Targeting genetically associated childhood and adult obesity

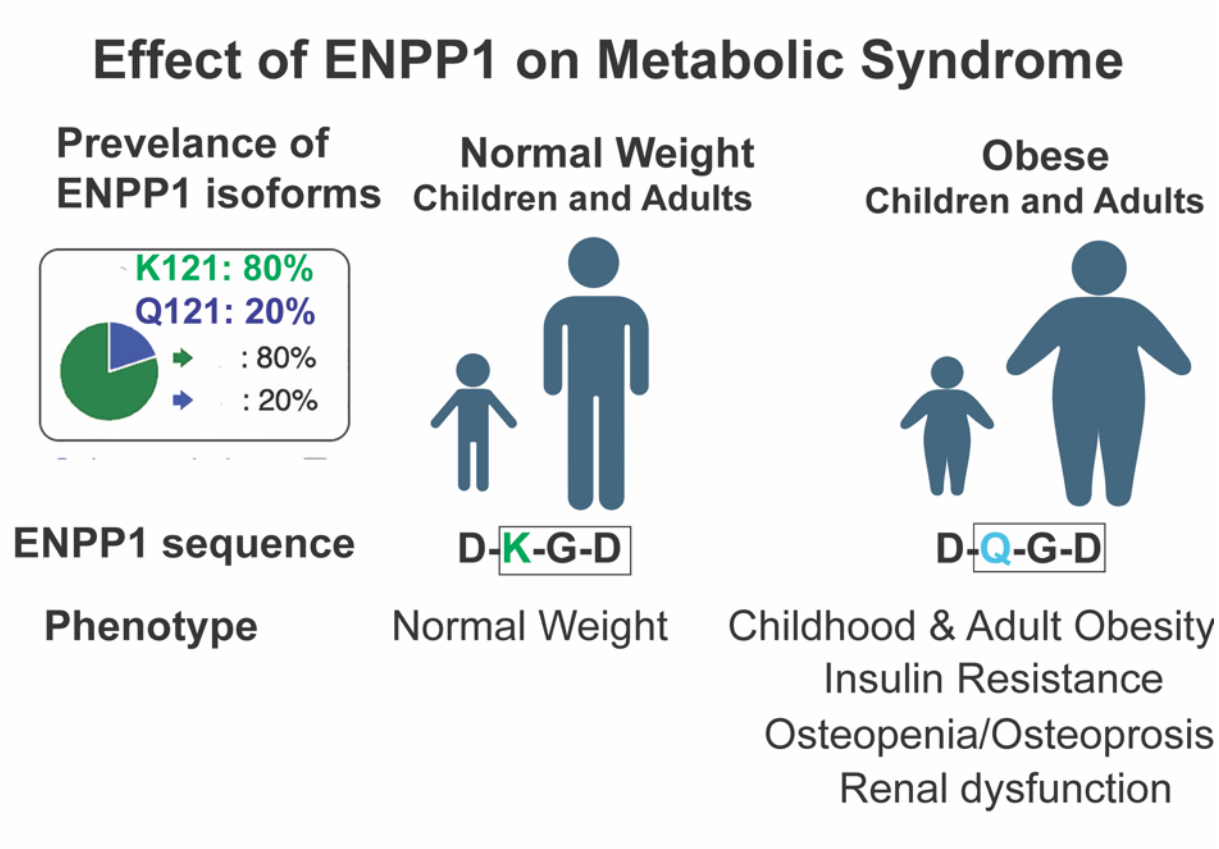
Demetrios Braddock, Assoc. Prof. Pathology

