Targeting genetically associated obesity and metabolic syndrome

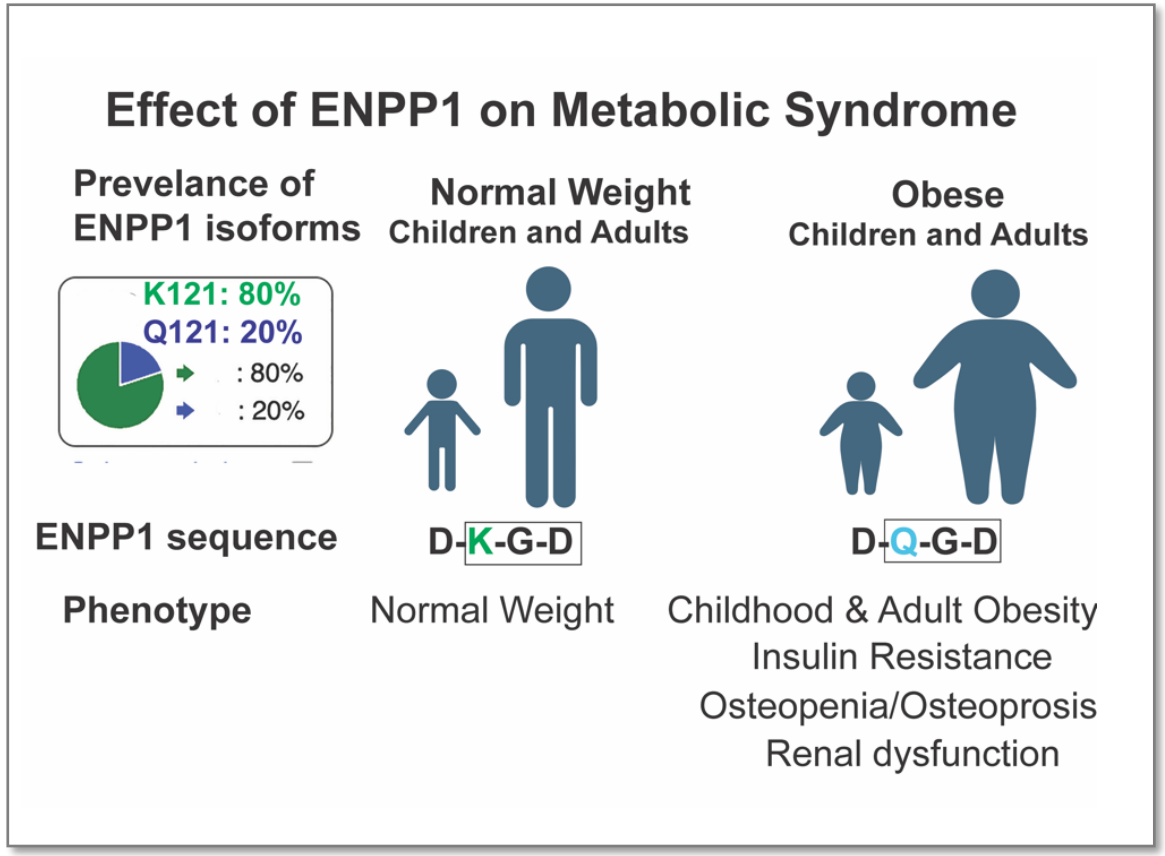
Demetrios Braddock, Assoc. Prof. Pathology

- Scientific Founder Rheumalogics (2024)
- Scientific Founder Petrogen (2021)
- Scientific Founder Inozyme (2017)

Matthew Rodeheffer, Prof. Comparative Medicine

Blavatnik Fund Presentation

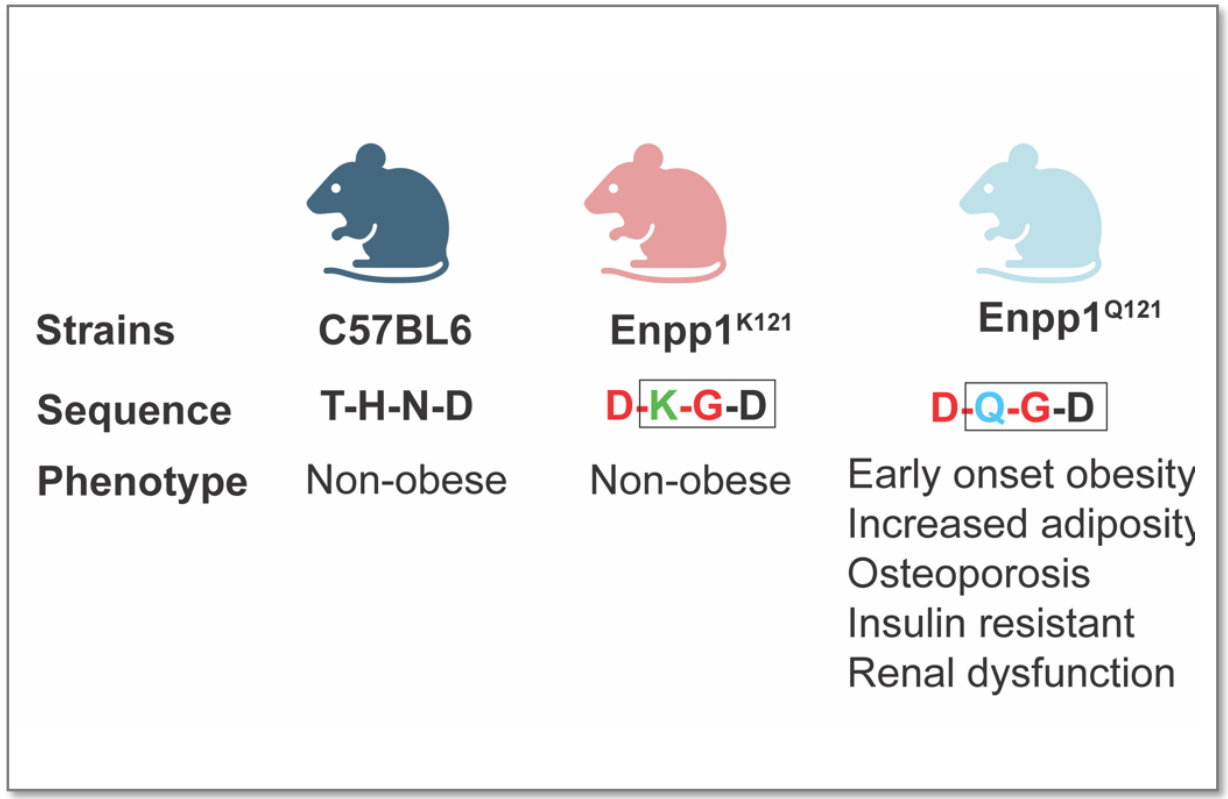
66 M US adults and children are at risk for genetic obesity associated with a ENPP1^{Q121} SNP



