Recombinant human ENPP1-Fc prevents ectopic tissue calcification and restores growth in Enpp1 deficient mice

Zhiliang Cheng, Kevin O'Brien, Caitlin Sullivan, Jennifer Howe, Steve Jungles, Denis Schrier, David Thompson, Yves Sabbagh

Inozyme Pharma

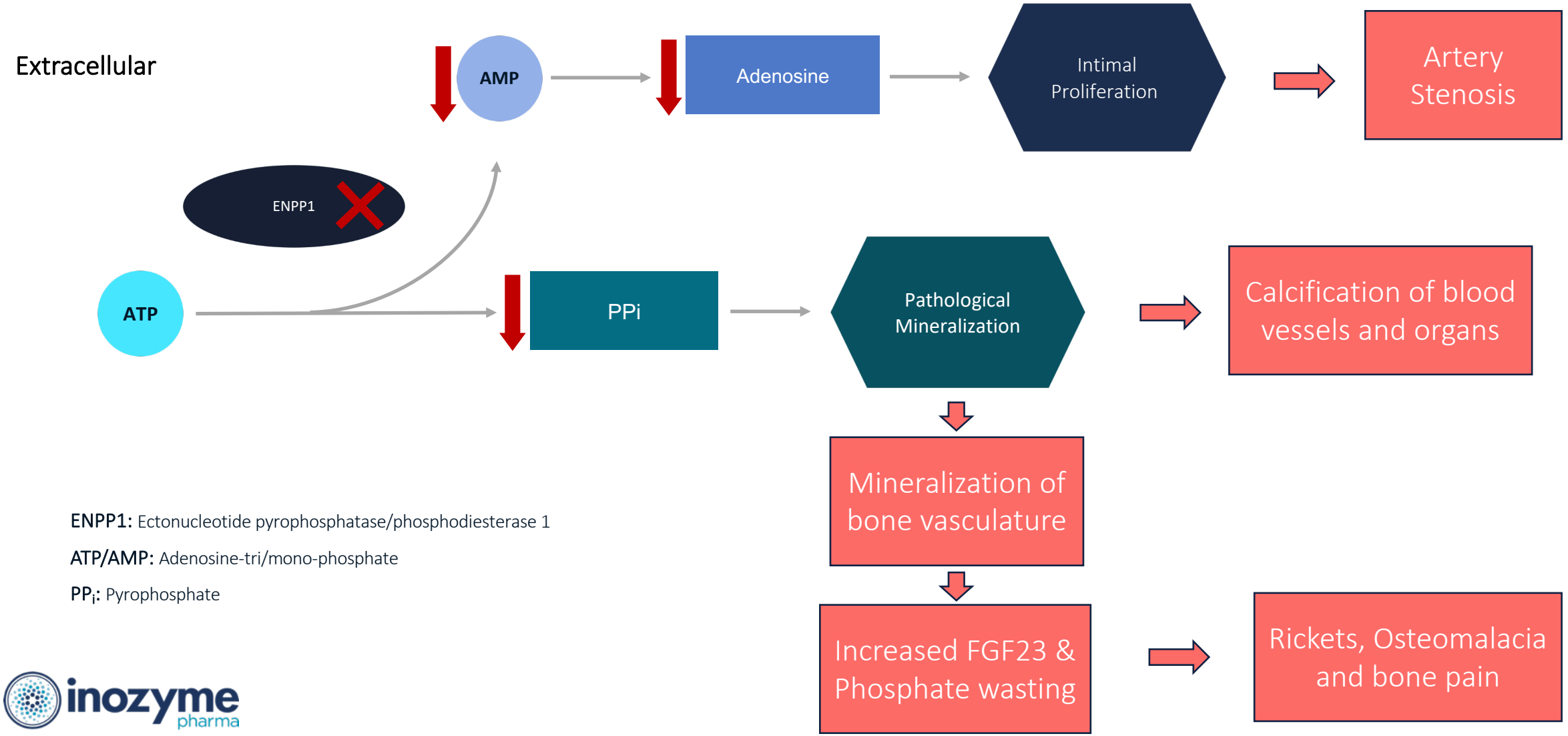
ICCBH 2020

inozyme pharma

DISCLOSURE

- *The authors are employees of Inozyme Pharma.*
- *The work reported is sponsored by Inozyme Pharma.*