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

Matthew Rodeheffer, Prof. Comparative Medicine

Blavatanik Fund Presentation

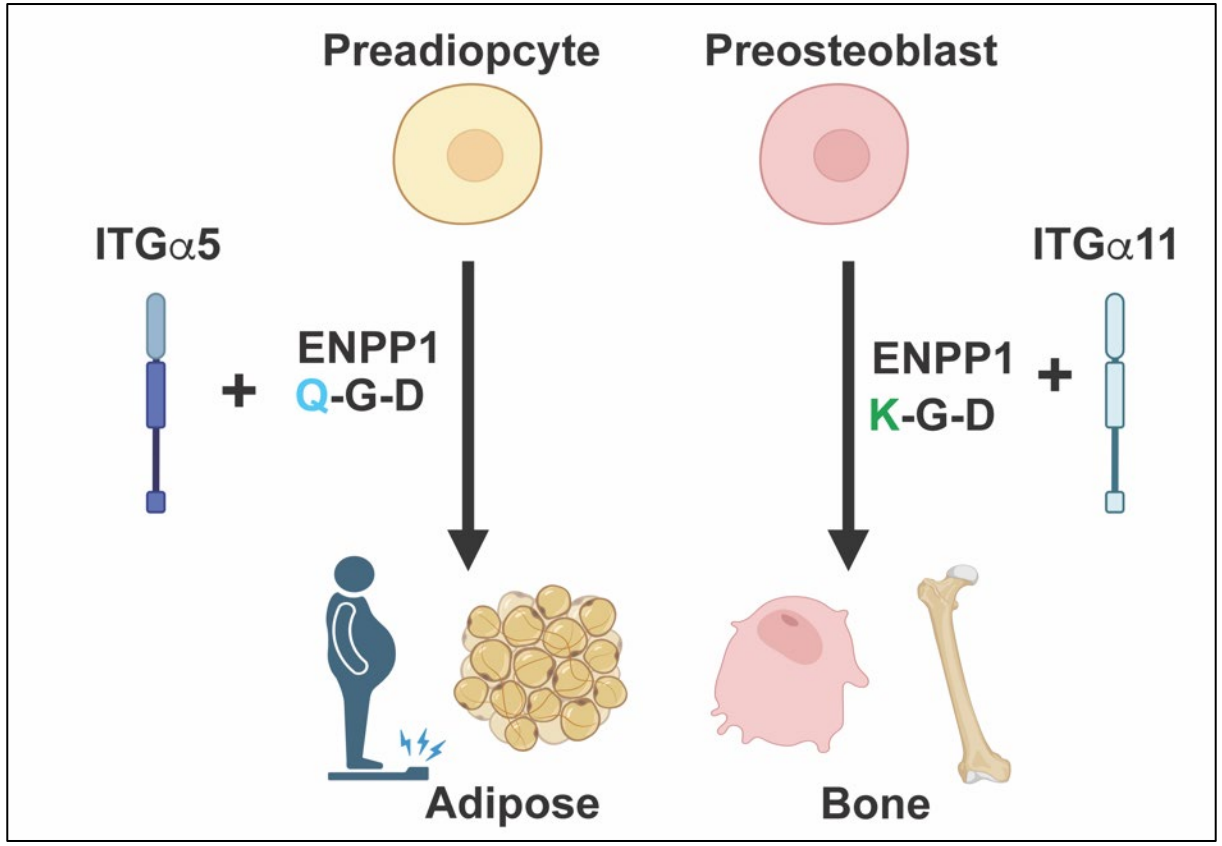
66 M US children and adults are at risk for genetic obesity associated with a ENPP1^{Q121} SNP



- Childhood obesity rates have tripled over the last three decades
  - Today one in three children are classified as either overweight or obese.
- 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.

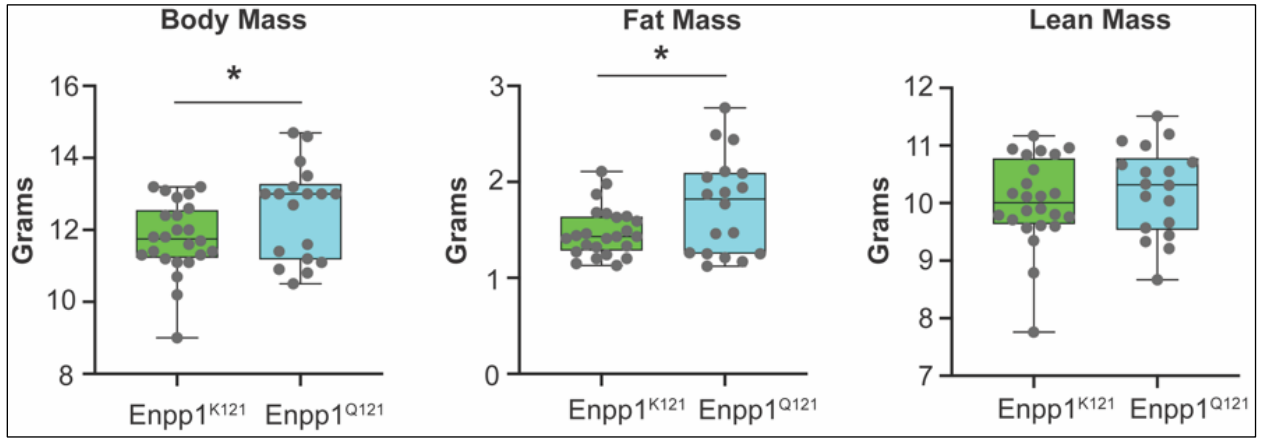
We developed a predictive mouse model to defined disease mechanism

Strains	**C57BL6**	**Enpp1^{K121}**	**Enpp1^{Q121}**
Sequence	**T-H-N-D**	**D-K-G-D**	**D-Q-G-D**
Phenotype	Non-obese	Non-obese	Early onset obesity Increased adiposity Osteoporosis Insulin resistant Renal dysfunction