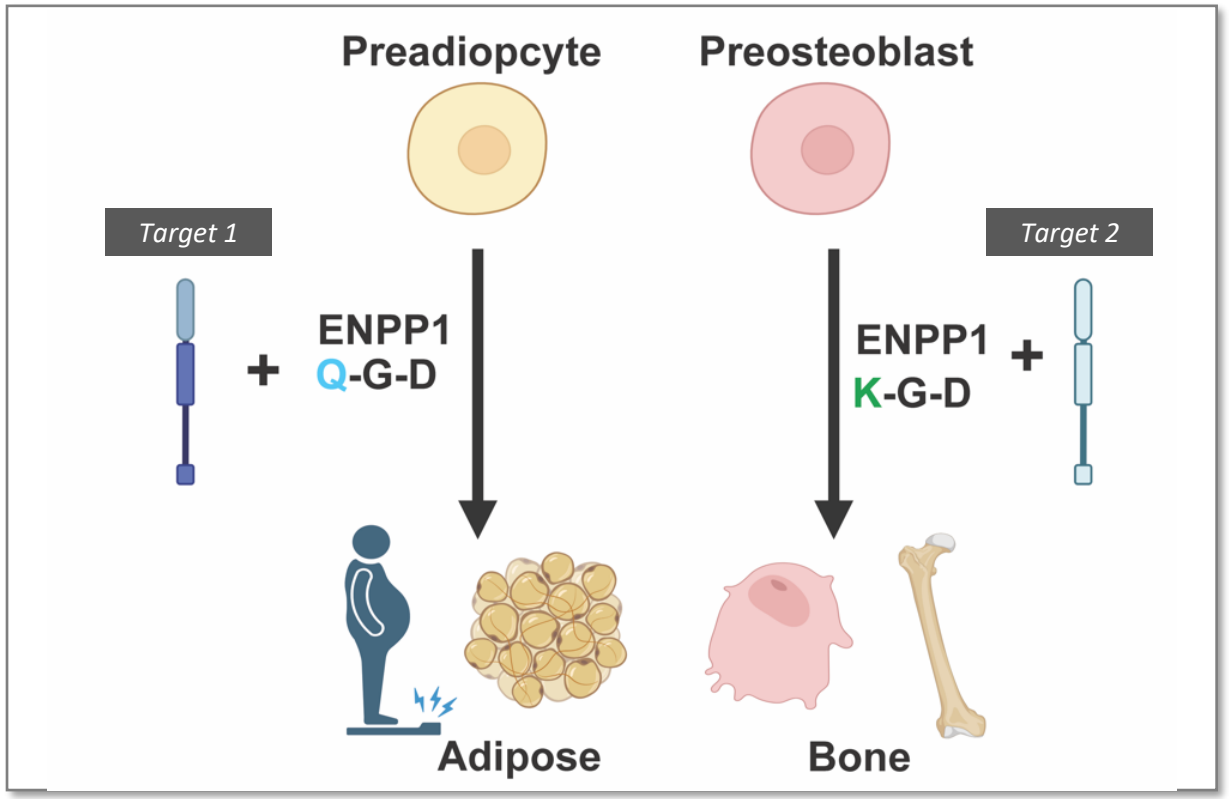
- Obesity rates have more than doubled over the last three decades
- Obesity is known to be regulated by genetic factors
- **We are targeted the Strongest genetic risk factor for childhood obesity** (ENPP1^{Q121}, rs1044498)
- Associated with profoundly obese children **BMI ≥ 95th-99th percent**
- Affecting **34% of the population worldwide and 20% of the American population**, or 66M persons in the US
- The obesity persists into **adulthood**, where it is associated with obesity, **metabolic syndrome, T2D, and renal failure**