ENPP1 as a key regulator of biological mineralization and intimal proliferation



ENPP1: Ectonucleotide pyrophosphatase/phosphodiesterase 1

ATP/AMP: Adenosine-tri/mono-phosphate

PP_i: Pyrophosphate

inozyme pharma

ENPP1 Deficiency is a systemic disease with high mortality and morbidity

Historical Definition

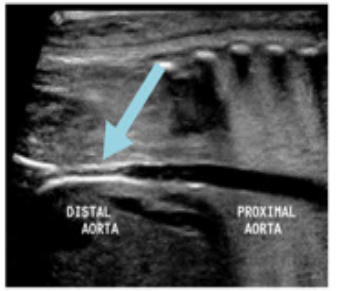
Generalized Arterial Calcification of Infancy (GACI):
Calcification and narrowing of arteries leading to early morbidity and mortality, often resulting in death (45-50% of infants, within 12 months of birth)

Autosomal recessive hypophosphatemic rickets type 2 (ARHR2):
Survivors of the infant stage develop skeletal issues including weak bones/muscles and rickets in children as well as adults

ENPP1 Deficiency - New Definition

COMPLICATIONS

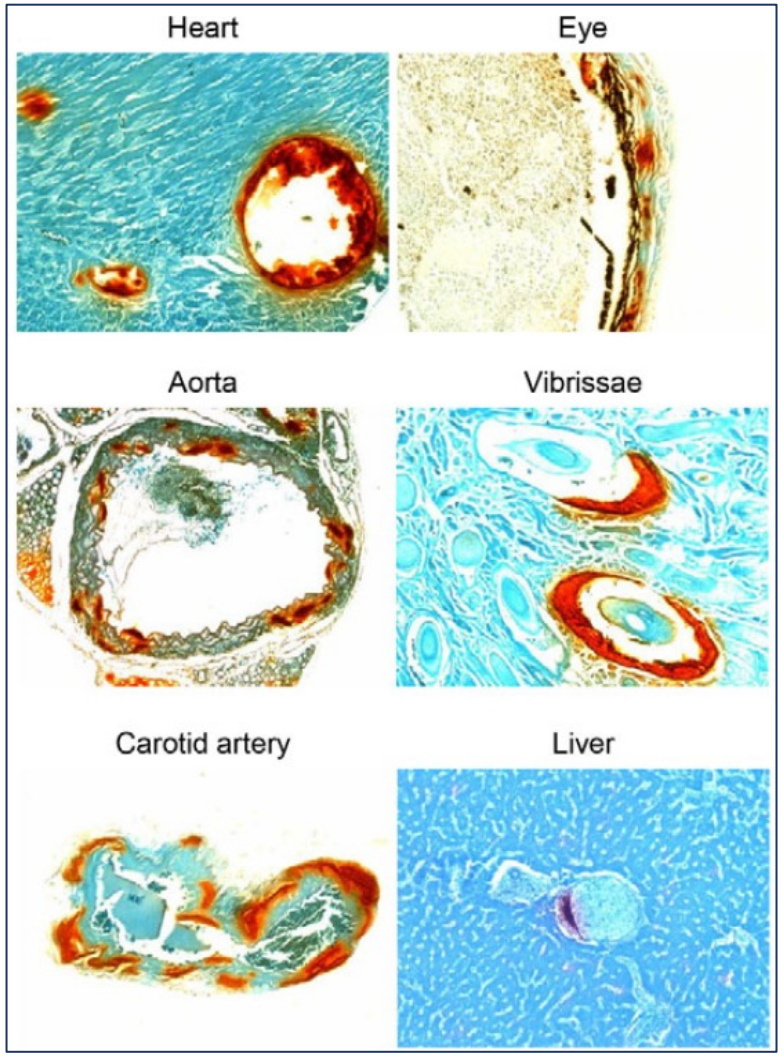
- Calcification
- Narrowing of arteries (stenosis)
- Heart failure
- Cardiomegaly
- Death
- Short stature
- Skeletal deformities
- Weakened bones and muscles
- Fractures
- Bone pain



