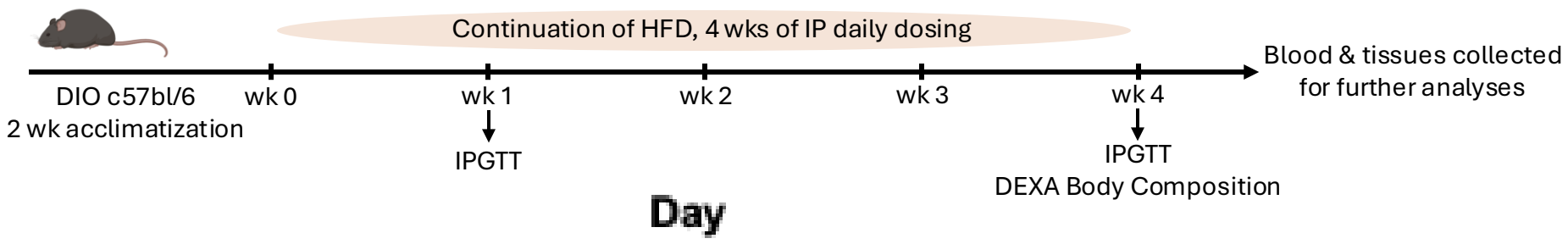
Pyruvate Kinase – **the ideal obesity target**