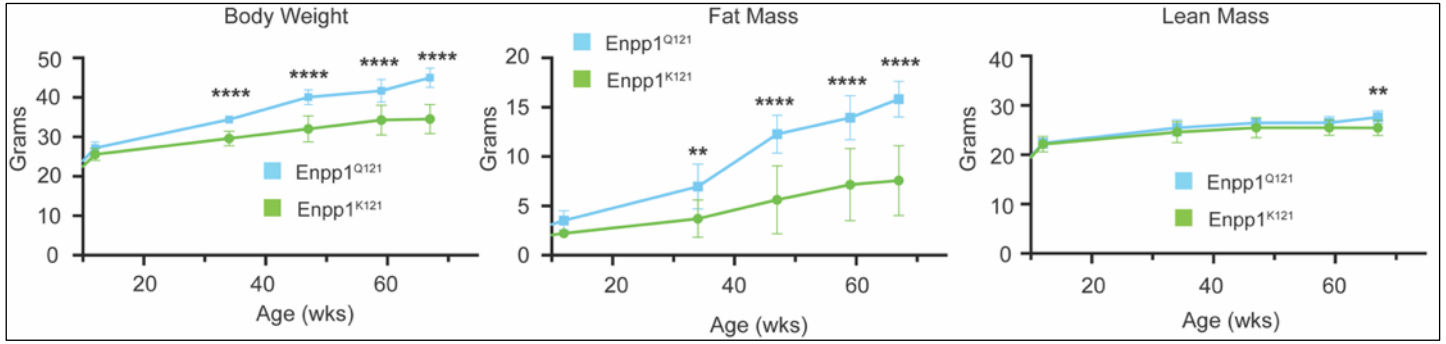


Mouse model recapitulates body composition of ENPP1^{Q121} humans

Enpp1^{Q121} mice have more fat

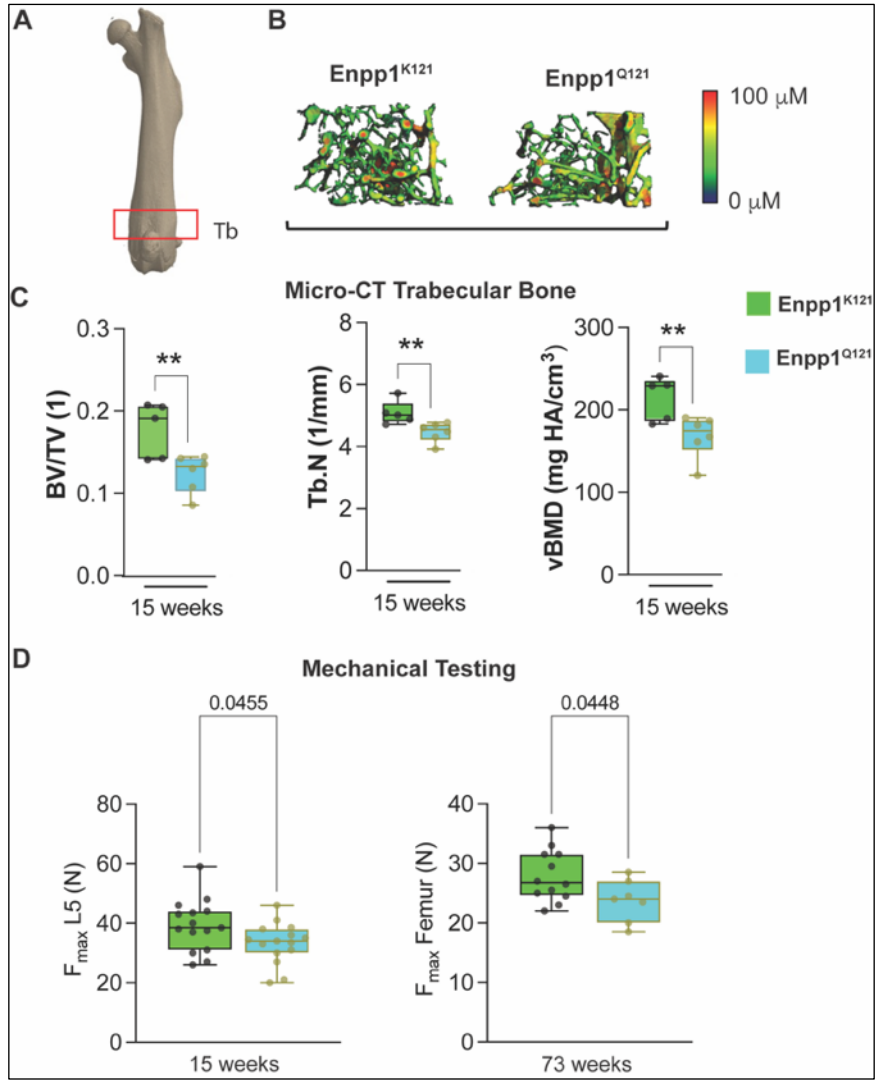


Body composition at 3 weeks

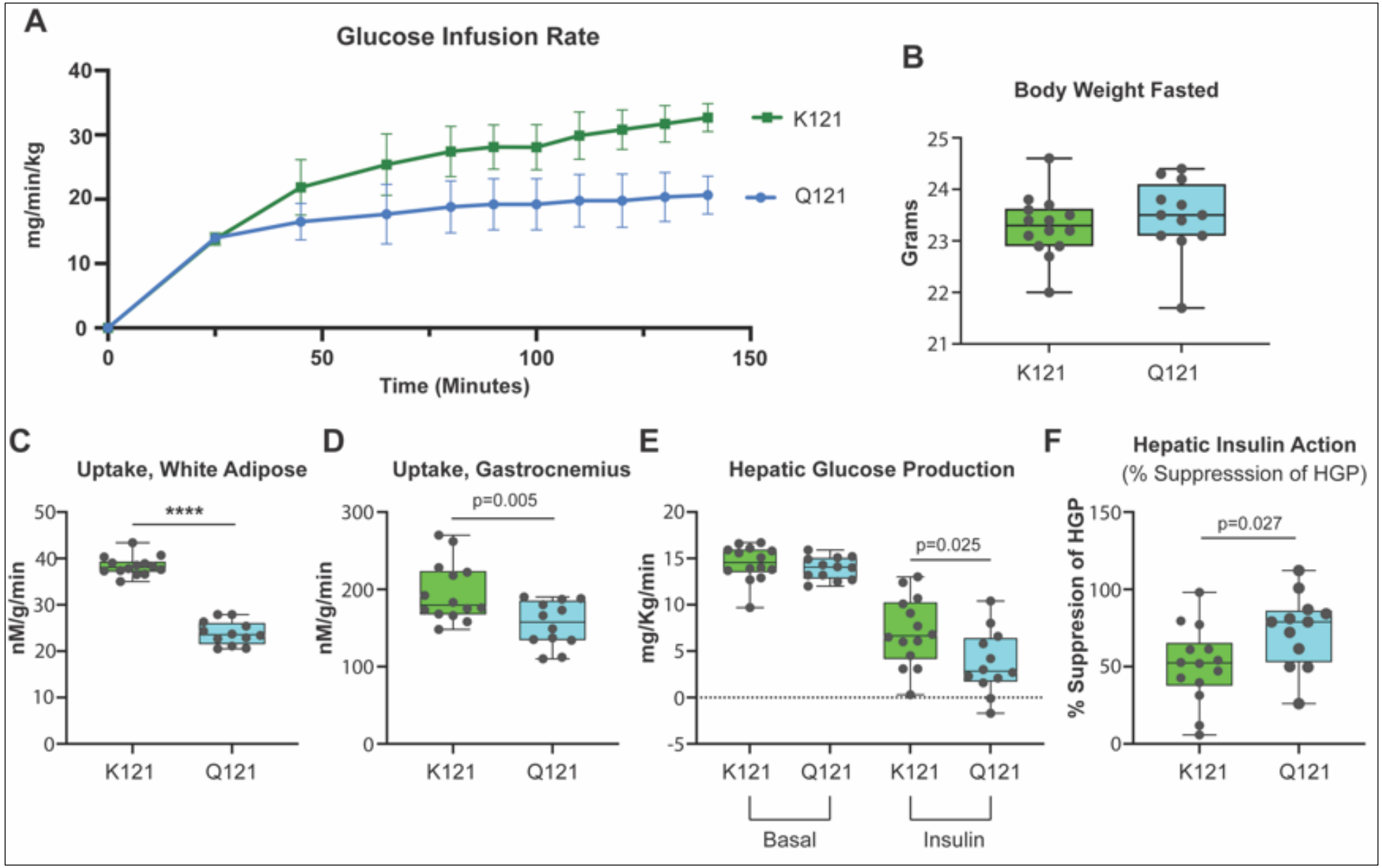