inozyme pharma

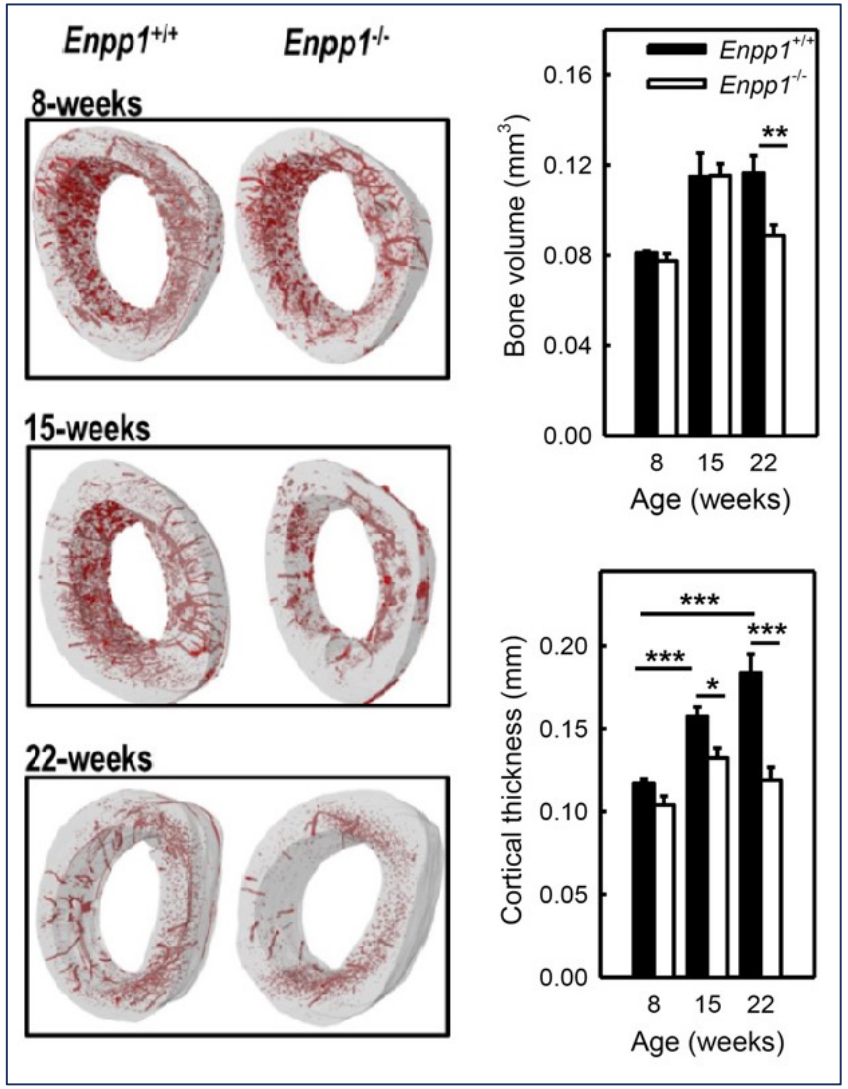
Enpp1 deficient mice recapitulate phenotypes of human disease