We developed a predictive mouse model to define disease mechanism

Model



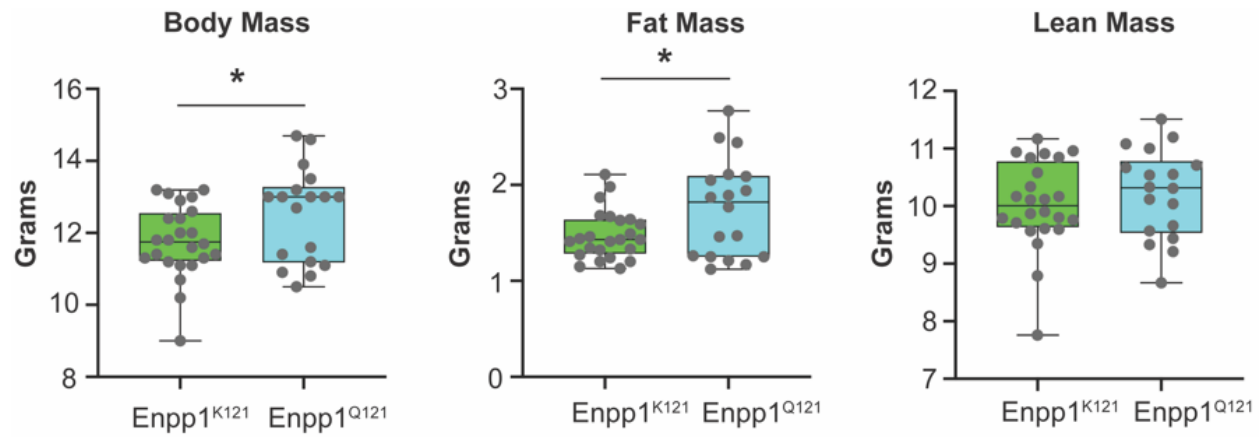
Mechanism



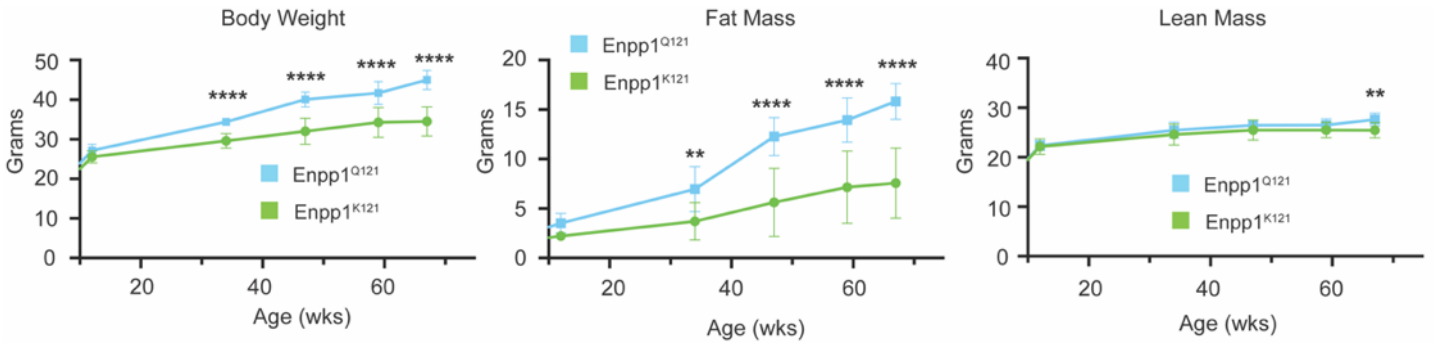
Enpp1^{Q121} model recapitulates obesity and osteoporosis