Body composition weeks 12-67

Enpp1^{Q121} mice have less bone

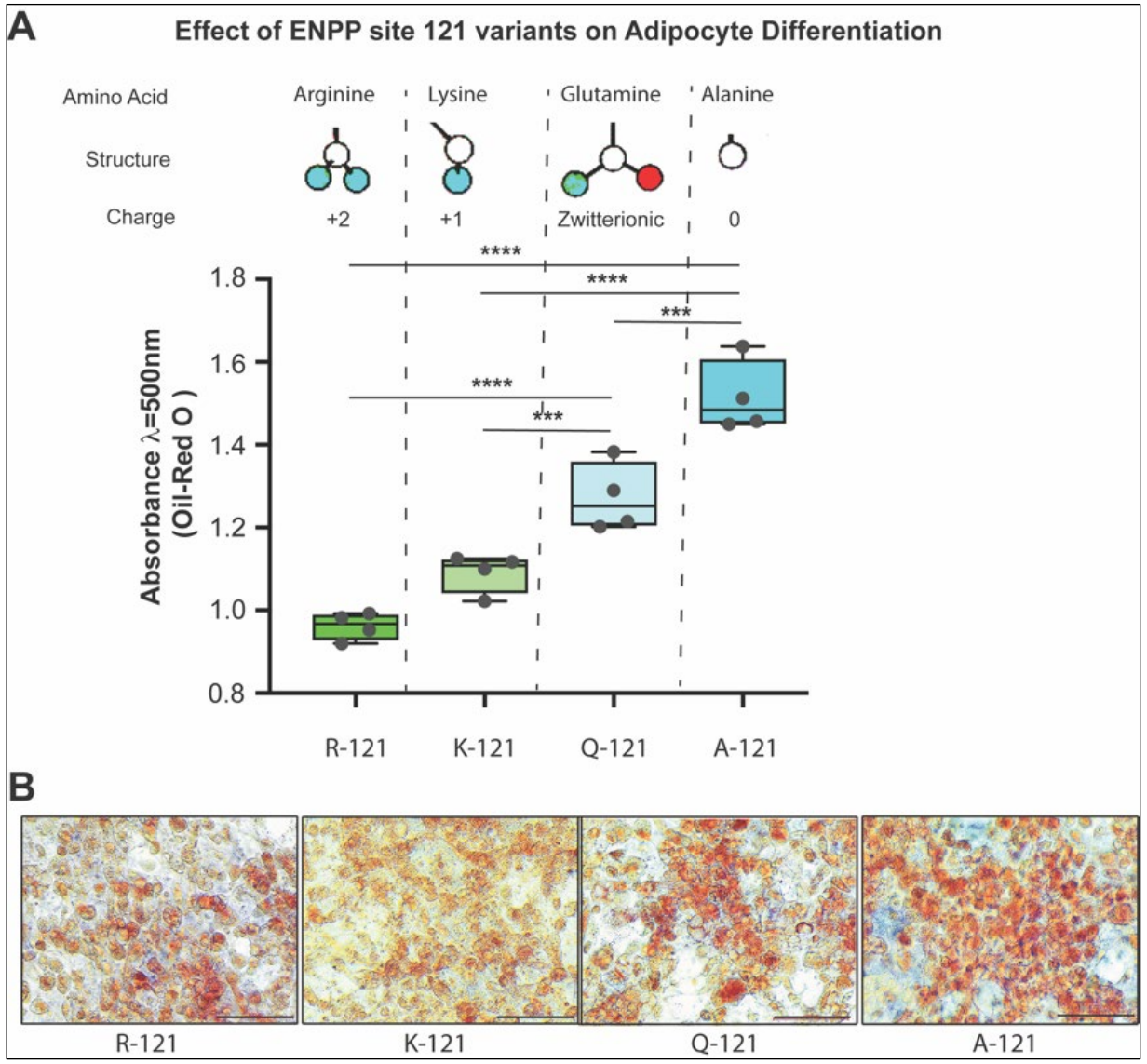


Enpp1^{Q121} mice are insulin resistant

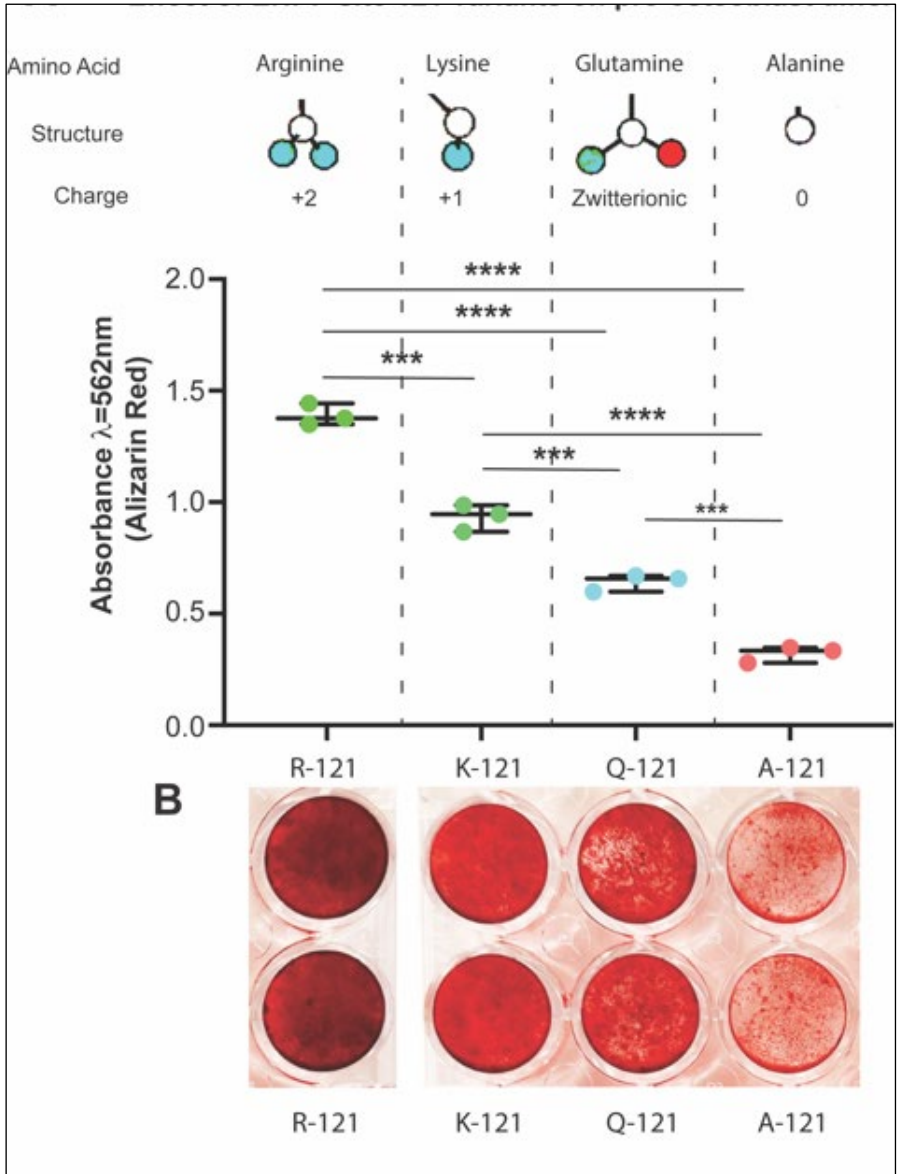


In vitro assay to screen candidate therapeutics