Enpp1$^{asj/asj}$ mice develop tissue calcification



Li, 2013

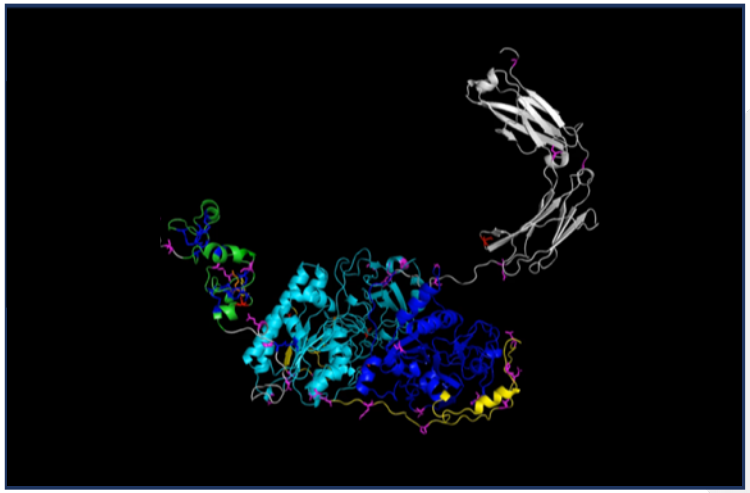
Enpp1$^{-/-}$ mice develop bone defects



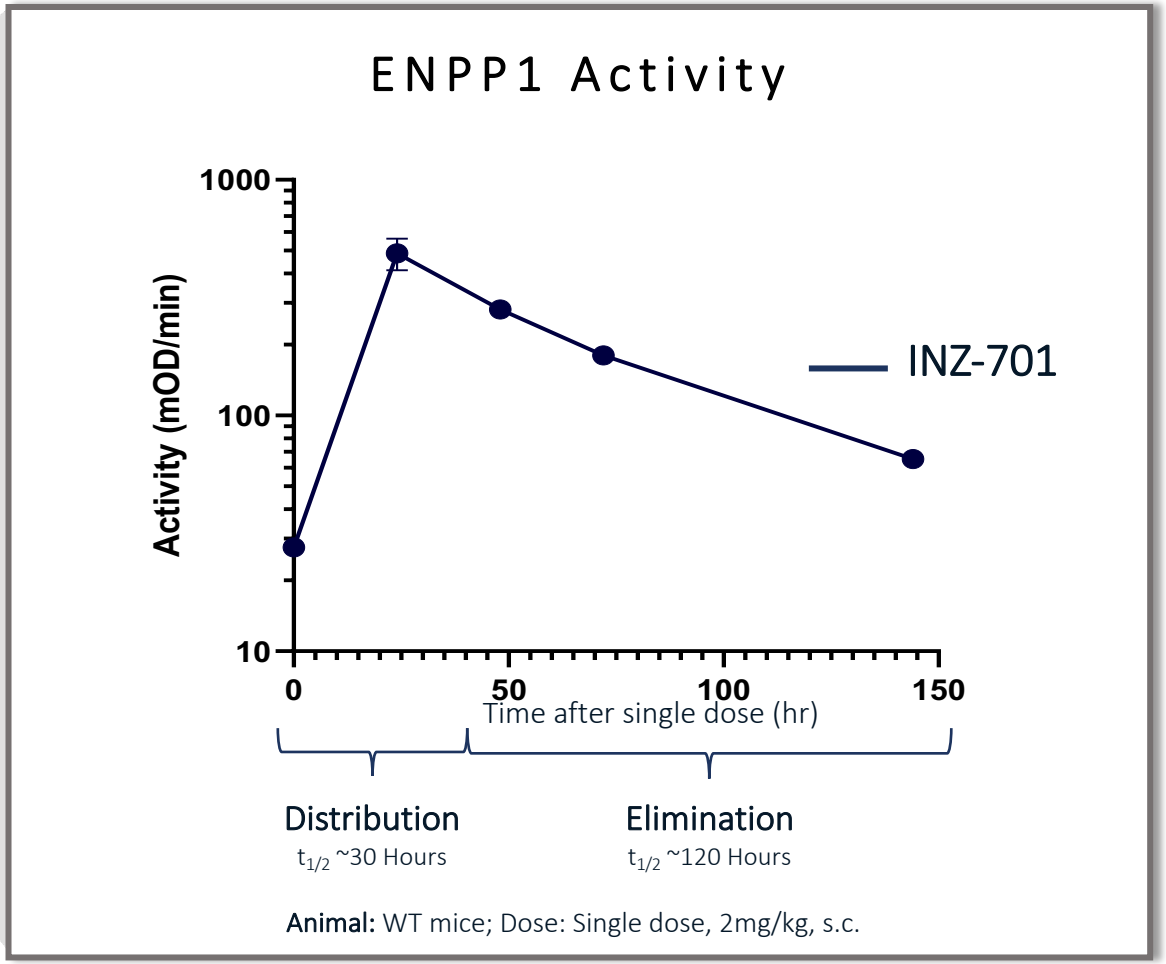
Hajjawi, 2014

INZ-701 as an ERT in development for ENPP1 Deficiency

INZ-701 (ENPP1-Fc)



- **Protein:** Recombinant human ENPP1 (Ectonucleotide pyrophosphatase/phosphodiesterase 1)
- **Construct:** Recombinant Fc fusion protein with soluble extracellular domain of ENPP1
- **Dosing:** TBD
- **Enzymatic Properties:** High catalytic efficiency (Kcat/Km)