Enpp1^{Q121} mice have more fat

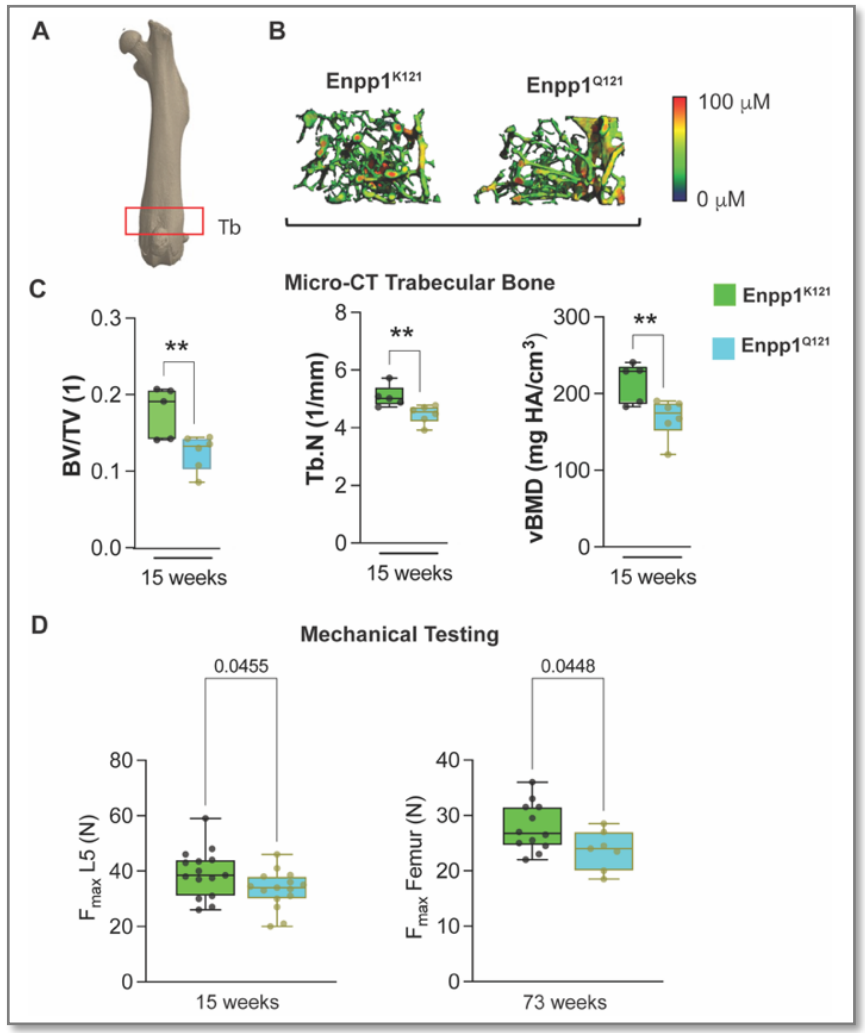
Body composition at 3 weeks



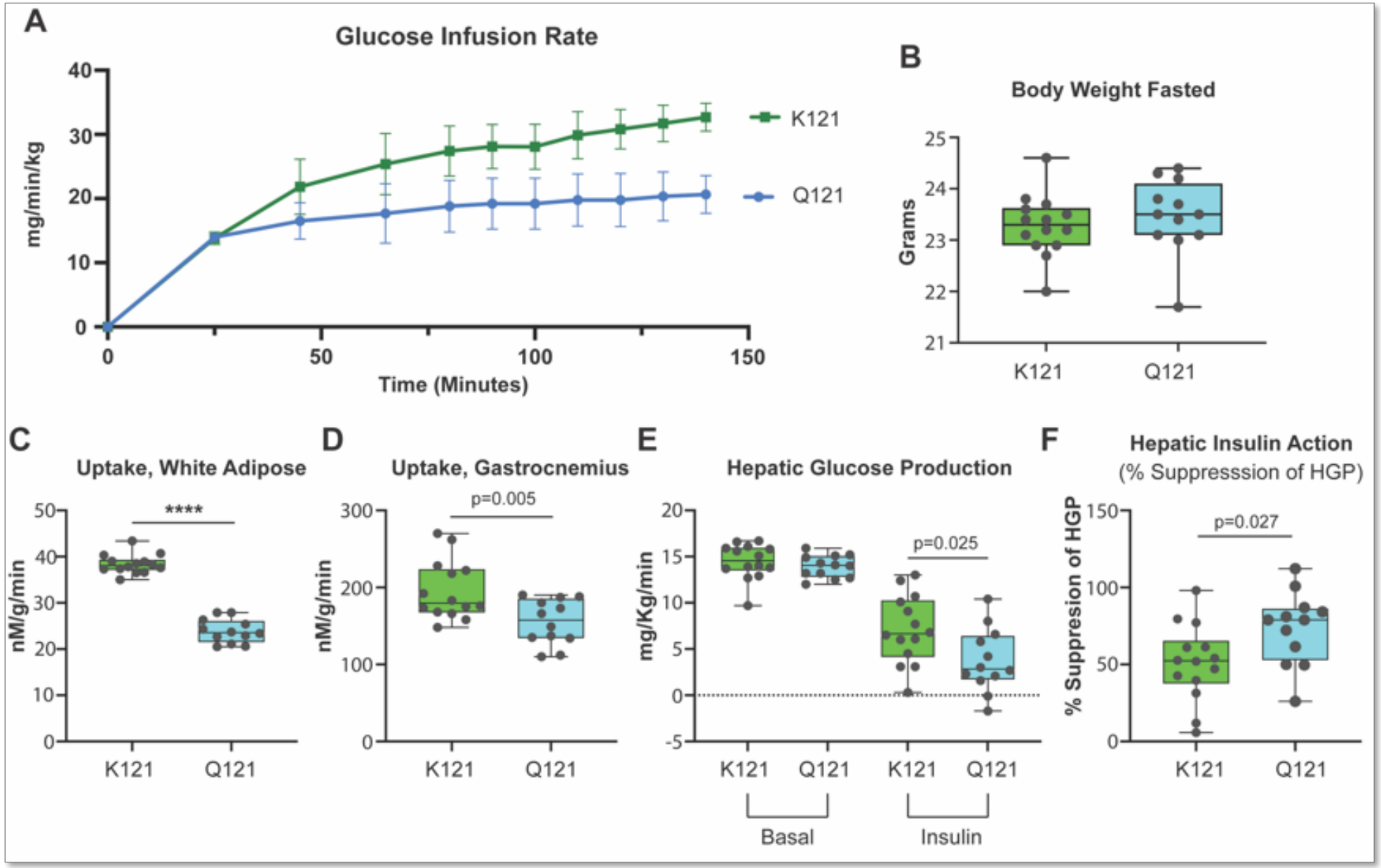
