

Dual-Function AAV₉ *BCKDHA-BCKDHB* Vector

Gene Therapy for Classic MSUD in Murine & Bovine Models

Kevin A. Strauss, MD, *Clinic for Special Children*



Clinic for
Special Children



UMass Chan
MEDICAL SCHOOL



Needs, Outcomes, and Biomarkers

184 patients and **12,443** samples over **30** years

Outcomes: Dietary Burden, Cognitive Function, Biomarkers



Prescription Diet



Metabolic Crises



Liver Transplant

Gene Therapy for Classic MSUD in Newborn Calves

The Dual-Function AAV9 *BCKDHA-BCKDHB* Vector

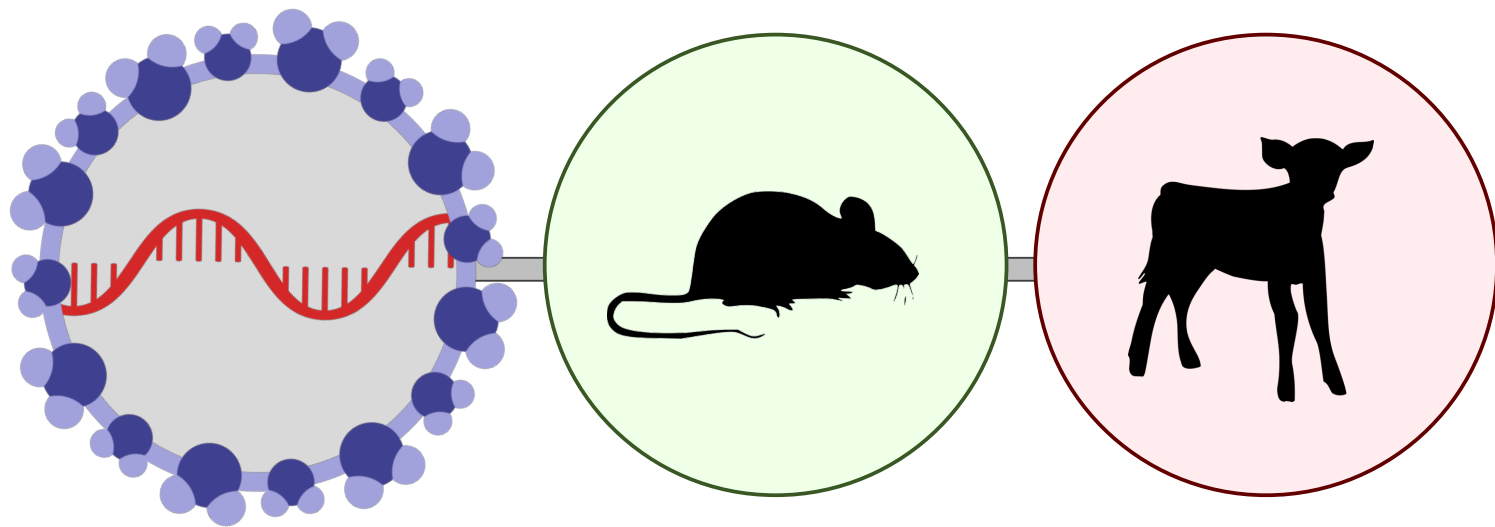


Clinic for
Special Children



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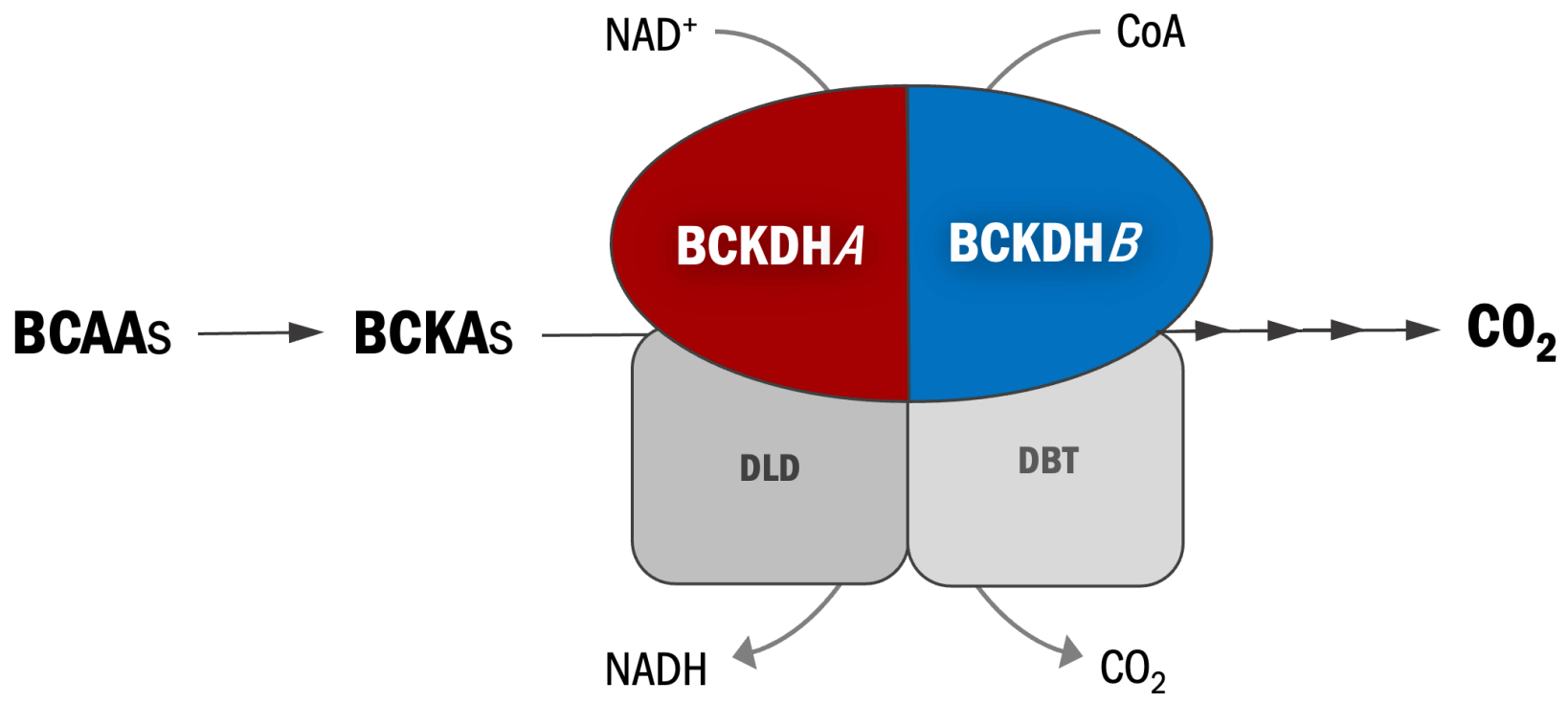
This letter is merely an encouragement to put your heart into finding a cure for the MSUD. Life with it is very discouraging and depressing. I pray daily that God would lead you and guide you and help you thru' the process of ~~research~~ that something could be found and come from it.