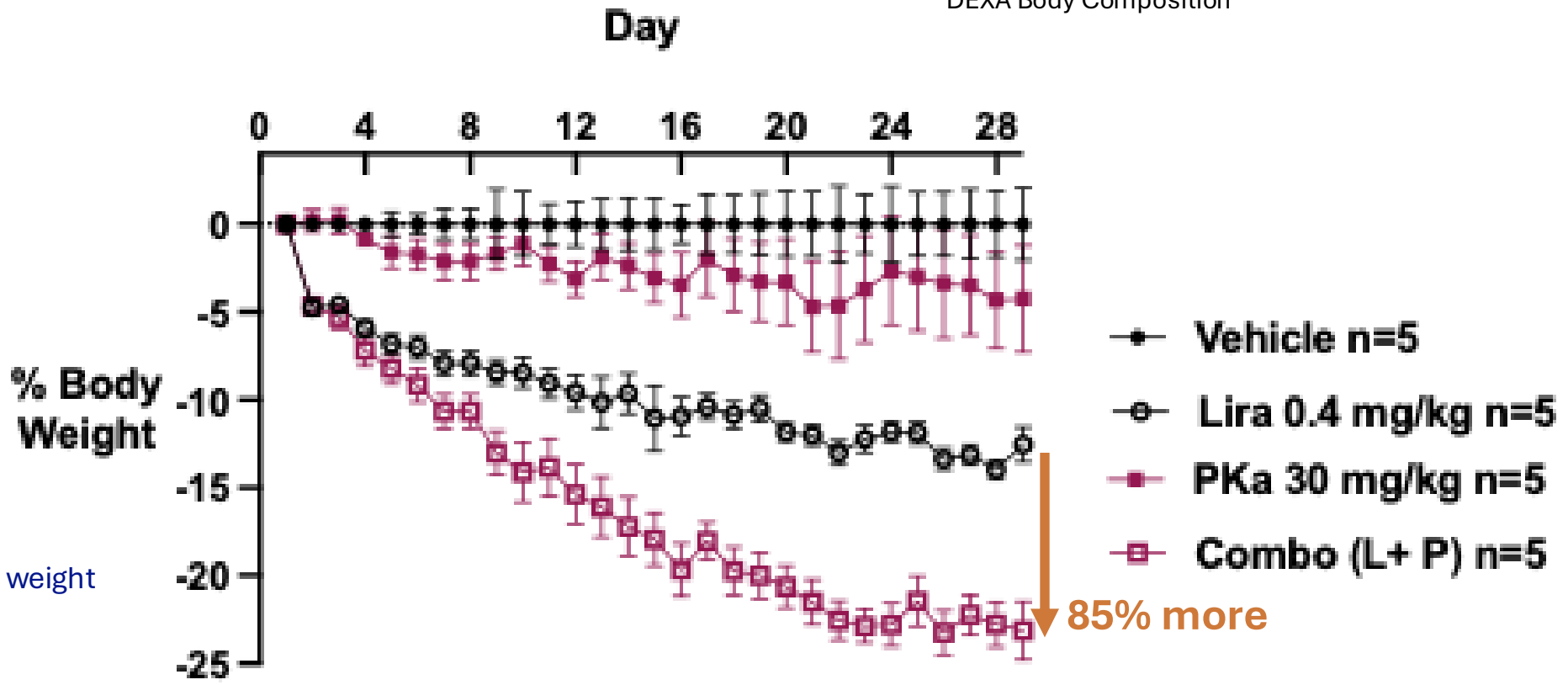


- PK activation **energizes mitochondria**
- **Peripheral** PK controls energy utilization, islet function, carbohydrate and lipid homeostasis, and augments muscle mass.
- **Central** PK activation works with GLP-1RA to treat obesity
- GLP-1 signaling is **dependent on** and **amplified** by PK activity



PK Activation ***amplifies*** GLP1RA in DIO mouse model



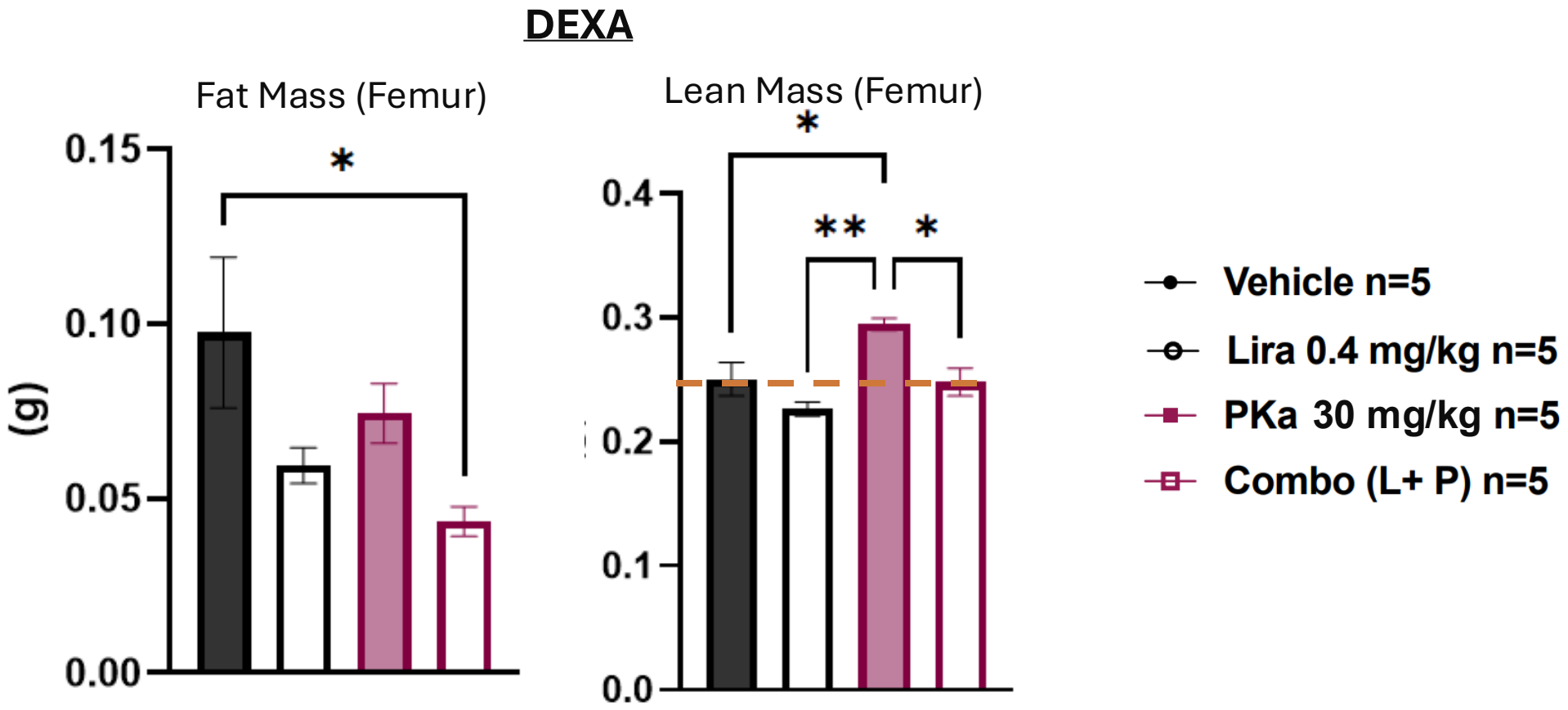


Vehicle subtracted weight

Diet-induced obesity (**DIO**); High fat diet (**HFD**); Pyruvate Kinase activator (**PKa**);
Liraglutide (**Lira**) = GLP-1 receptor agonist; dual energy X-ray absorptiometry (**DEXA**); Intraperitoneal Glucose Tolerance Test (**IPGTT**)