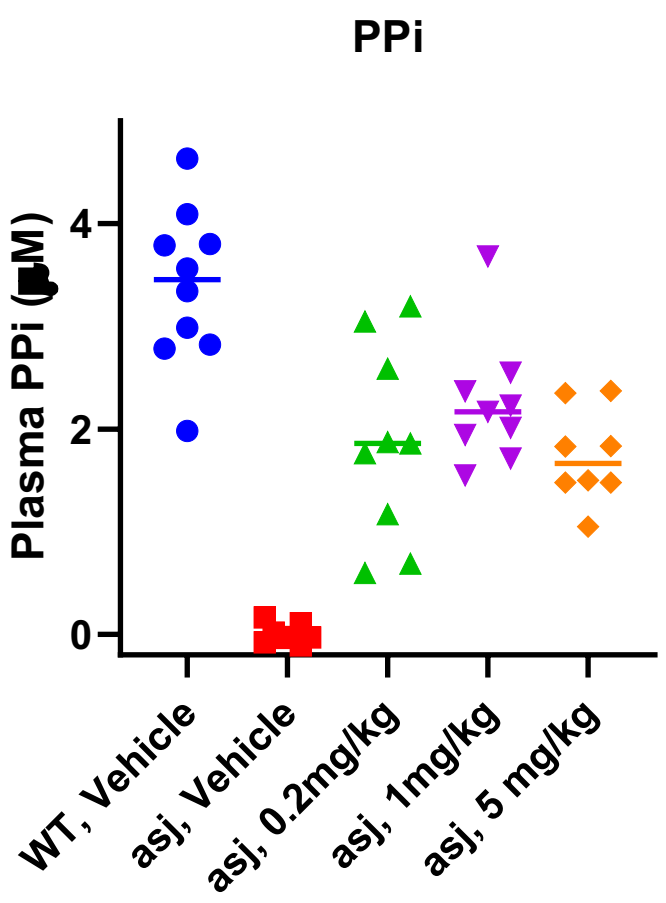
Dose response study design

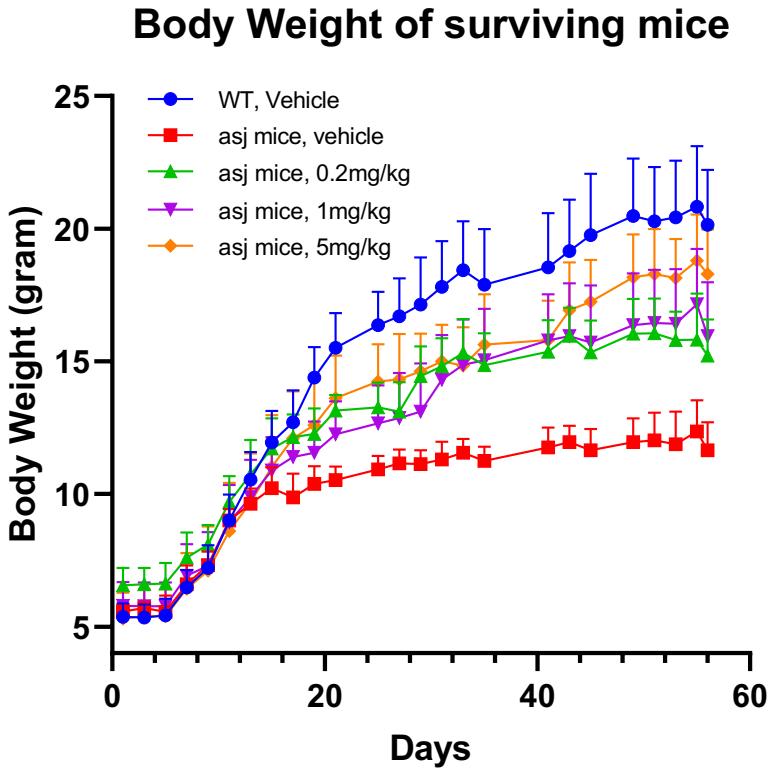
Animal	Diet	Test Article	Dosing	Start	End	Readouts
WT	Acceleration diet* from gestation	vehicle	s.c.; q.o.d	2wk of age (D1)	10wk of age (D56)	• Enpp1 activity • Plasma PPi • Tissue calcium • Body weight • Bone parameters • Clinical signs
Enpp1$^{asj/asj}$		vehicle				
Enpp1$^{asj/asj}$		INZ-701, 0.2mg/kg				
Enpp1$^{asj/asj}$		INZ-701, 1mg/kg				
Enpp1$^{asj/asj}$		INZ-701, 5mg/kg				