*Gene
Vector*

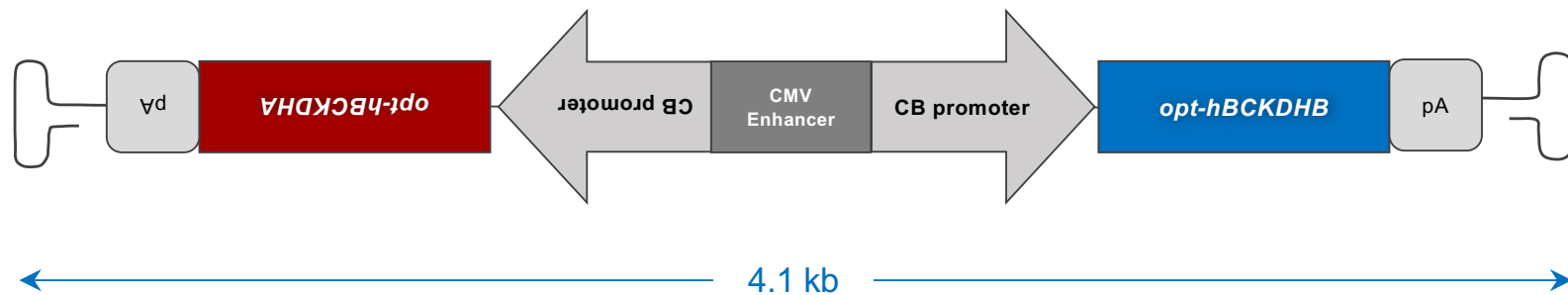
*Small
Animal*

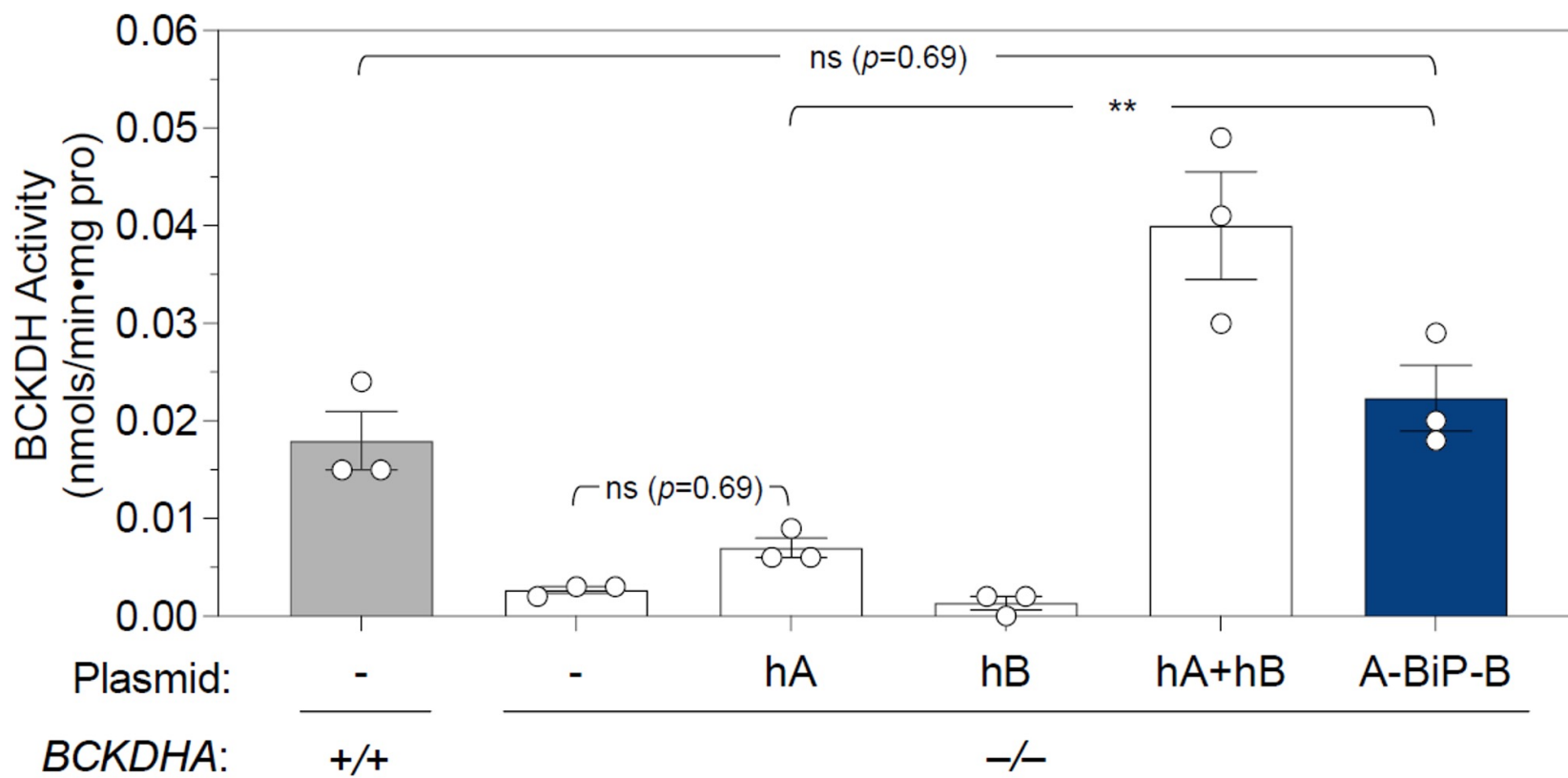
*Large
Animal*



Bidirectional *BCKDHA-BCKDHB* Gene Replacement Vector

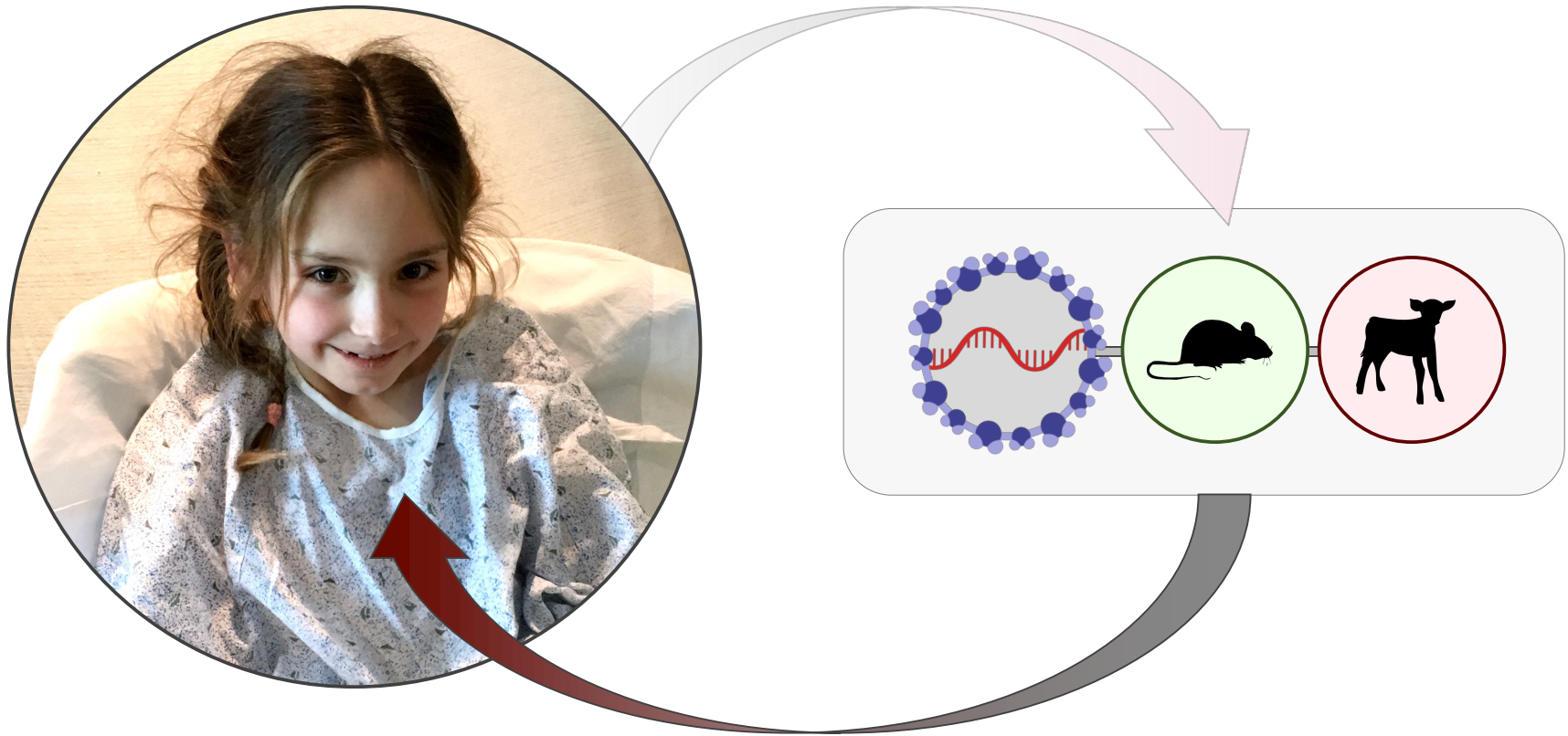
'A-BiP-B'



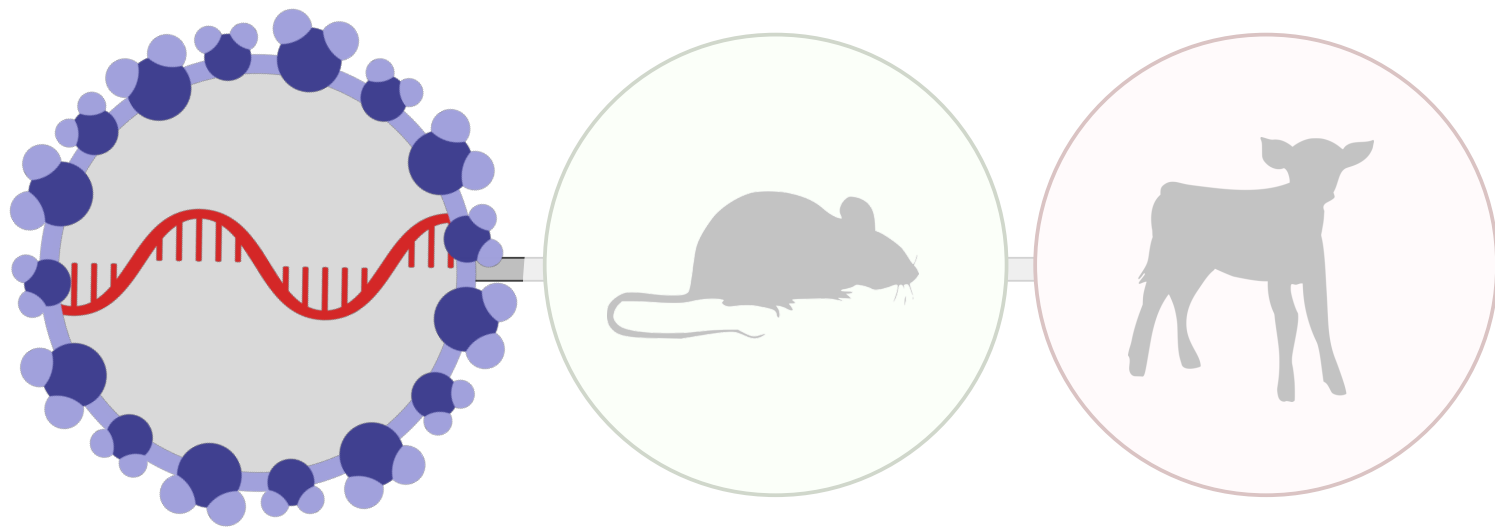


trans·late (*verb*).

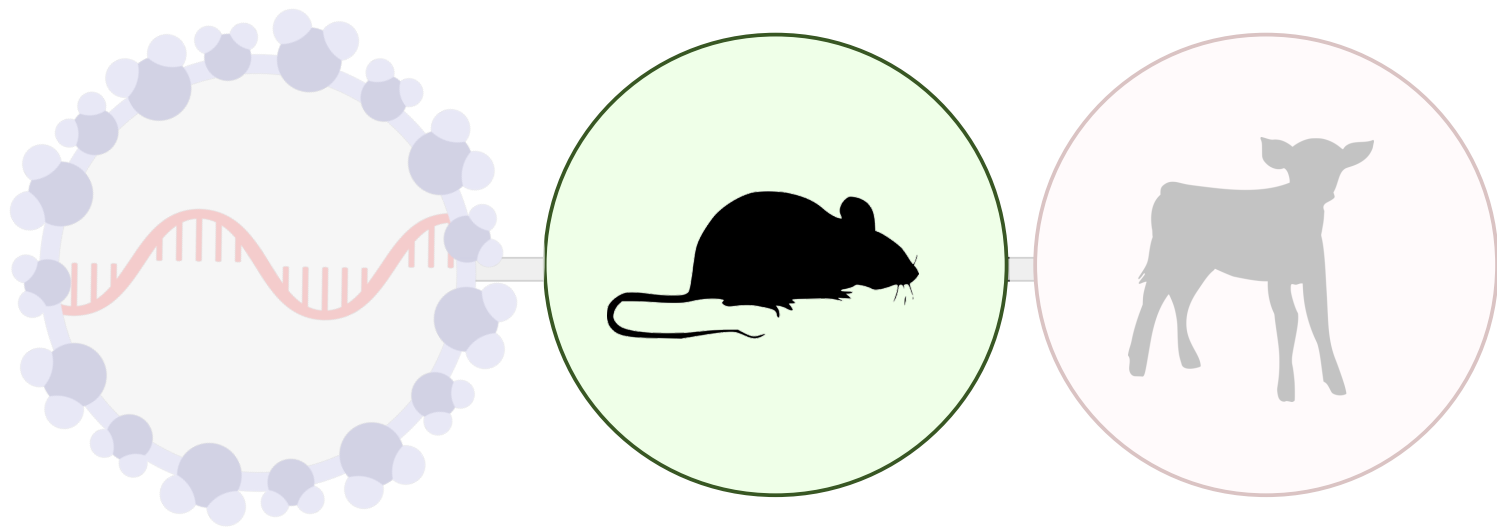
Latin: *trans* "across, beyond" + *lātus* "borne, carried"