PK Activation ***increases muscle*** in DIO mice

Higher quality weight loss



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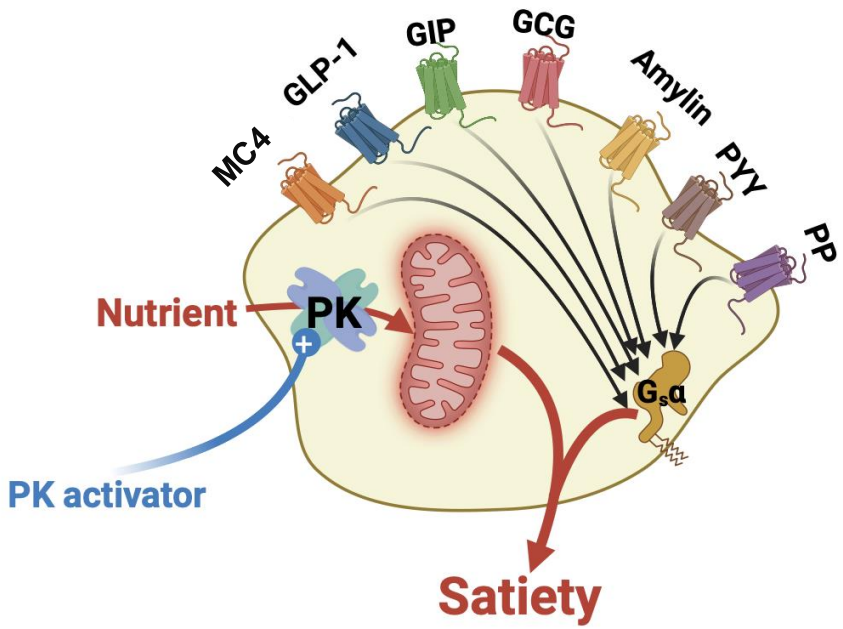
ST4TE's Solution: small molecule PK activators optimized to treat obesity



Recent chemistry breakthrough results in strong lead candidate

- CNS penetrant
- Orally available

Foundational Intellectual Property

- Compositions of matter (filed 04/25)
- Methods of use (filed 12/24)

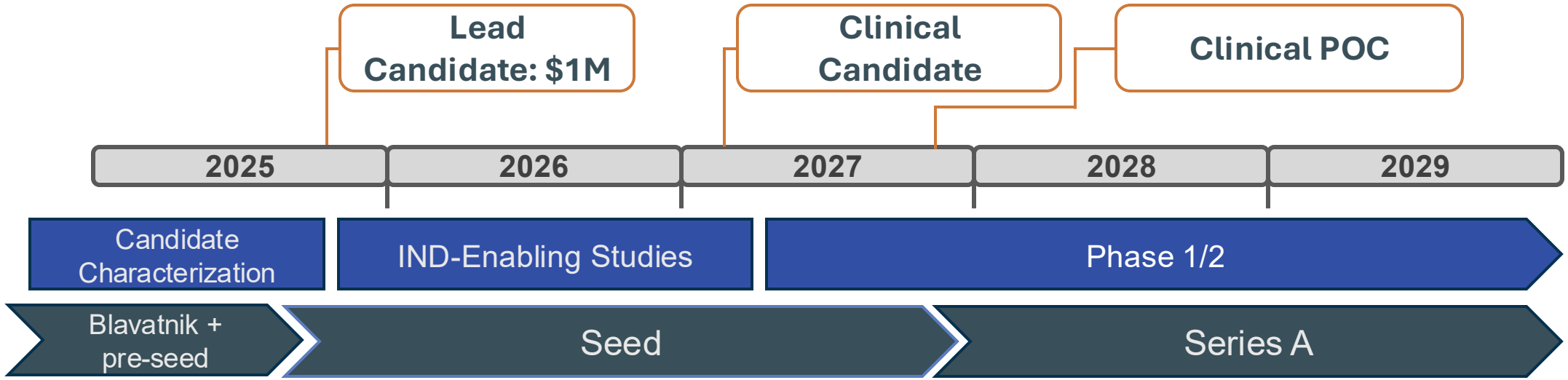
PK activation will *synergize* with most current (and proposed) NuSH therapies