*Acceleration diet: high in phosphate and low in magnesium

inozyme pharma

INZ-701 normalizes plasma PPi levels and improves clinical signs



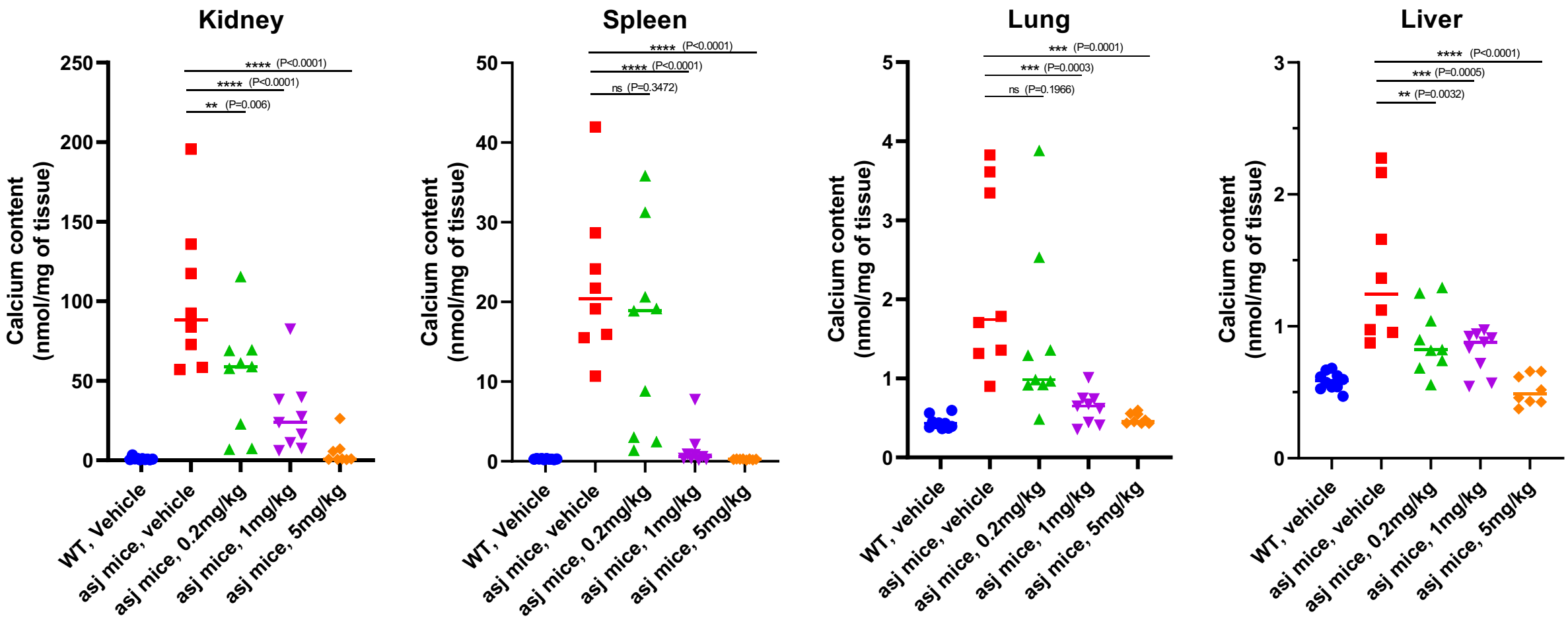