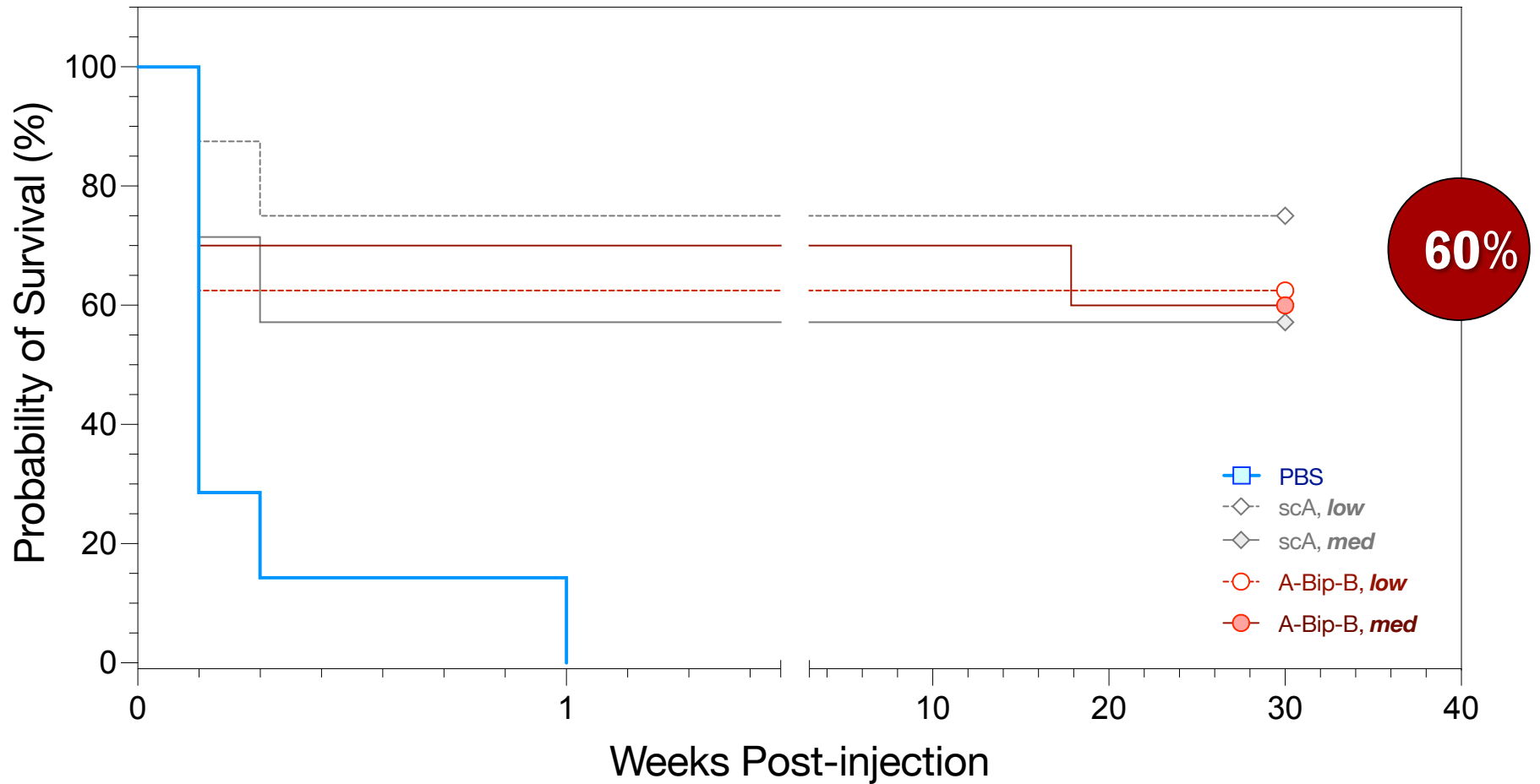
"To Carry Across"