Differentiation of preadipocytes into fat

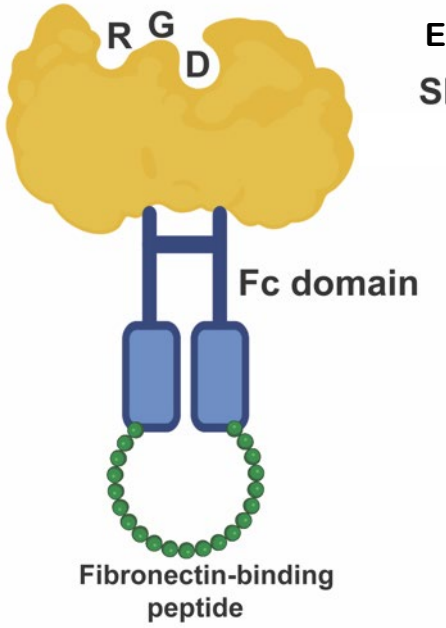


Differentiation of pre-osteoblasts into bone



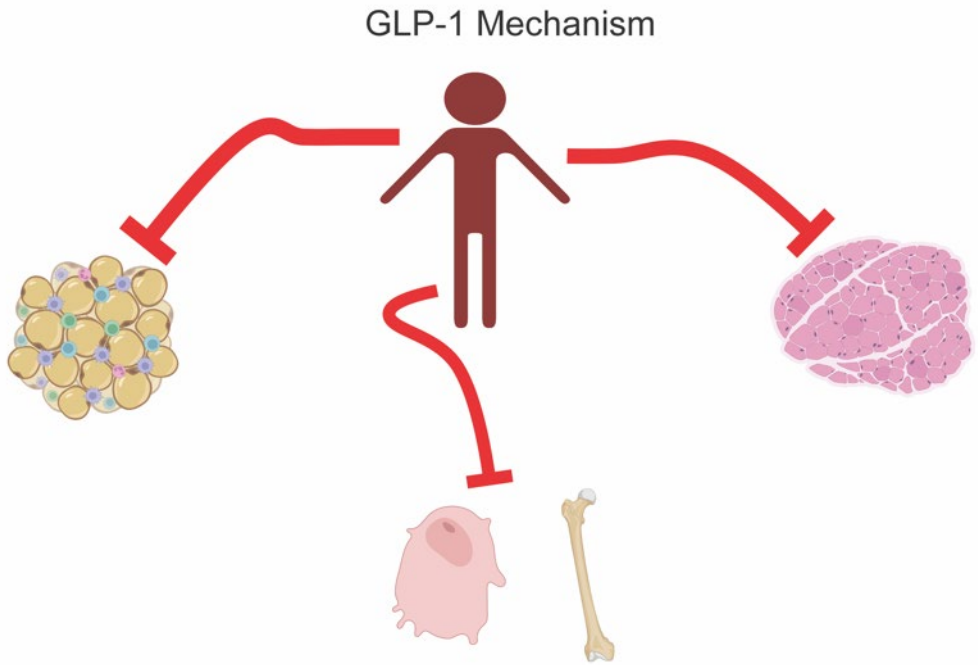
Yale YV8905

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



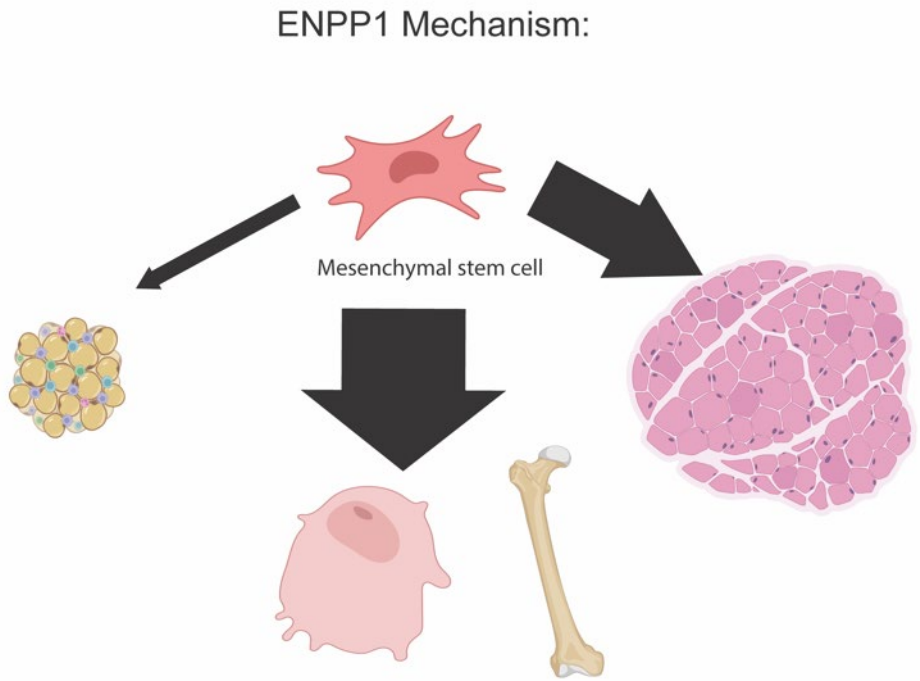