Body composition at 12-67 weeks



Enpp1^{Q121} mice have less bone



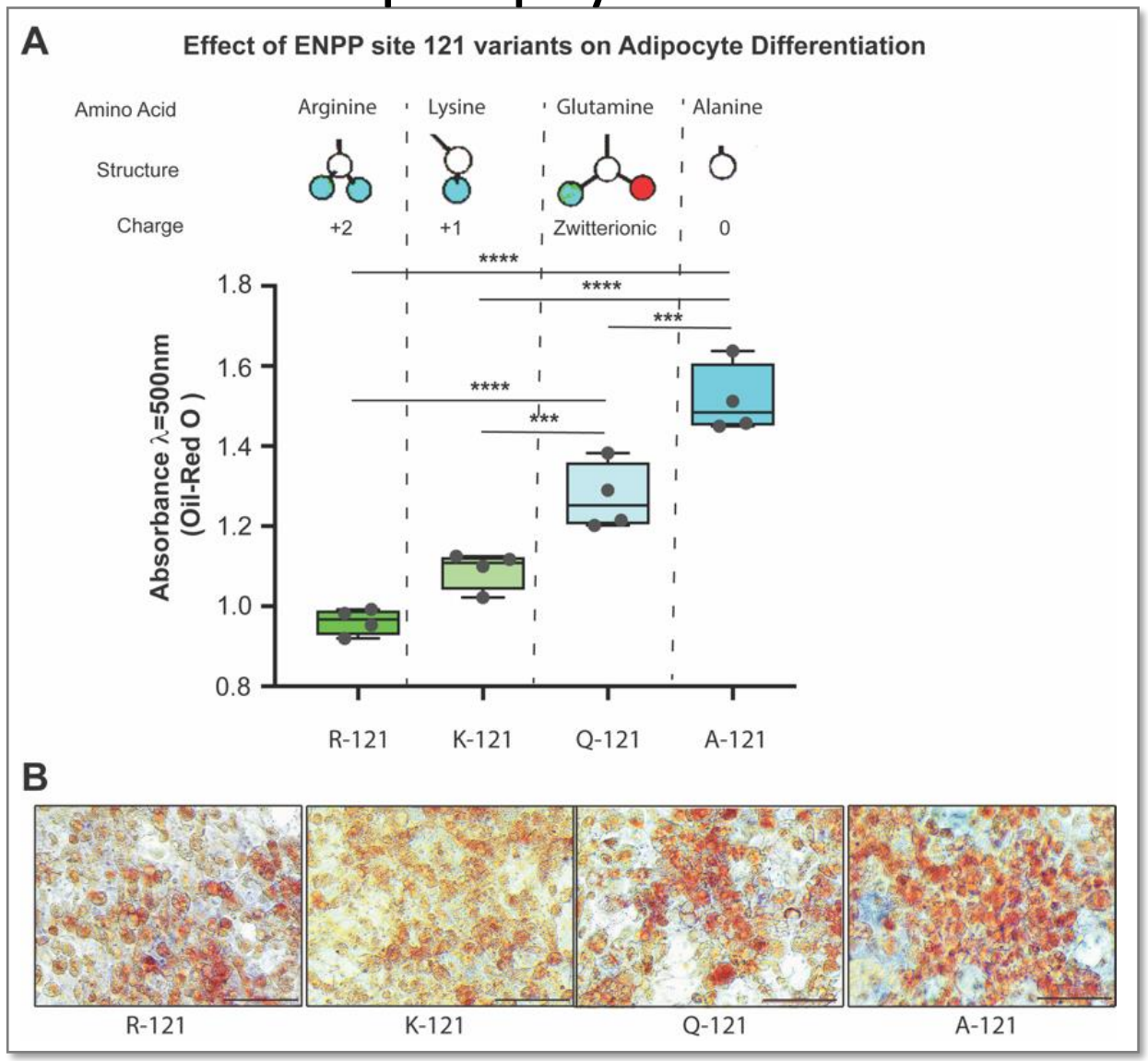
Enpp1^{Q121} model recapitulates insulin resistance