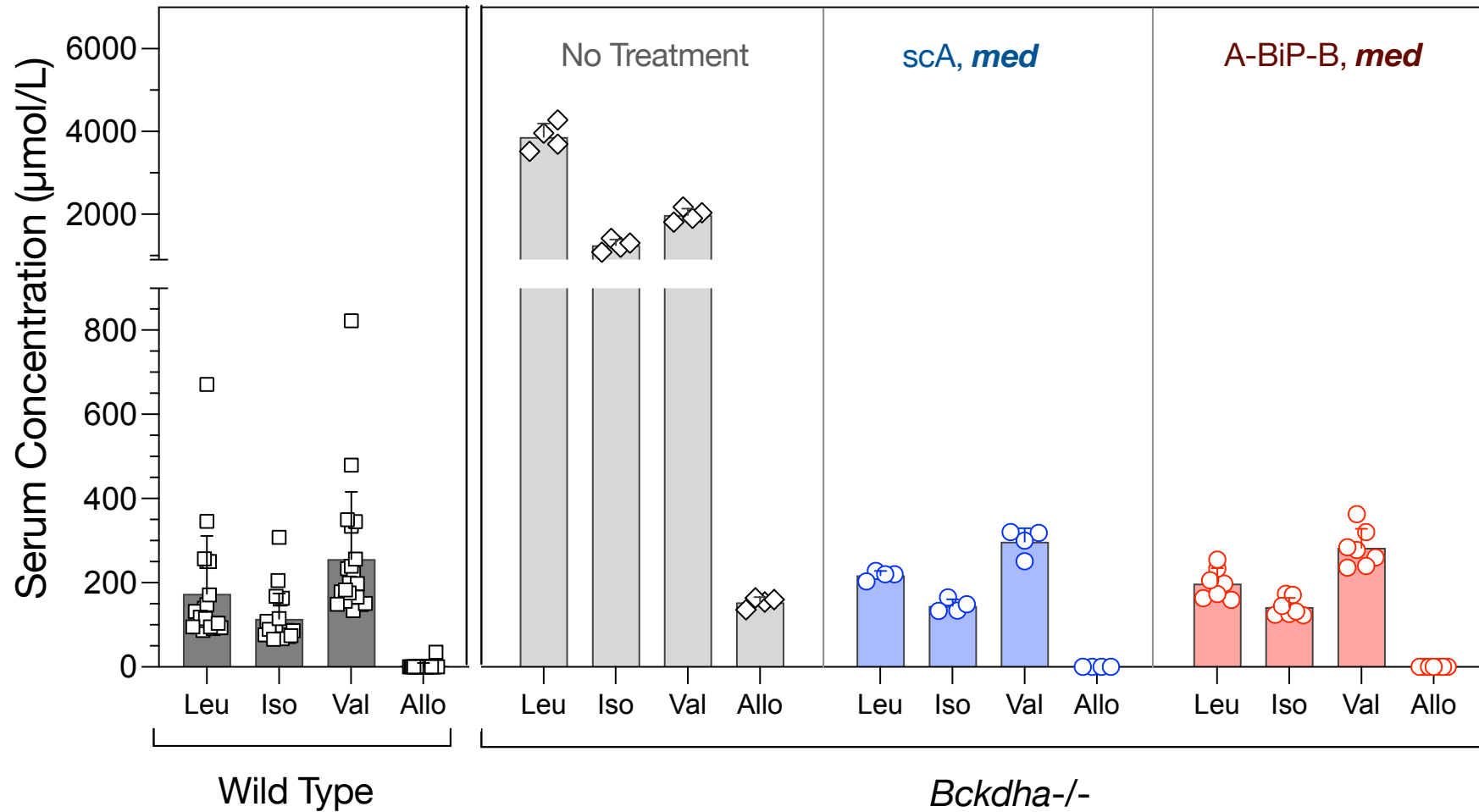
*Gene
Vector*



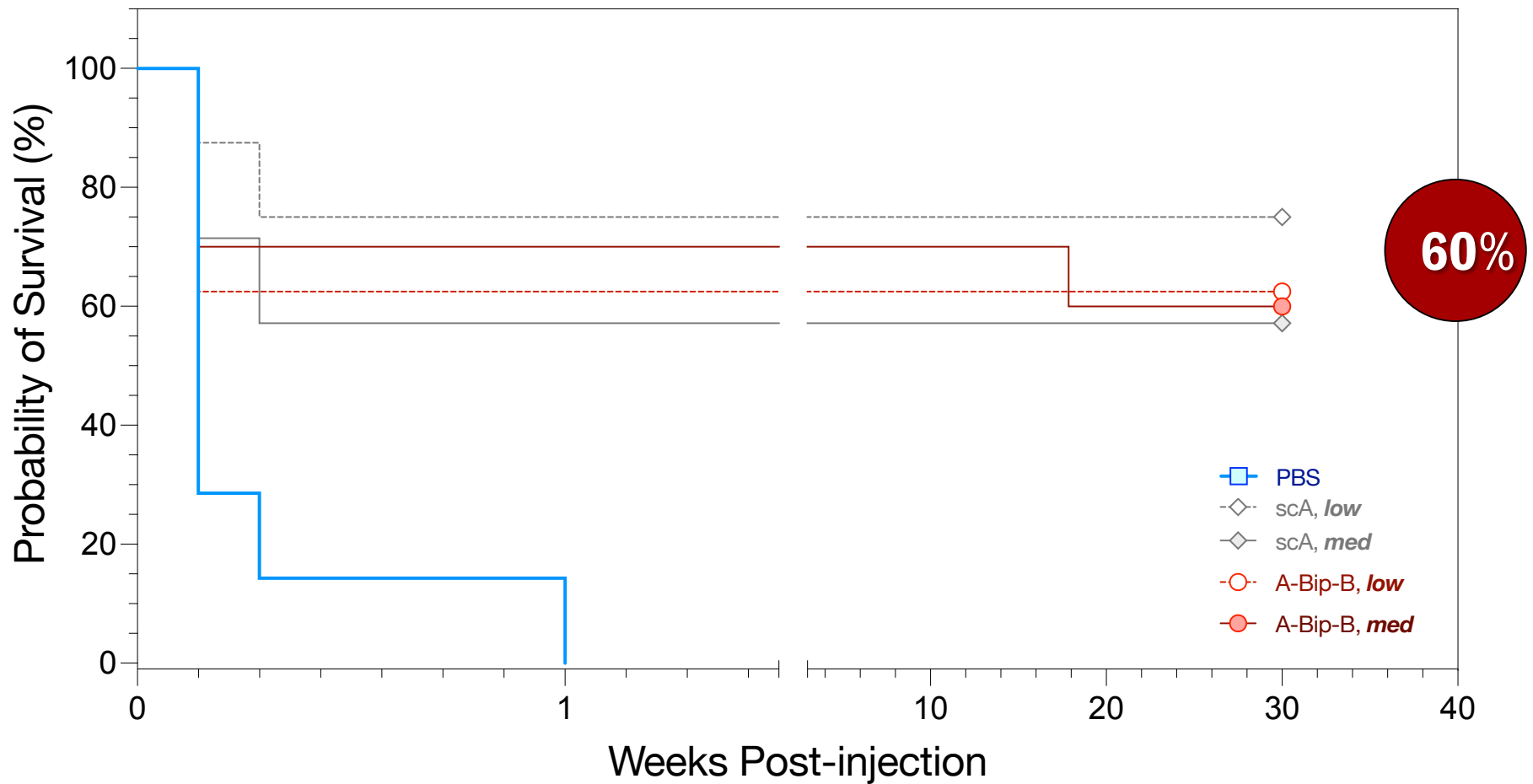
Outcomes: **Survival** & Biomarkers



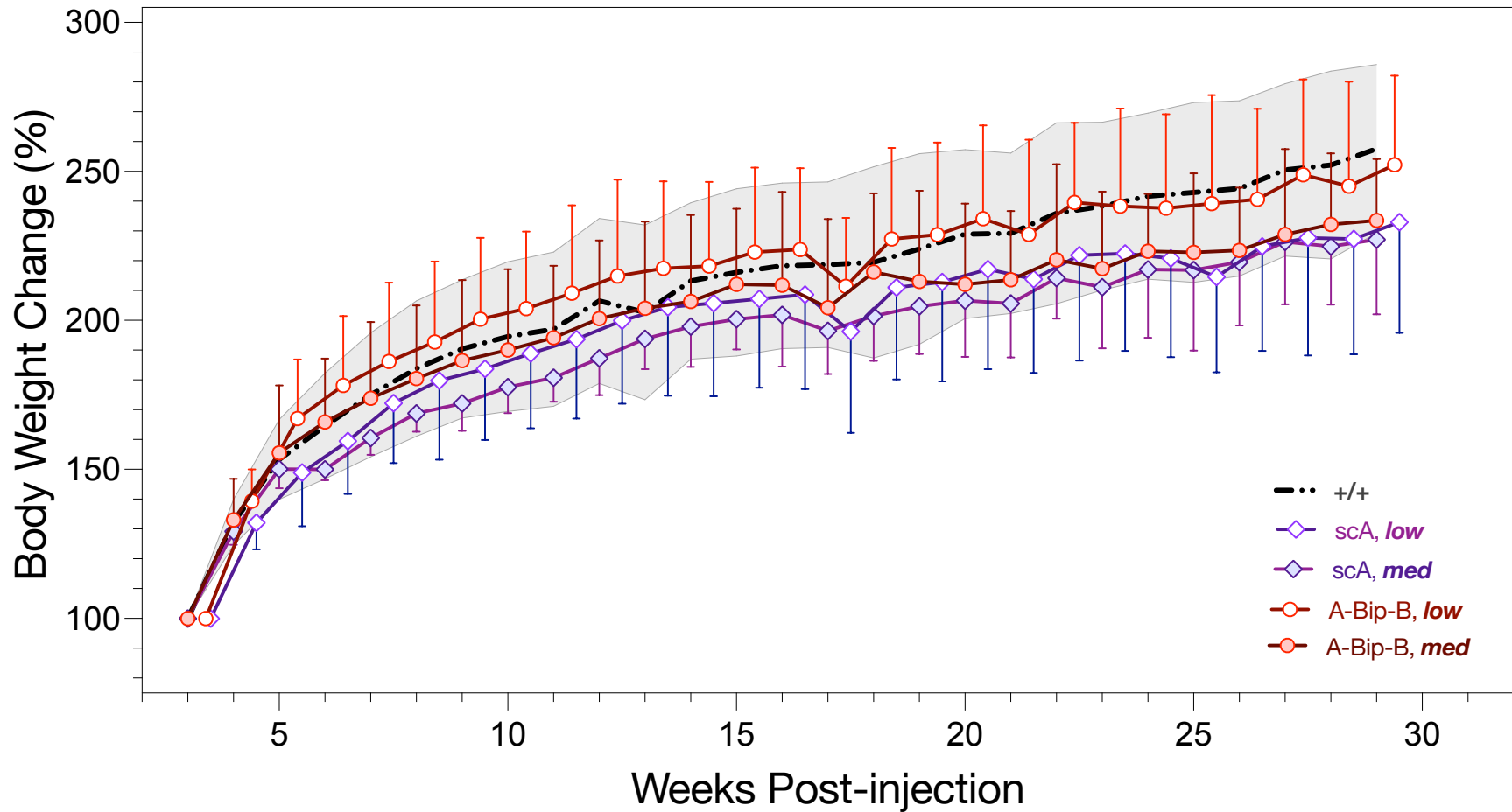
Outcomes: Survival & Biomarkers