U.S. Provisional Patent Application No. 63/643,792 filed May 7, 2024
Title: "CONSTRUCTS, COMPOSITIONS, AND METHODS FOR TREATING, AMELIORATING, AND/OR PREVENTING OBESITY"
By: Demetrios Braddock, et al.
Yale Ref.: YV 8905
Saul Ref.: 047162-7501P1(02202)

We have filed provisional patents on biologics to address this condition



Induced malnutrition via feeding neglect

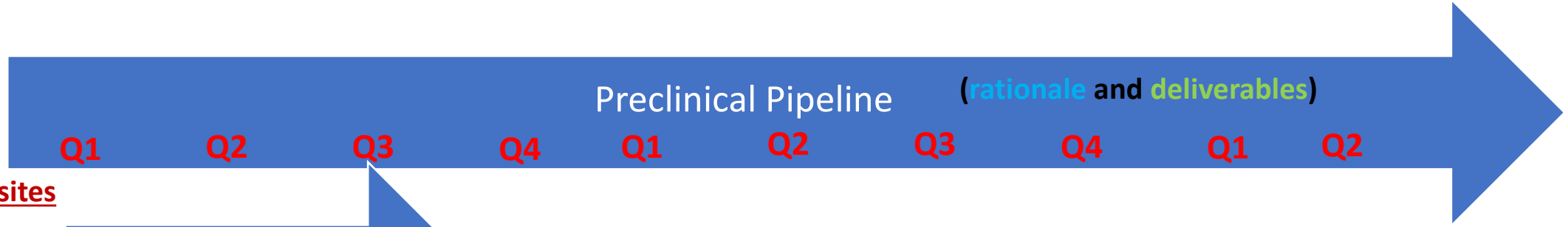
Reduced bone mass
Reduced muscle mass
Poor compliance
Rebound adiposity upon discontinuation