- Monotherapy
- Adjunct Amplification combined with NuSH

NuSH = Nutrient-Stimulated Hormone

ST4TE's PKa program status: **Lead Characterization**

6-8 months from initiating IND-enabling studies; 2 years from clinic
Supported by non-dilutive support from Blavatnik Fund @ Yale, NCATS @ NIH



$1M pre-seed: Development Candidate Election

- CMC scale up, synthesis optimization, oral formulation
- Target engagement
- Tox/Safety Pharmacology
- *in vivo* efficacy

$10M-15M: IND-enabling studies to clinical proof-of-concept, plus:

- IP expansion
- Next gen compound screening

STATE 4 Therapeutics

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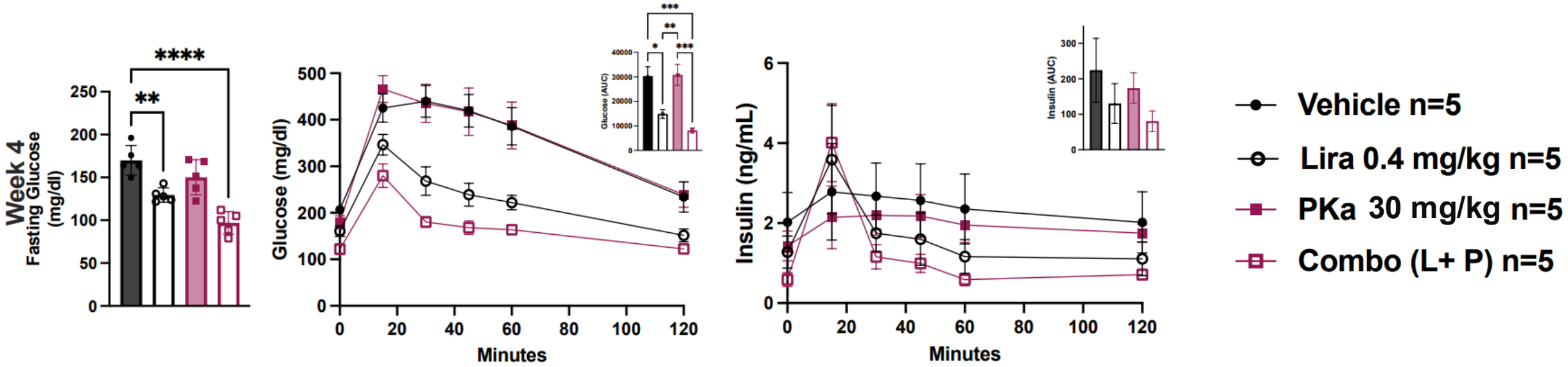
PK Activation + GLP1RA ***improves glucose tolerance*** in DIO mice at 1 and 4 weeks

Intraperitoneal glucose tolerance test (IPGTT)