Clinical signs

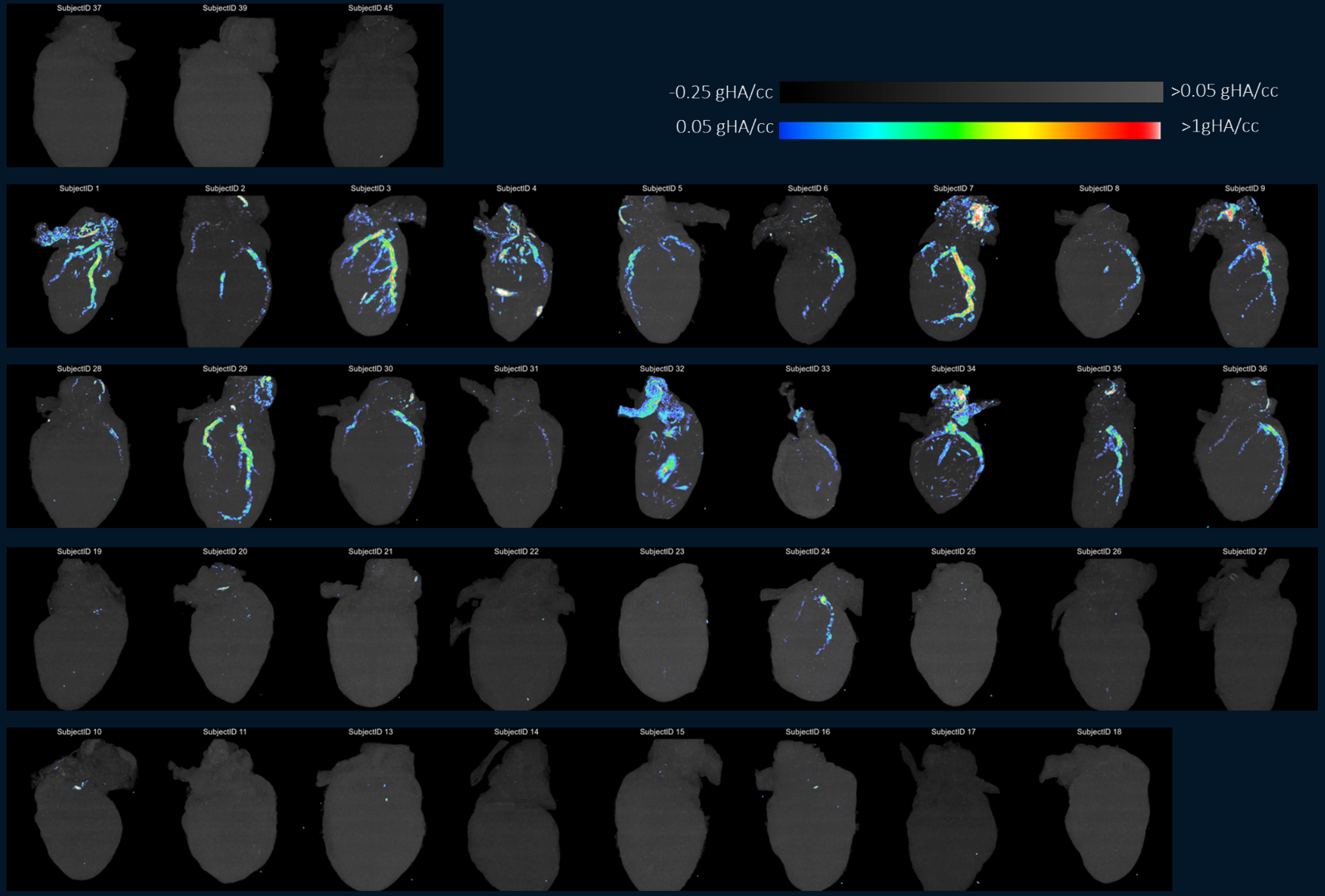
- *Enpp1*$^{asj/asj}$ mice treated with **vehicle** showed pinned ears, stiff legs, stilted gait, hunched back, dehydration