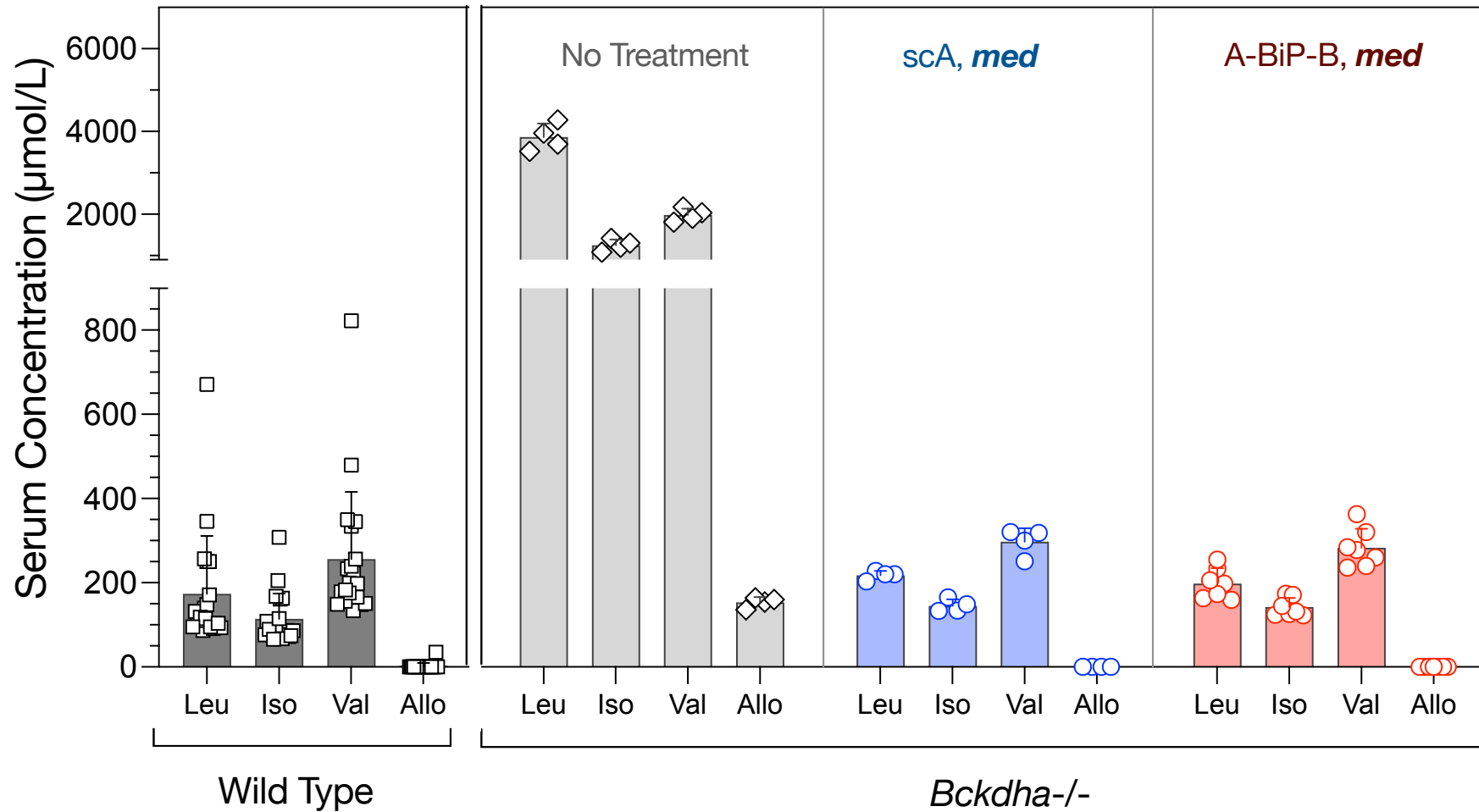
Outcomes: **Survival**, Growth, Biomarkers



Outcomes: Survival, Growth, Biomarkers

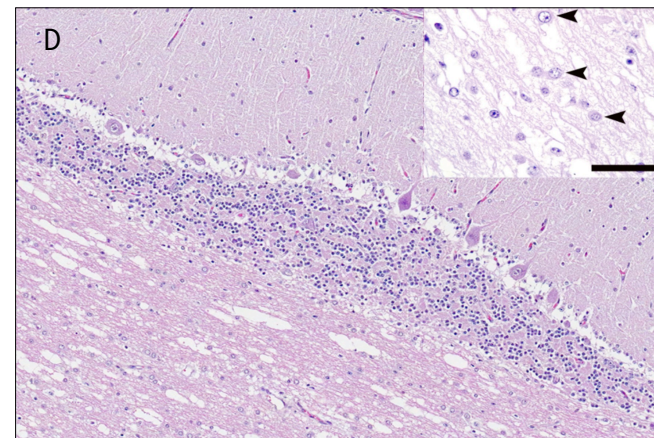
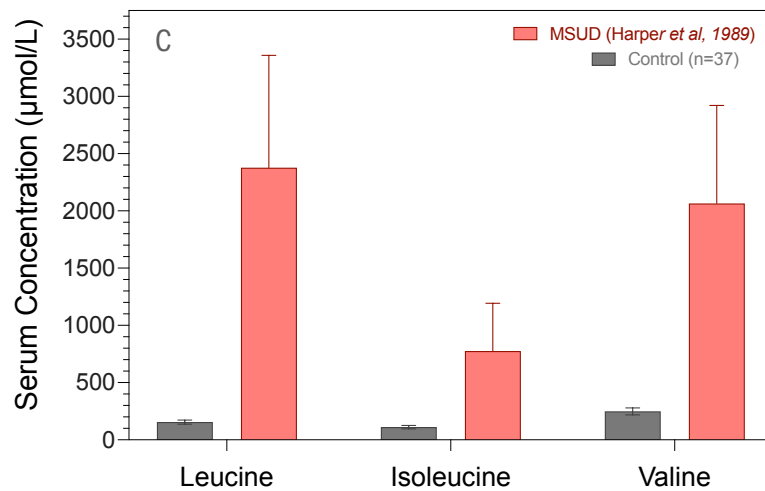
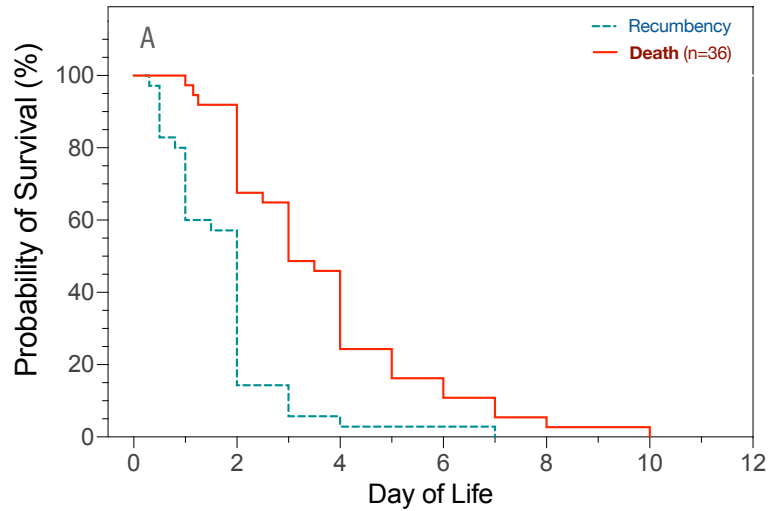