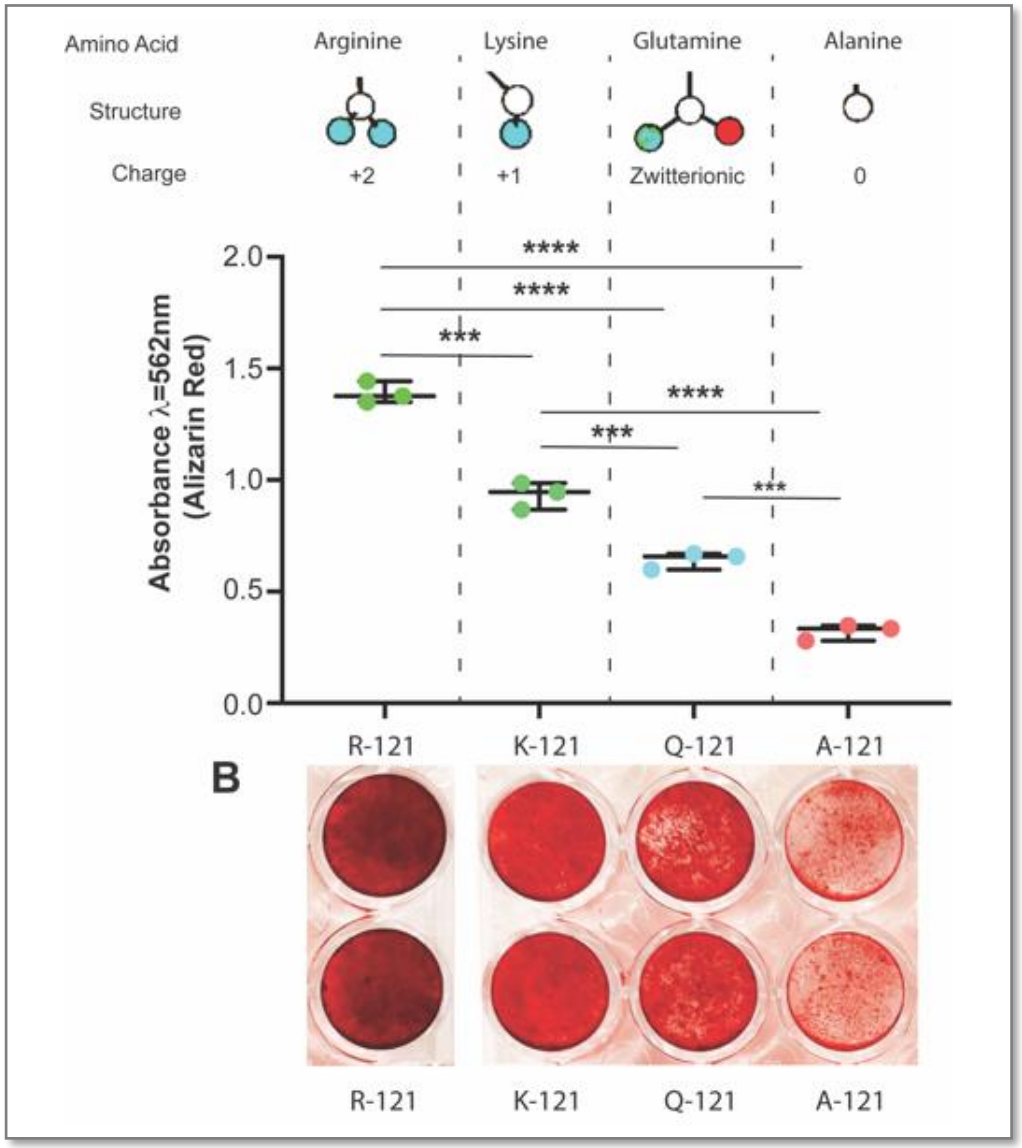
Yale YV8905

Stem cell differentiation into fat and bone is regulated by ENPP1 residue 121

Differentiation of preadipocytes into fat

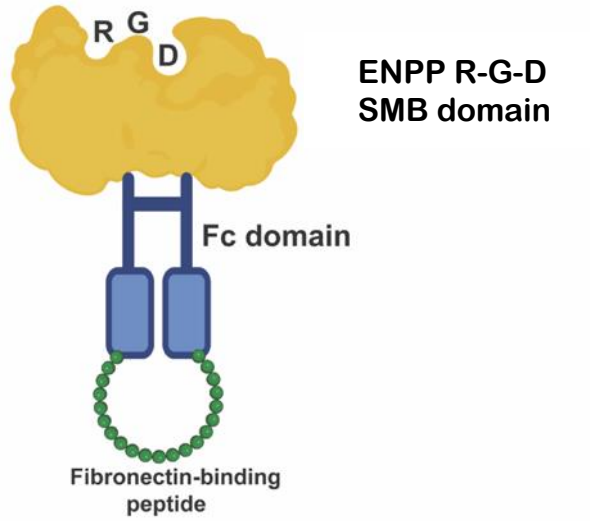


Differentiation of pre-osteoblasts into bone



Yale YV8905

We have identified a lead asset (via in vitro-assay)



ENPP R-G-D SMB domain

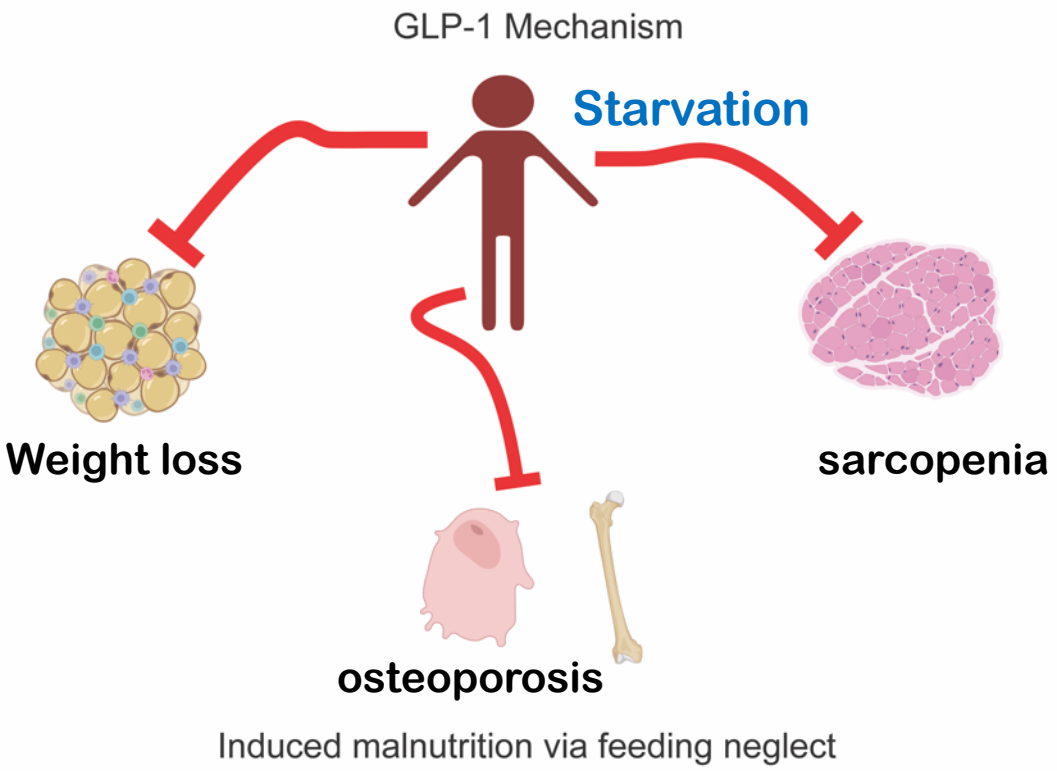
U.S. Provisional Patent Application No. 63/643,792 filed May 7, 2024. Title: "CONSTRUCTS, COMPOSITIONS, AND METHODS FOR TREATING, AMELIORATING, AND/OR PREVENTING OBESITY" By: Demetrios Braddock, et al.