- *Enpp1*$^{asj/asj}$ mice treated with **5mg/kg INZ-701** showed no abnormality

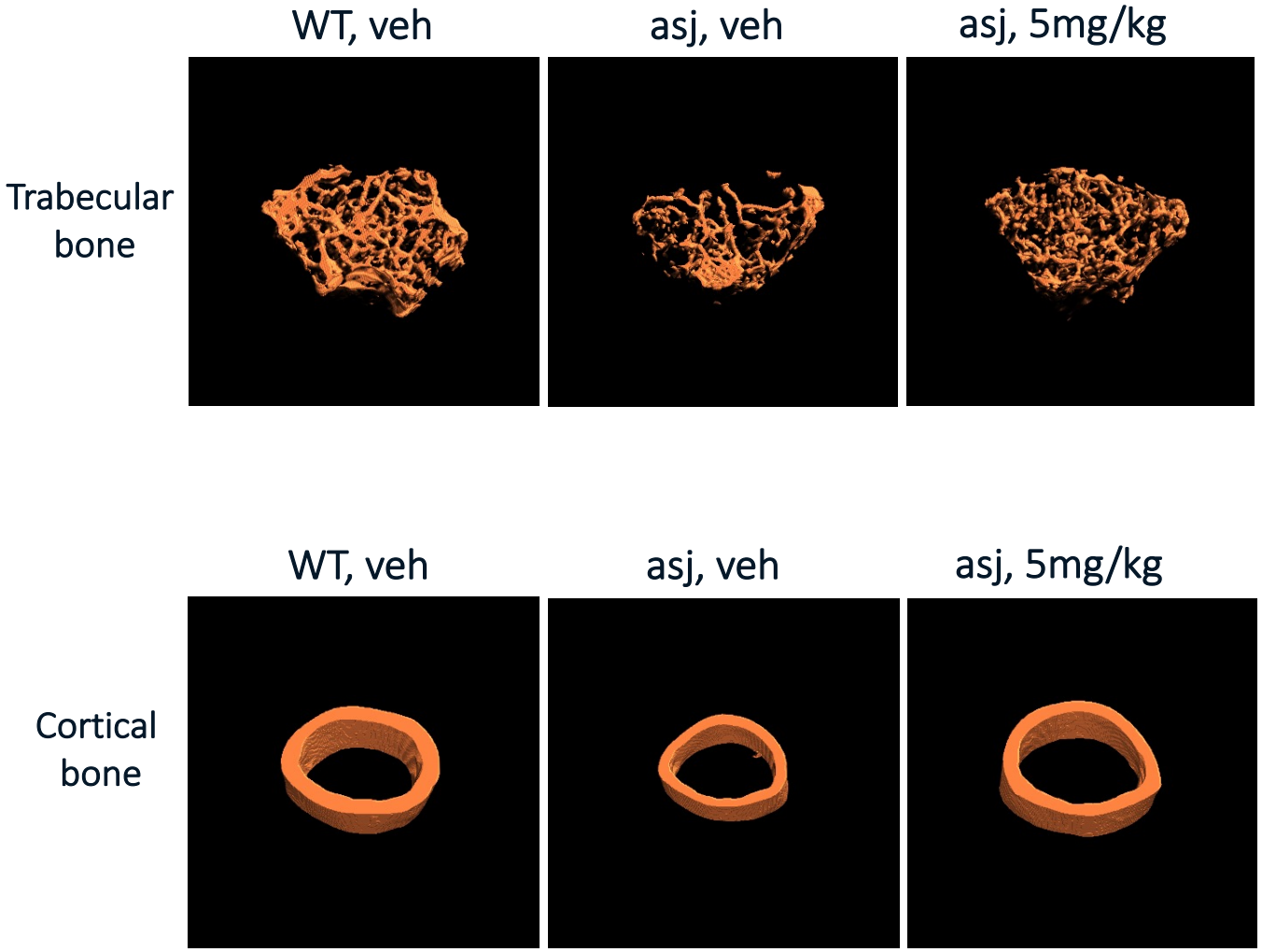
INZ-701 prevents tissue calcification

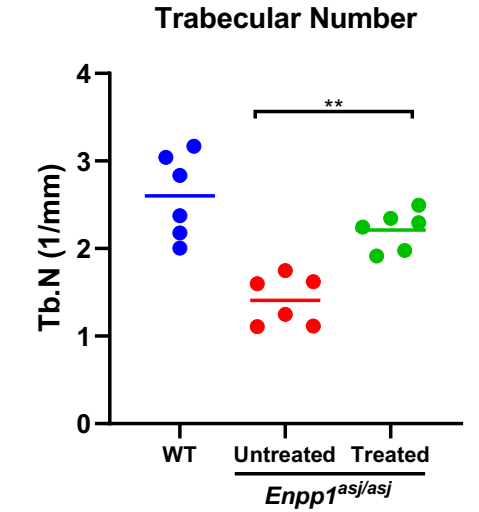


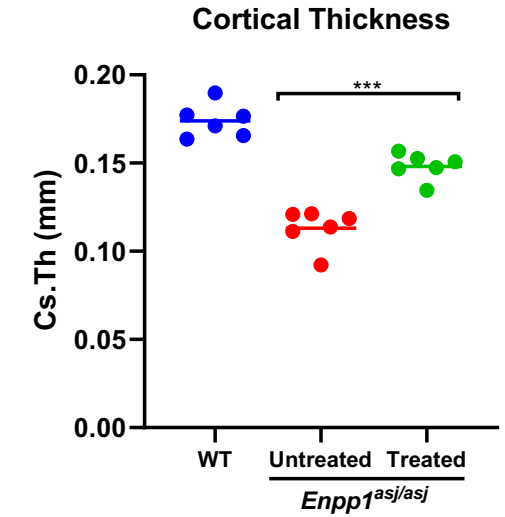
Dose response_µCT of hearts and aorta



hENPP1-Fc corrects bone defects in Enpp1 deficient mice







inozyme pharma

Summary

INZ-701, a human ENPP1-Fc ERT, shows dose-dependent therapeutic effects in an Enpp1 deficient mouse model.

- Normalizes plasma pyrophosphate (PPi) levels
- Prevents tissue calcification
- Corrects bone defects
- Restores growth and improves clinical signs

Acknowledgment

Inozyme Research Team
Kevin O'Brien
Jennifer Howe
Caitlin Sullivan
Daniel Michaels

David Thompson (CSO)
Denis Schrier
Angela Lynch
Steve Jungles
The whole Inozyme team!

Yale
Demetrios Braddock
Joseph Schlessinger

Biomere
Chris Hogan
Sue Champagne
Kristin Sapp

Invicro
Rachel Stewart
Surabhi Nair

Covance
Arun Tatiparthi