Outcomes: Survival, Growth, Biomarkers

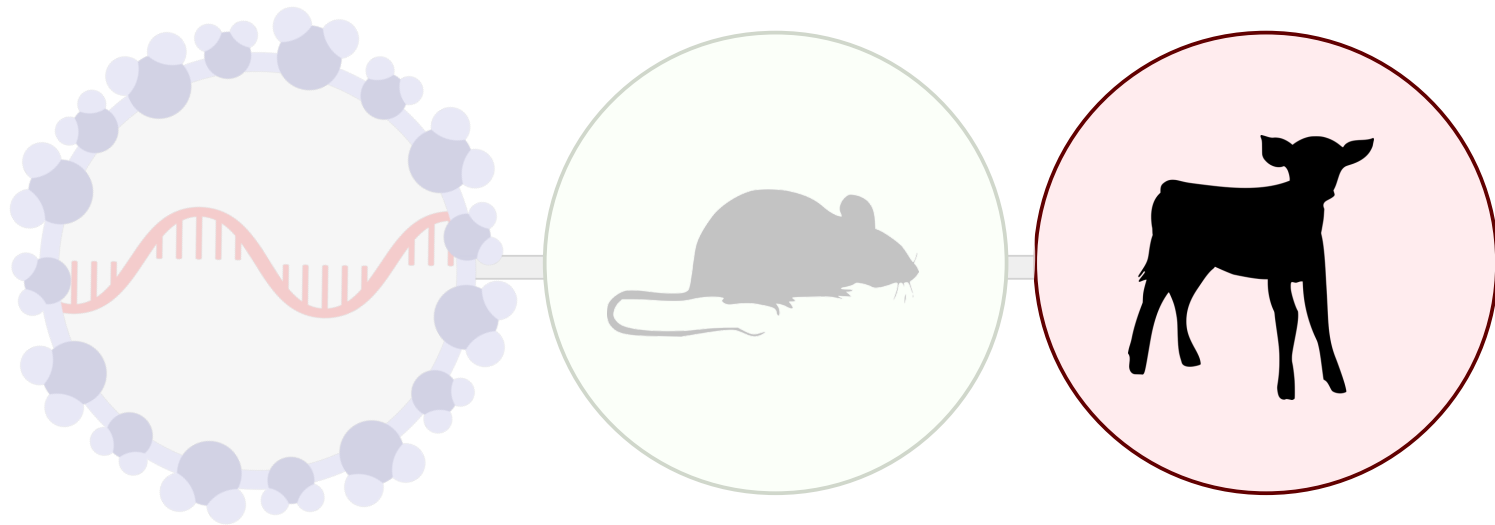


Maple syrup urine disease as a cause of lethal brain disease in calves

PAW Harper, PJ Healy, JA Dennis (*The Veterinary Record*, 1986)

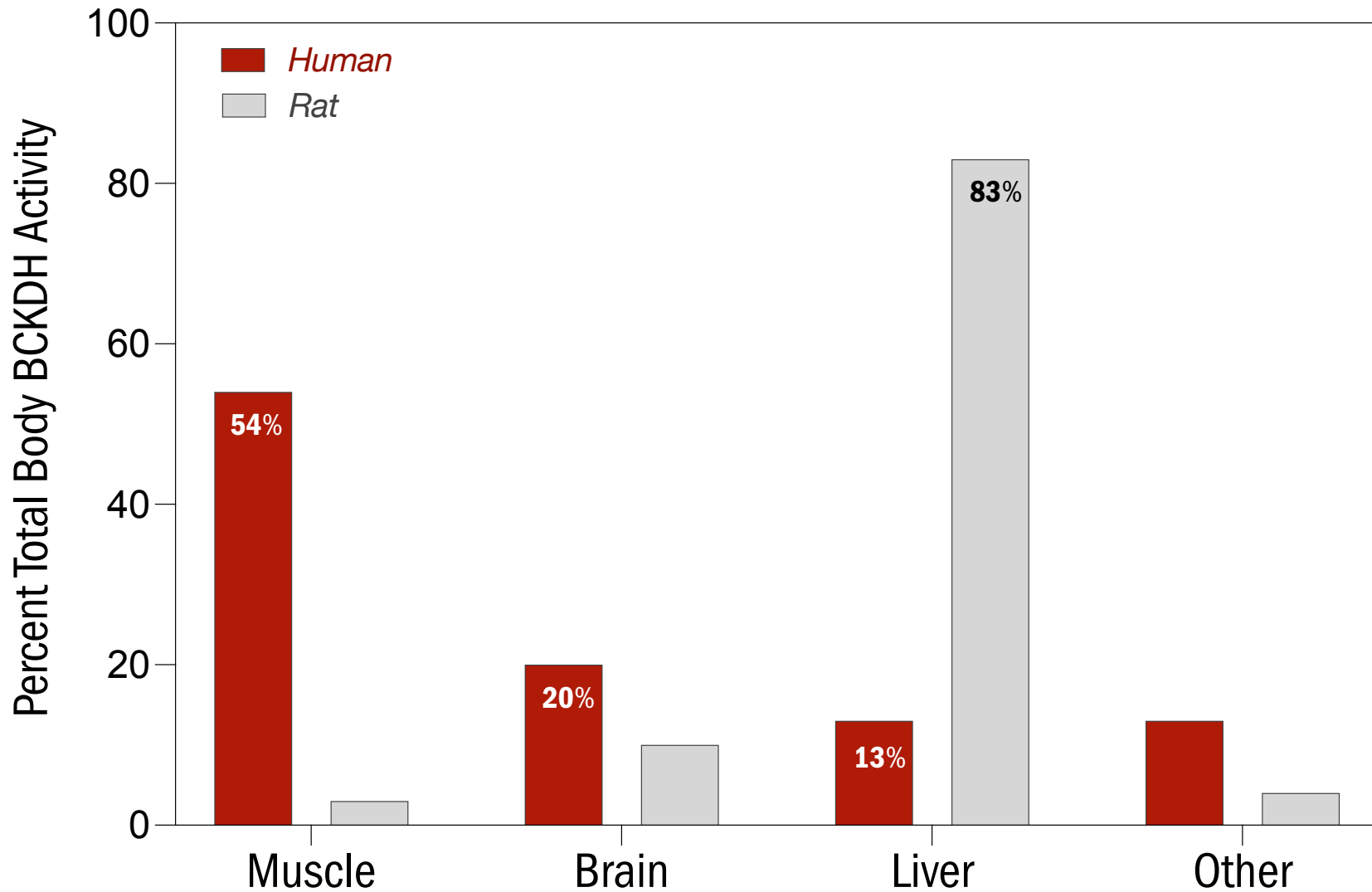


Why Gene Therapy?



Why a Cow?

BCKDH Activity: *Tissue Distribution*





“Whatever it takes, **find that cow.**”

Mariah Everett

Longview Farms, Iowa

October 2018



Don's son!

Don Hardin

Mark Martin

Dan Wang



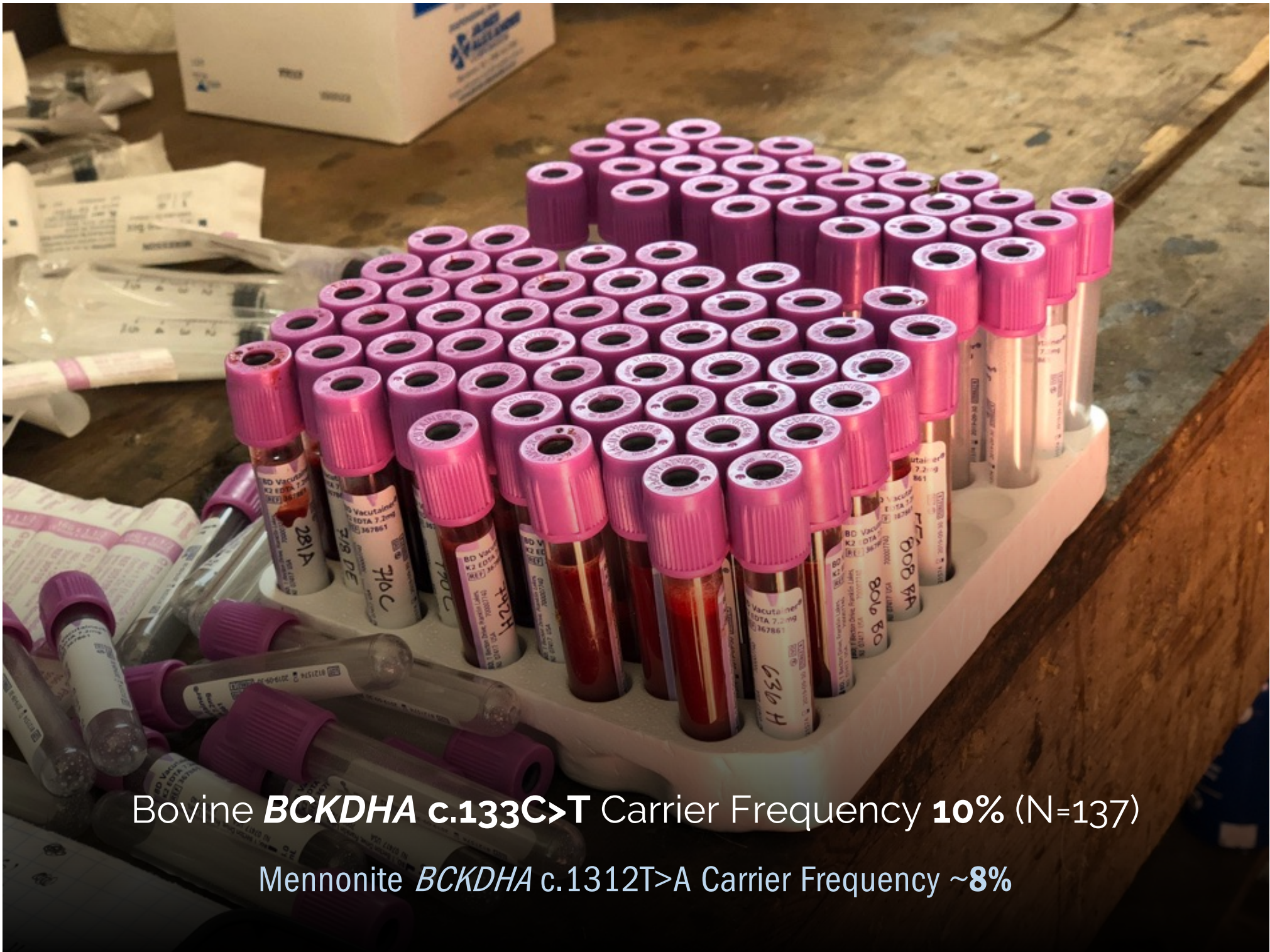
Erik Puffenberger

Jon Beaver

Lorraine Martin



Longview Farms, Iowa
October 2018



Bovine ***BCKDHA*** c.133C>T Carrier Frequency **10%** (N=137)