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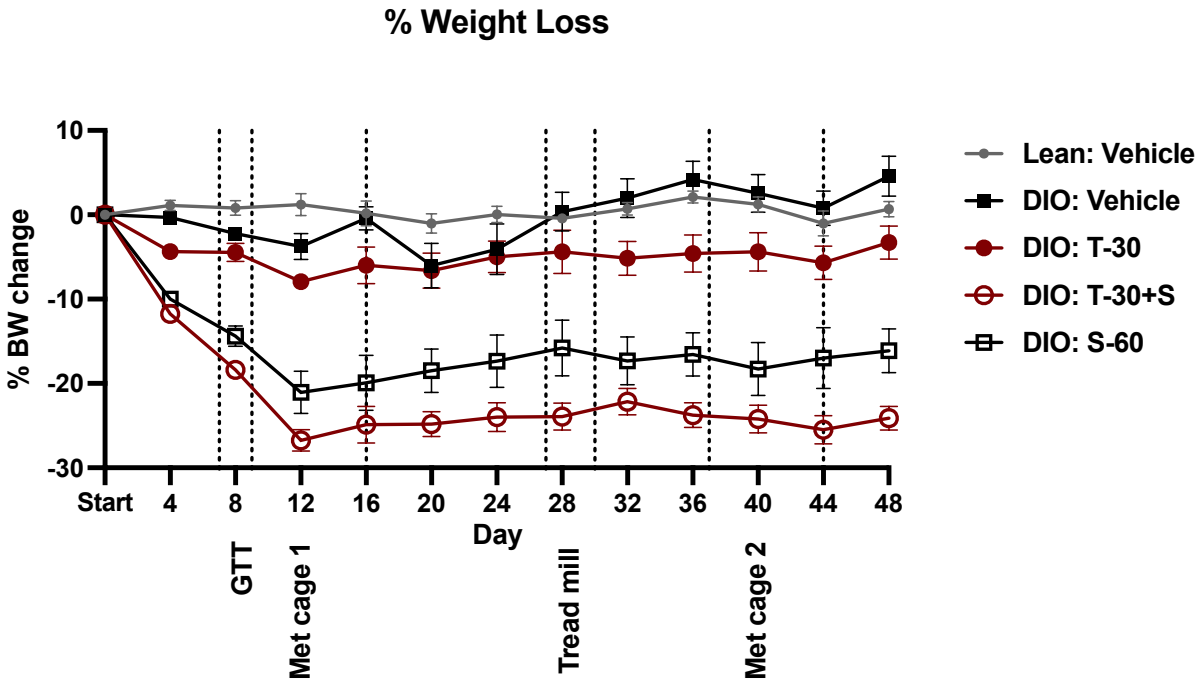
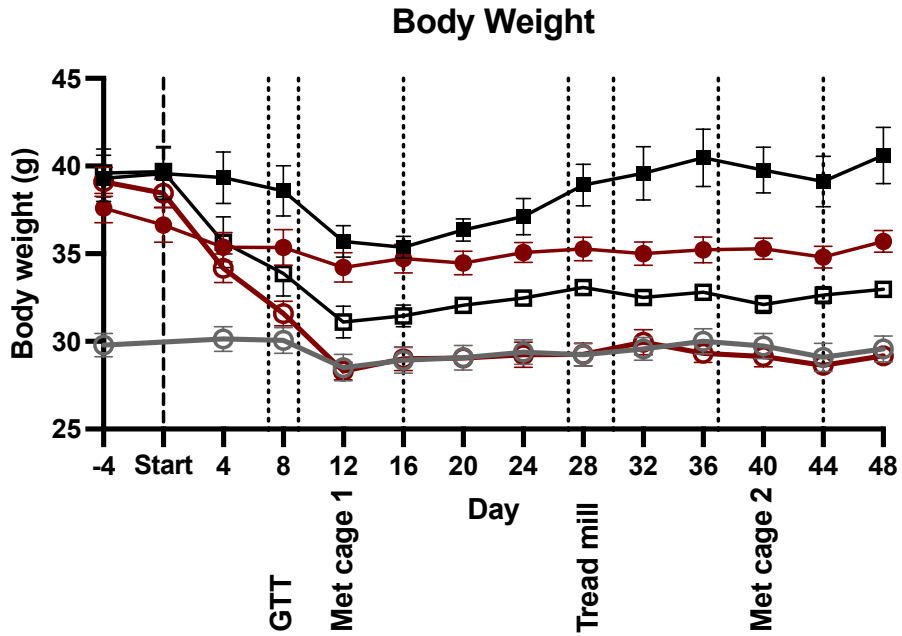
PK activator + Semaglutide results in weight loss to lean vehicle levels





A sustained appetite for preclinical and clinical obesity assets

Deal-making activity is high. Notable March-April '25 transactions:

$1 Bn License
March 2025

Preclinical

$75M upfront, $1B in milestones to license Lexicon's oral small molecule ACSL5 inhibitor

Novo inks $1B deal for Lexicon's preclinical obesity prospect

$2.2 Bn License
April 2025

Preclinical

$200M upfront, $2B in milestones to license Septerna's oral small molecules that hit targets "including GLP-1"

Novo Nordisk inks $2.2B deal for Septerna's preclinical obesity programs

$2 Bn license
March 2025

Phase 1

$350M upfront, $1.87B in milestones for Gubra's phase 1 amylin analog

AbbVie pays Gubra $350M to make late play for obesity space

$2 Bn License
March 2025

Phase 1b

$200M upfront, $1.8B in milestones for United Biotechnology's Phase 1b triple G agonist