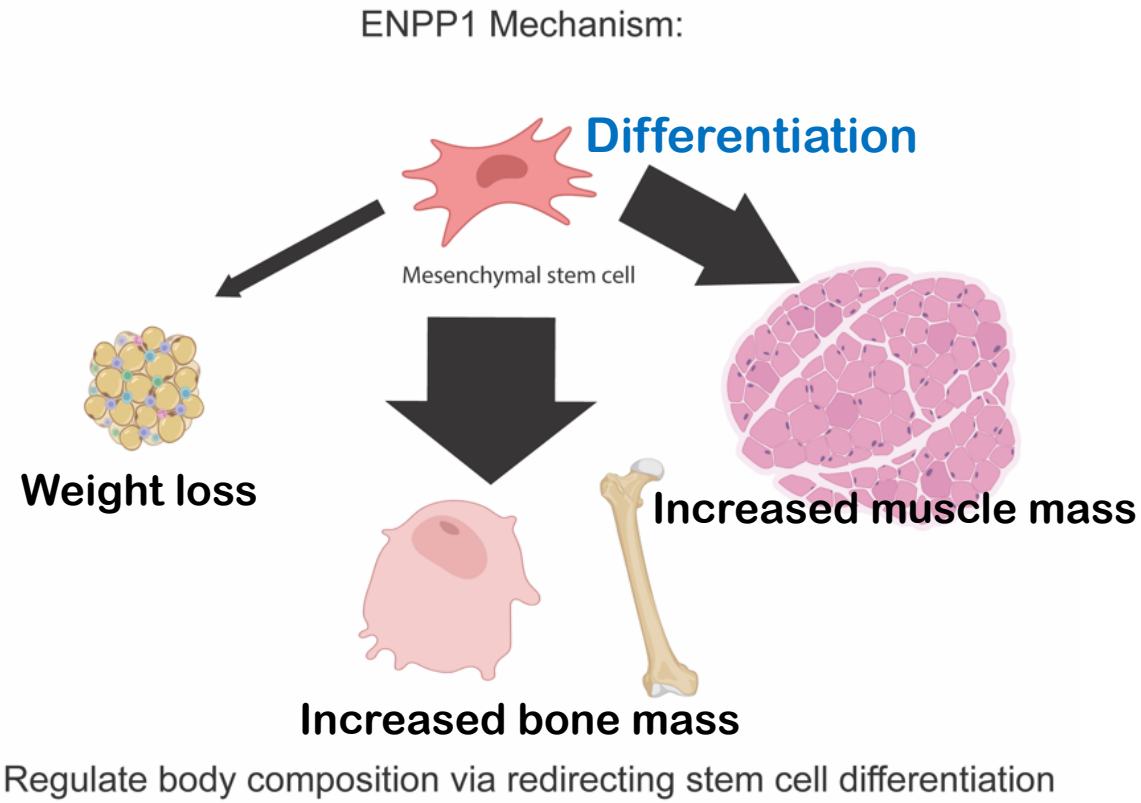
Yale Ref.: YV 8905

Saul Ref.: 047162-7501P1(02202)

We have filed provisional patents on biologics to address this condition

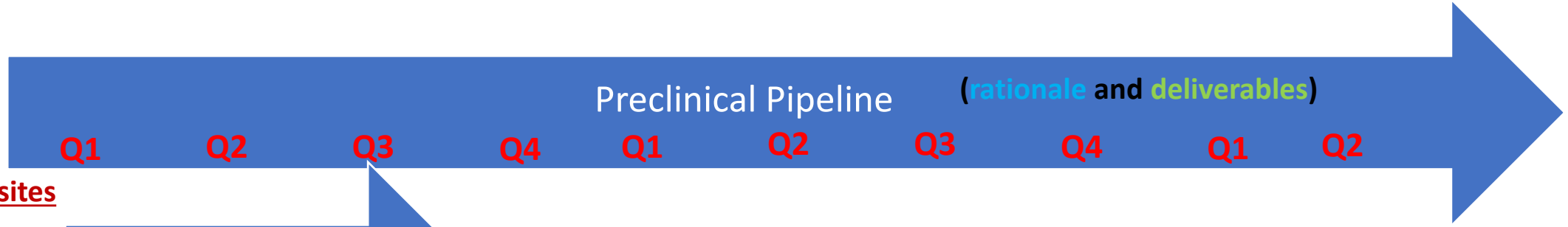
A unique mechanism regulating obesity, Type 2 diabetes, metabolic syndrome