Regulate body composition via redirecting stem cell differentiation

Reduced adiposity by increasing bone and muscle mass

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

Summary

- Dr. Rodeheffer, an expert in adipogenesis, has shown that mechanism regulating increased fat cell number in obesity are distinct from the mechanisms that control adipogenesis during the establishment of adipose mass during development
- He has also shown that altering the number of preadipocytes during development can have life-long effects on fat mass.
- We have discovered a novel mechanism of stem cell preadipocyte differentiation mediated by the ENPP1^{Q121} polymorphism, involving isoform specific recognition of stem cell integrins
- We have developed a predictive animal model in which to validate therapeutics that abrogate ENPP1^{Q121} mediated adipogenesis, obesity, and insulin resistance
- We are seeking funds to design and validate biologics to inhibit ENPP1^{Q121} stimulated adipogenesis, a therapeutic which will address the most significant genetic risk factor for childhood obesity, impacting some 66M children and adults in the US.

Bradddock Lab

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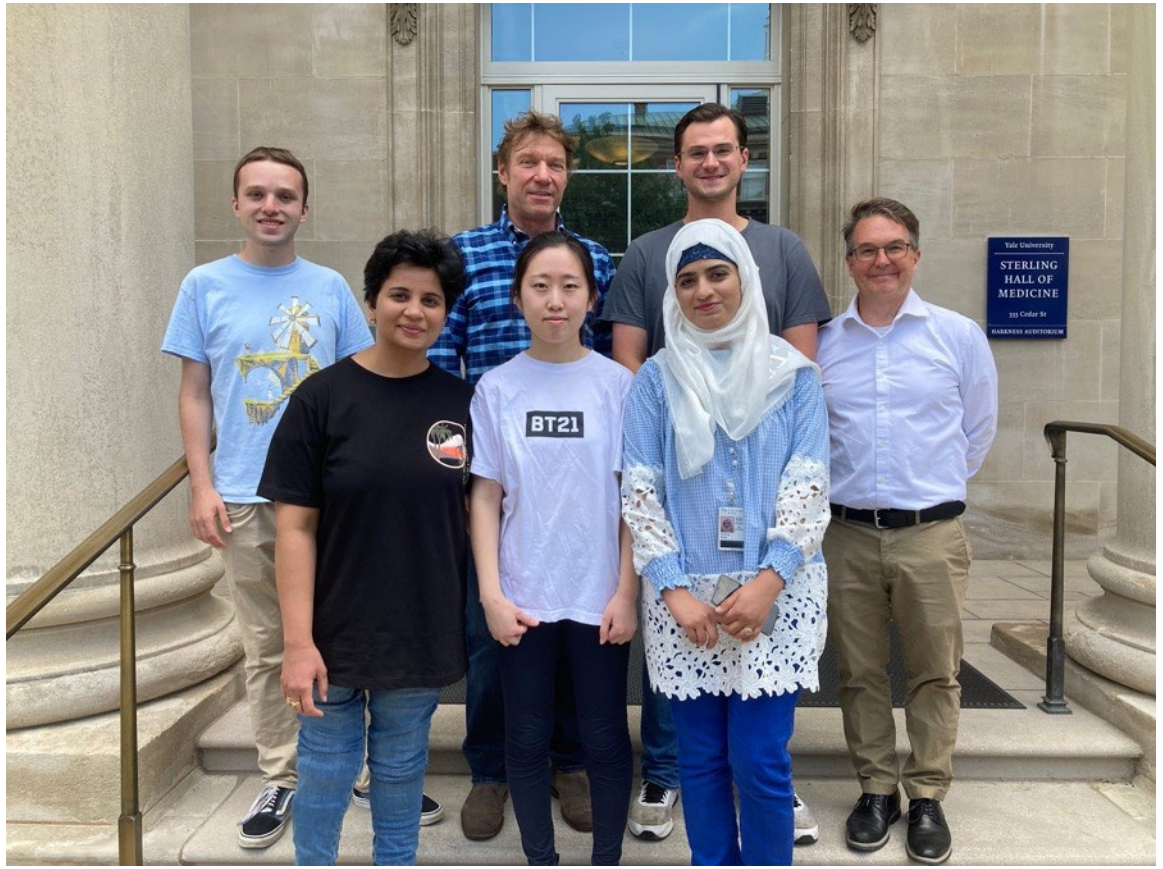

Yale University
School of Medicine

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)