Novo pens $2B deal for triple agonist weight loss drug

$5.2 Bn Deal
March 2025

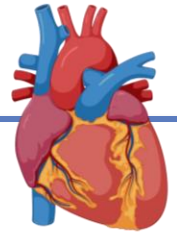
Phase 3

$1.65 B upfront, $3.6B milestones to codevelop Zealand's amylin analog to combine with GLP/GIP agonist

Roche pays Zealand $1.65B to co-develop amylin obesity asset

Opportunities for PK Activators Besides Obesity

With next-generation peripherally-restricted proprietary molecules when appropriate

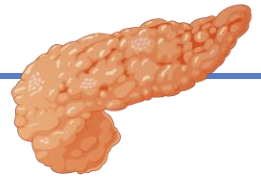


Heart Failure (HFpEF)

>30M people worldwide

> $5B market size

PKM2 activation mitigates hypertrophy and improves heart function

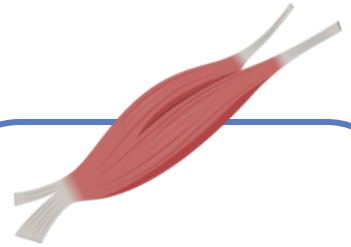


Type 2 Diabetes

> 500M People worldwide

>$20B market size

PK activation improves insulin secretion, islet function/health, glucose tolerance



Sarcopenia/ Cancer Cachexia

35-50% of solid tumor patients

> $2B Market Size

PKM2 activation results augments muscle

- Inflammatory diseases
- Aging
- Sickle Cell Disease, PK Deficiency (PKR isoform)
- Multiple cancers

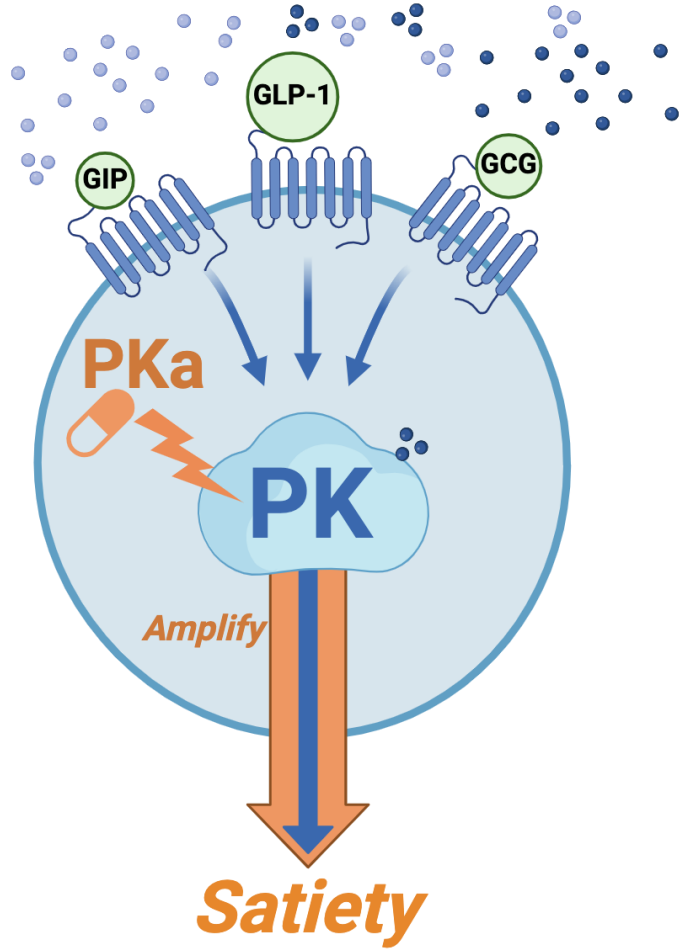
State 4 Therapeutics is Seeking Development Partners and Investors

Work is already underway:

- Multi-species PK with lead compound
- Multiple *in vitro* and *in vivo* efficacy readouts
- Pilot safety/tox readouts

Raising $10-15M seed to advance lead compound to the clinic

Recruiting experienced advisors and development partners



Upcoming Milestones

To advance our lead ST4-001 Program to IND-ready

In progress: Efficacy Confirmation and Lead Characterization

- Additional efficacy studies
- Multi-species pharmacokinetics
- Pilot tox

$1M: Development Candidate Election

- CMC scale up, synthesis optimization, oral formulation
- Target engagement
- Tox/Safety Pharmacology
- *in vivo* efficacy

$5.5M: IND-enabling studies