Menonite ***BCKDHA*** c.1312T>A Carrier Frequency **~8%**

Petunia

October 3, 2021





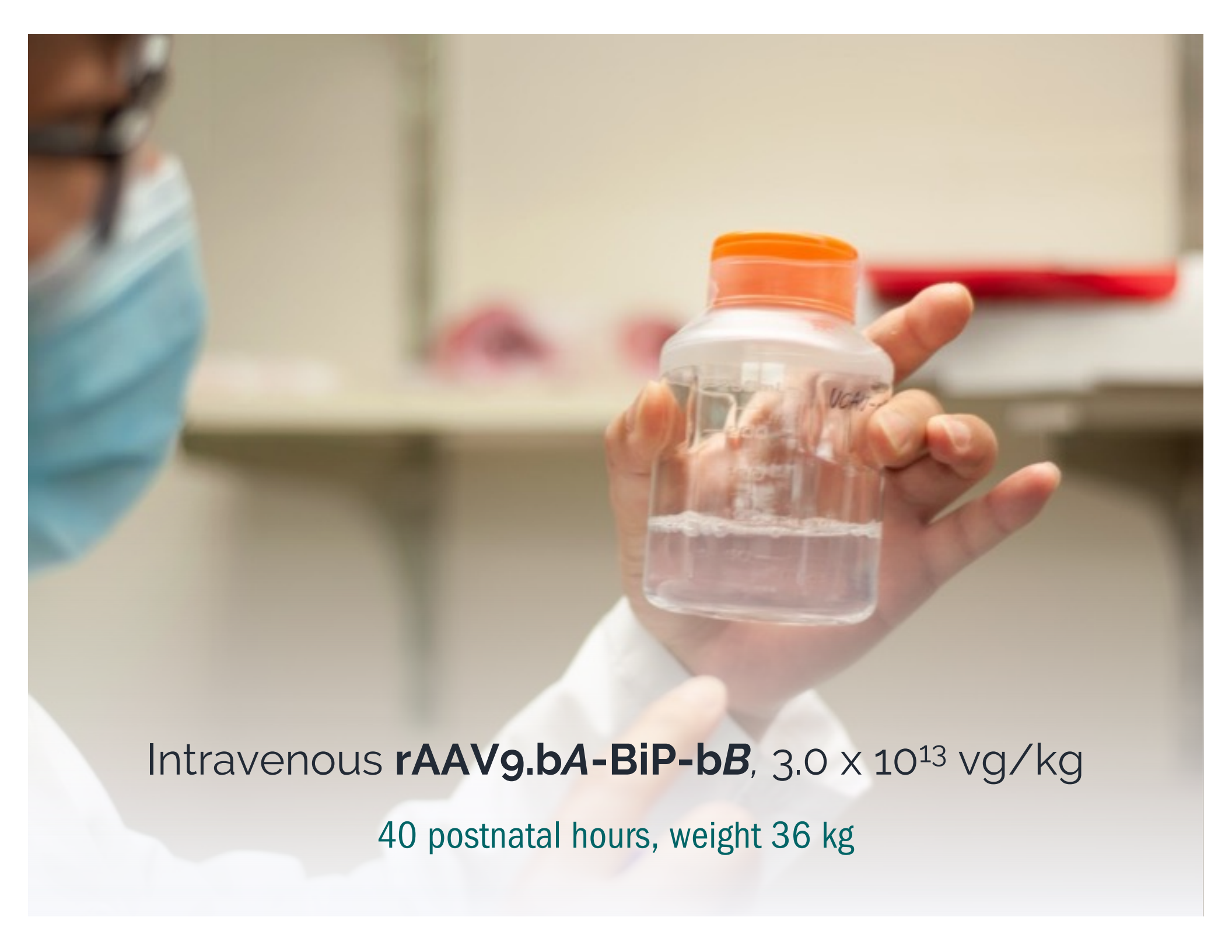
Metabolic Intoxication

Leucine **1314** $\mu\text{mol/L}$ (**10x normal**) at age **15 hours**



Metabolic Intoxication

Leucine **1314** $\mu\text{mol/L}$ (**10x normal**) at age **15 hours**

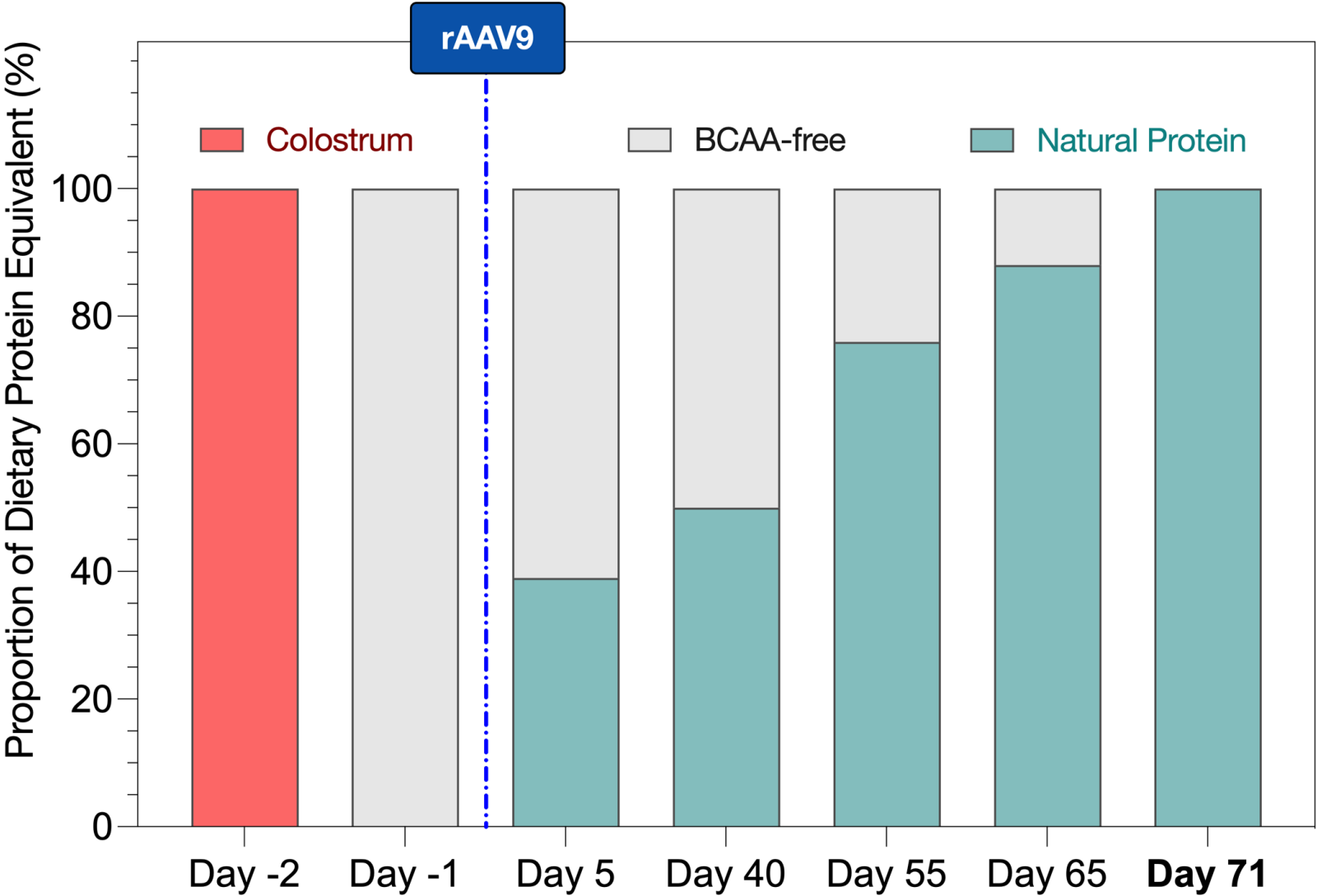


Intravenous **rAAV9.bA-BiP-bB**, 3.0×10^{13} vg/kg

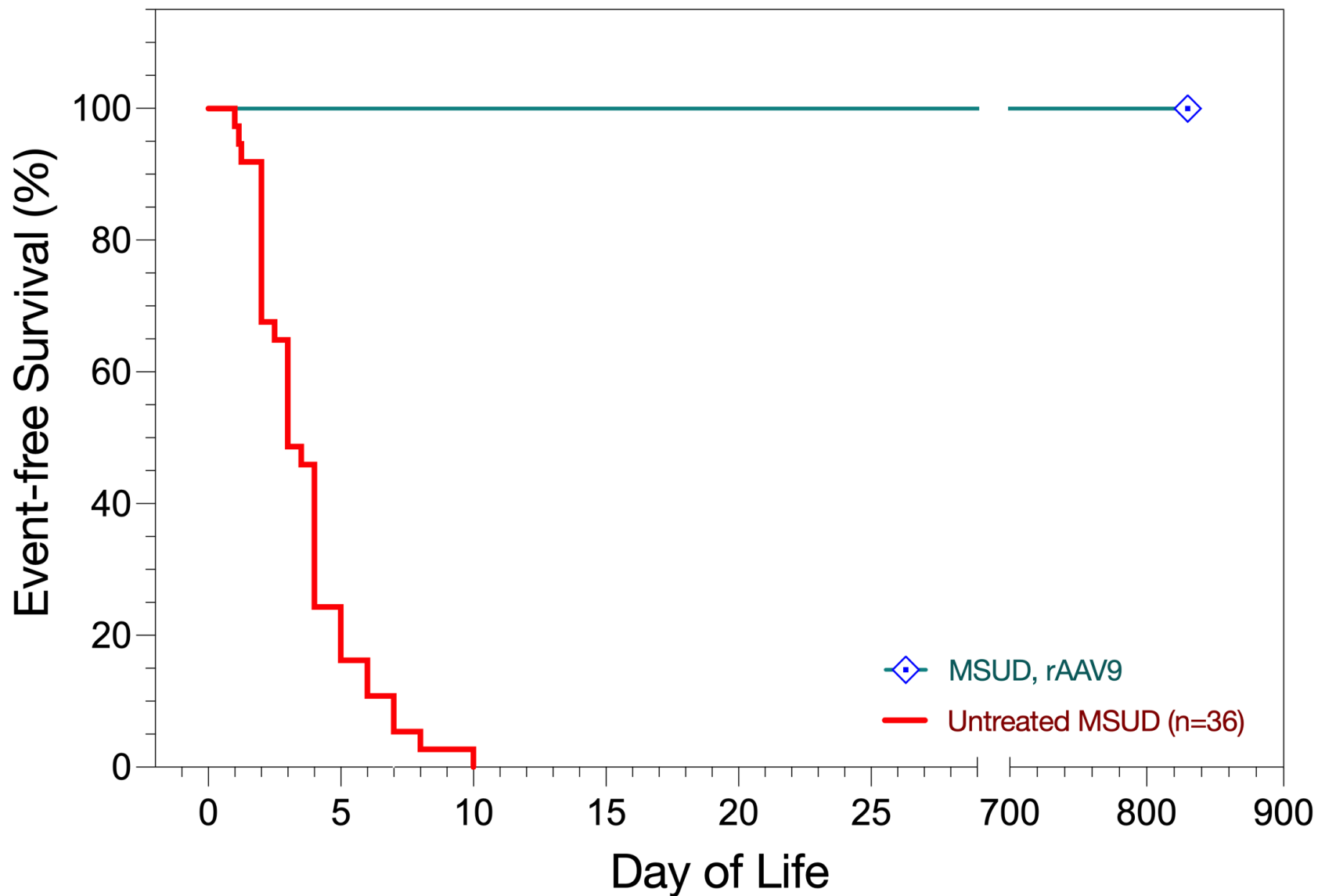
40 postnatal hours, weight 36 kg



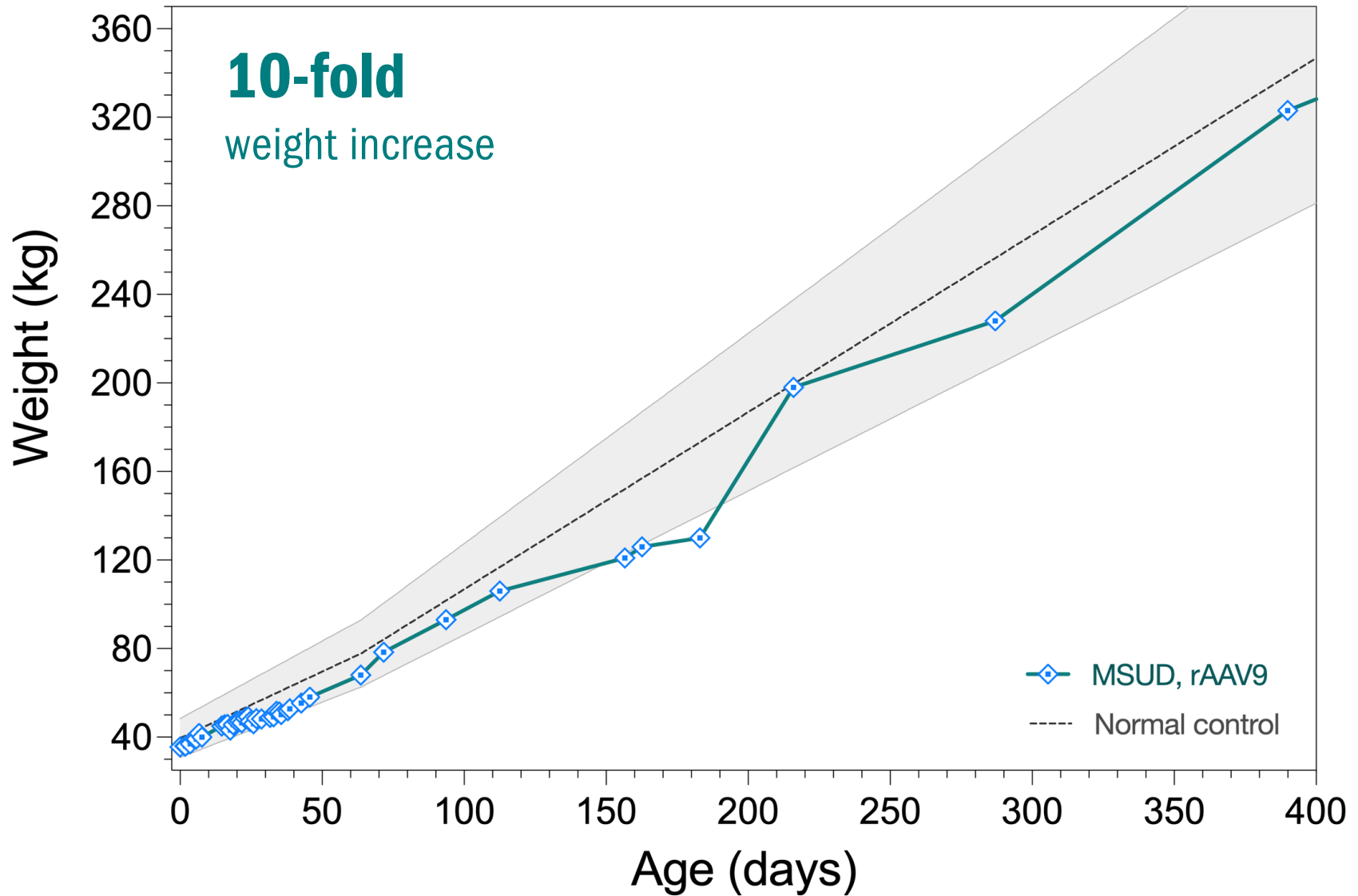
Transition to natural, **unrestricted diet**