Poor compliance
Rebound adiposity with sarcopenia upon discontinuation

Preclinical Indications, Timelines, Deliverables, Budget



Est. cost

Performance sites

Braddock lab & Metabolon

Establish biomarkers

Required for Investor diligence and design of phase 1 clinical trial

- **metabolomics, bulk and ssRNAseq, blood analytes**

$60,000

Braddock lab

In vitro validation and optimization

Validate and optimized leads for efficacy *in vitro*

- ***Lead biologic to move forward into in vivo testing***

$40,000

$70,000

Braddock Lab

In vivo validation in Enpp1^{Q121} murine model

In vivo validation

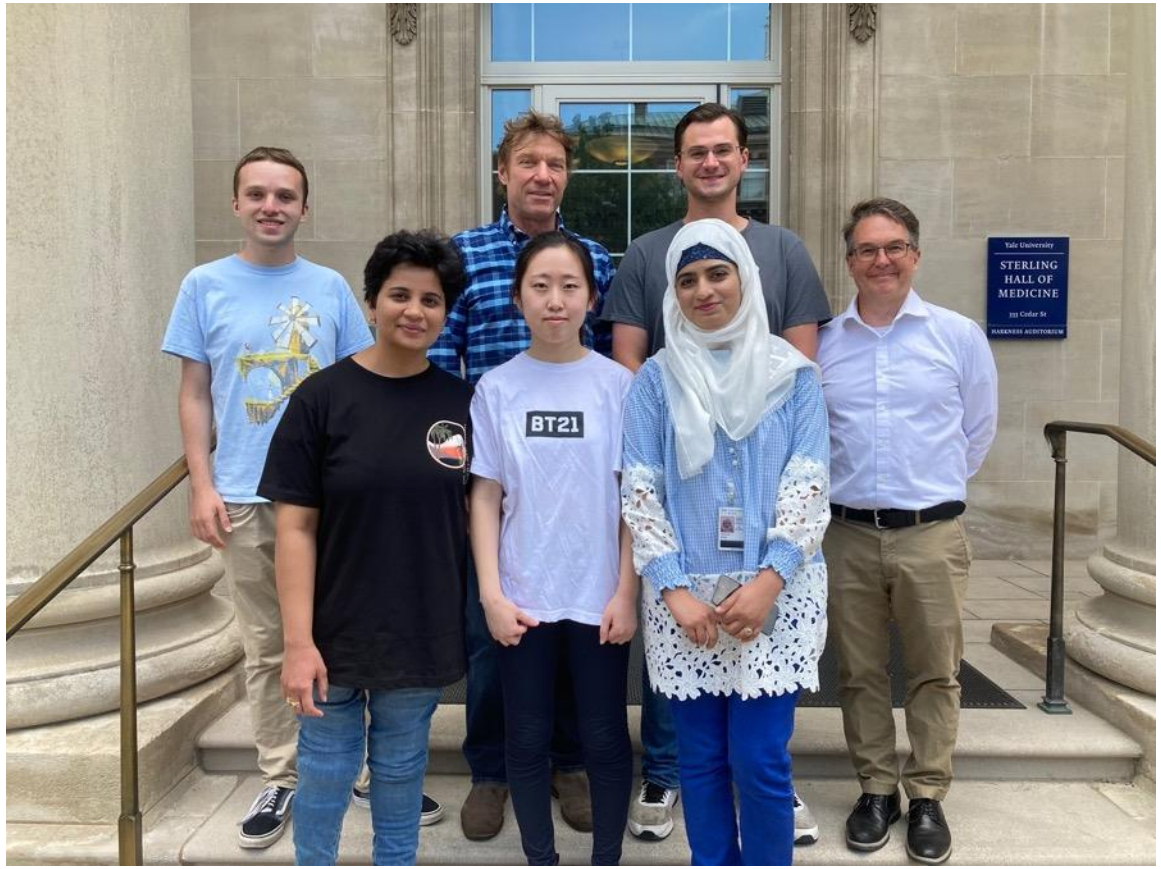
- **Wt. gain, insulin resistance, metabolic biomarkers, comparisons with Enpp^{K121} control murine model**

+ $130,000 for dosing / biologic production / Misc

Bradddock Lab

Shivani Srivastava
Paul Stabach
Tayyaba Ishaq
Sam Lopez
Hana Kim
Kennedy Obidoh

Yale Collaborators
Thomas Carpenter (Peds Endo)
Enrique De La Cruz (BM&B)
W. Charles O'Neil (Emory)



Yale University
School of Medicine

Yale YV8905

Funding:

inozyme pharma

NIH National Institute of Diabetes and Digestive and Kidney Diseases

NIH National Institute of Arthritis and Musculoskeletal and Skin Diseases

NIH National Institute on Aging

Blavatnik Fund
Yale Innovation

ClinicalTrials.gov:
NCT04686175 (GACI/ARHR2)
NCT05030831 (ABCC6)