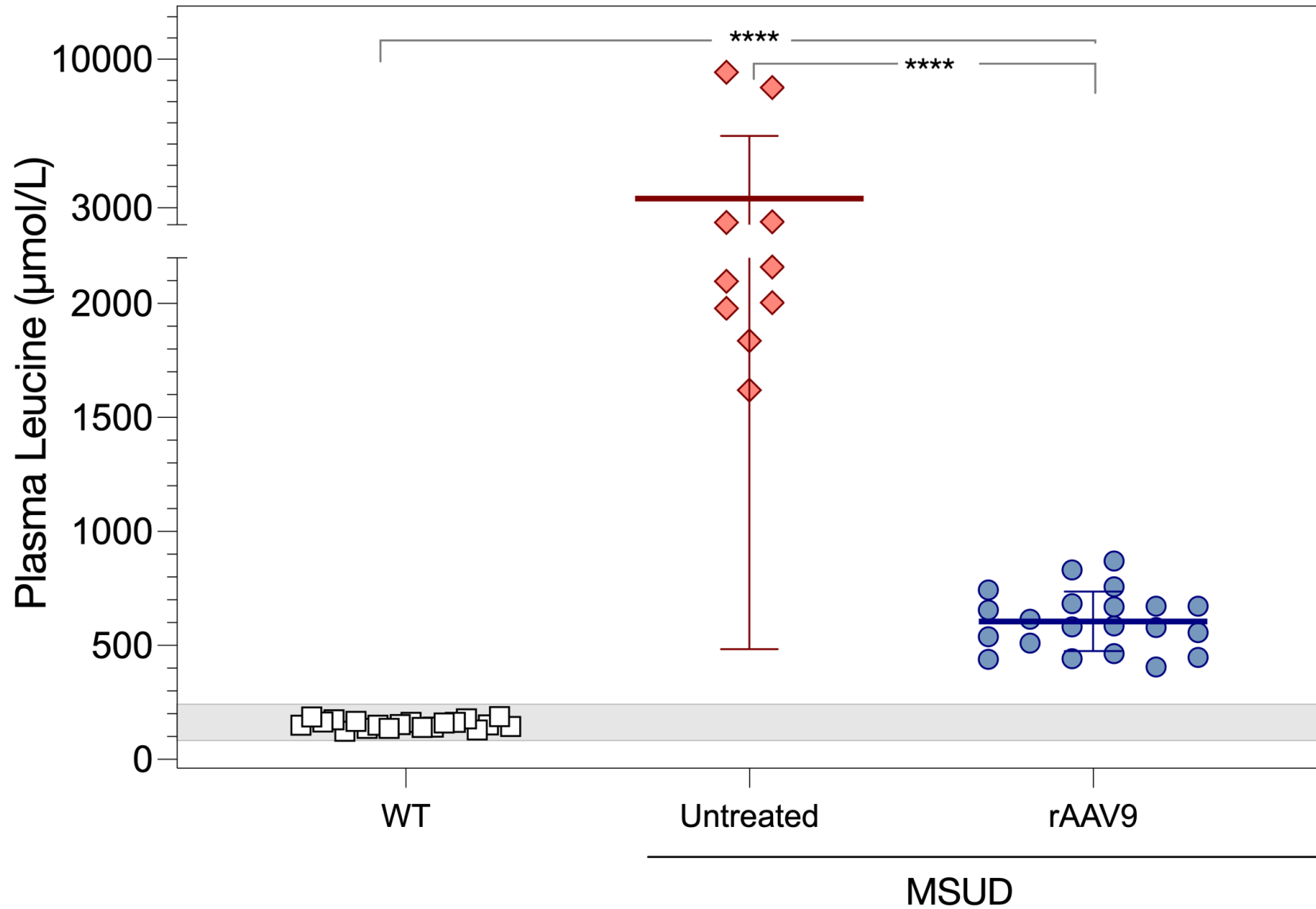
Alive and well nearly three years later



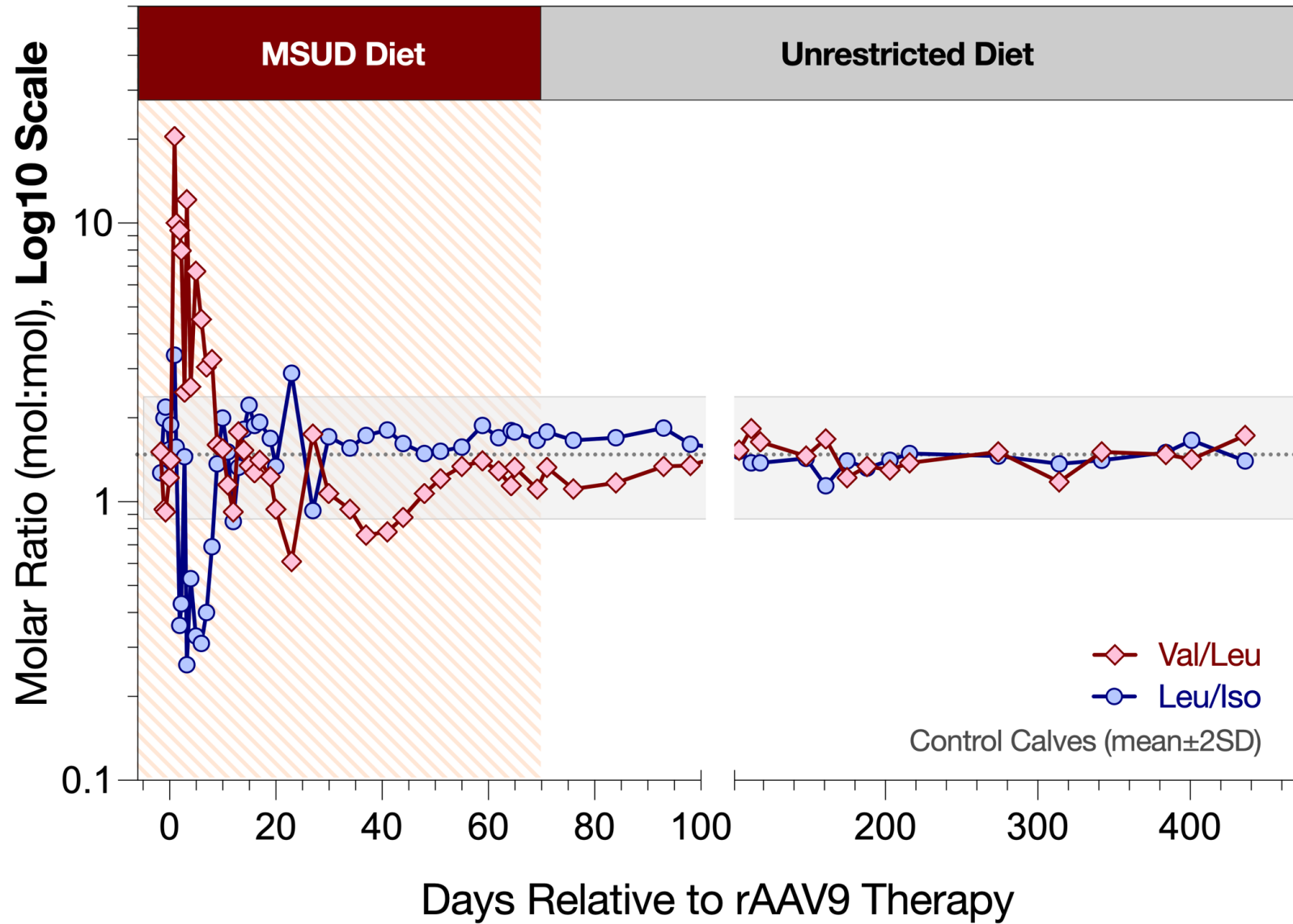
Normal **growth** and behavior



Stable (*but not normal*) biomarkers

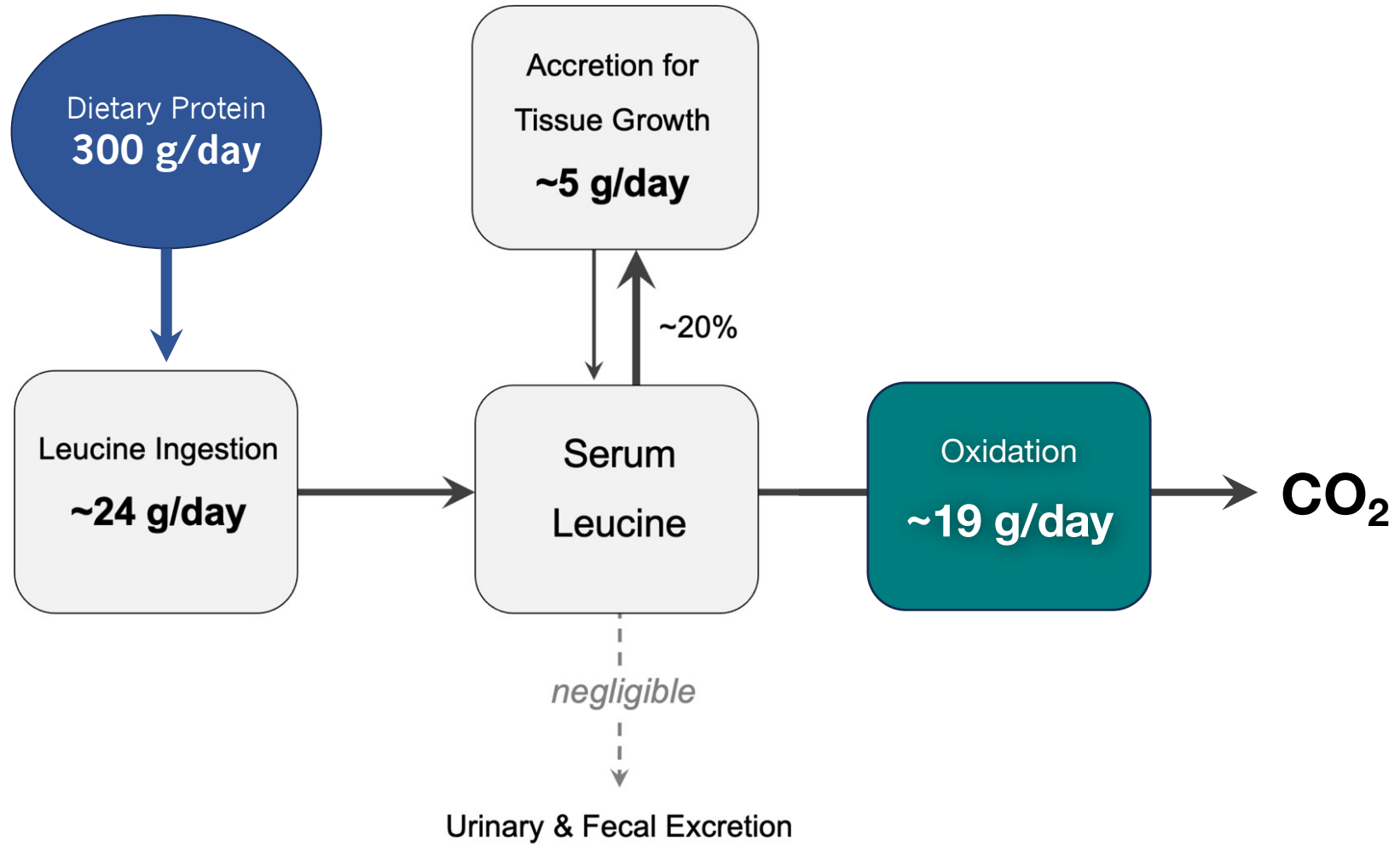


Restored enzymatic regulation

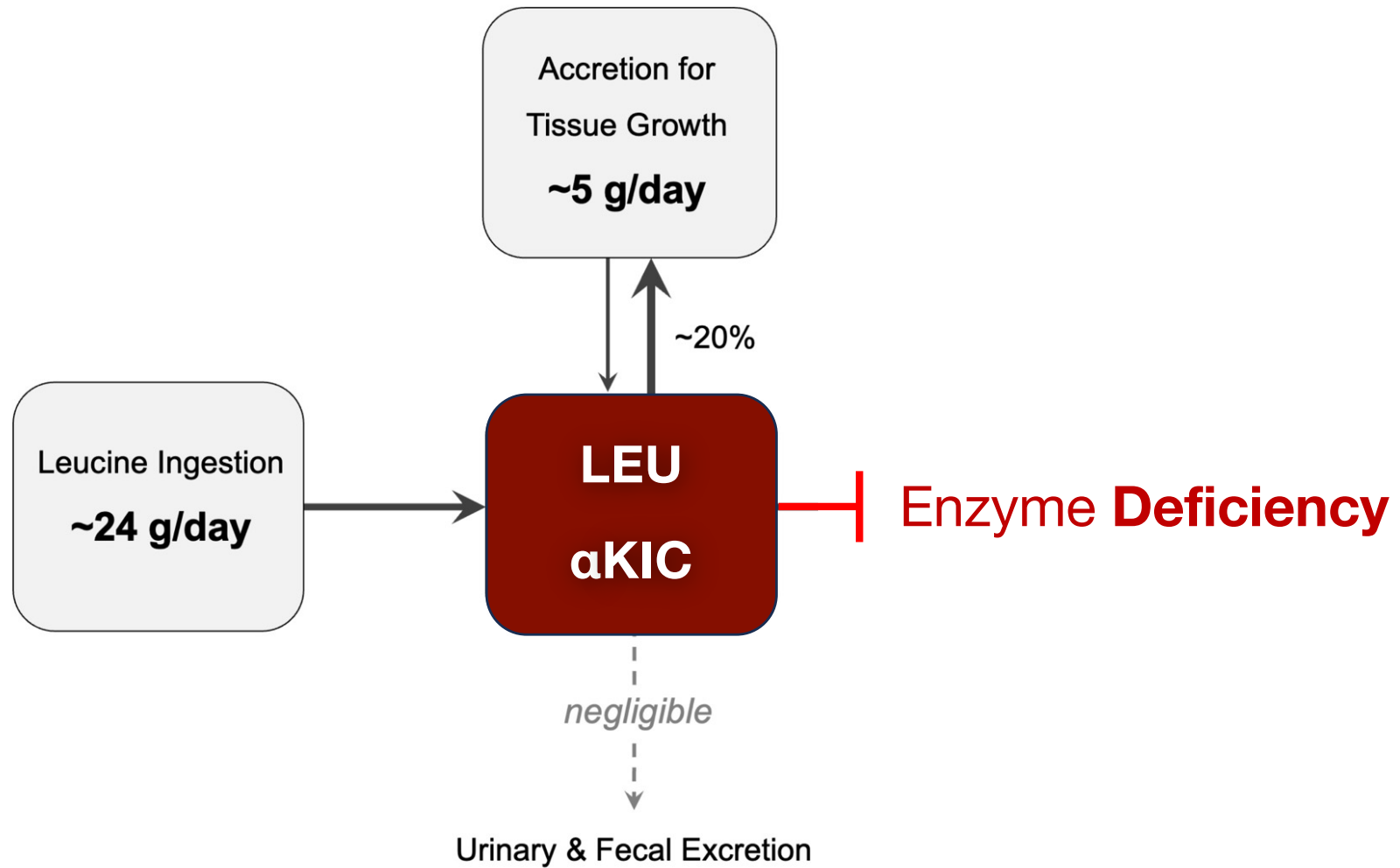




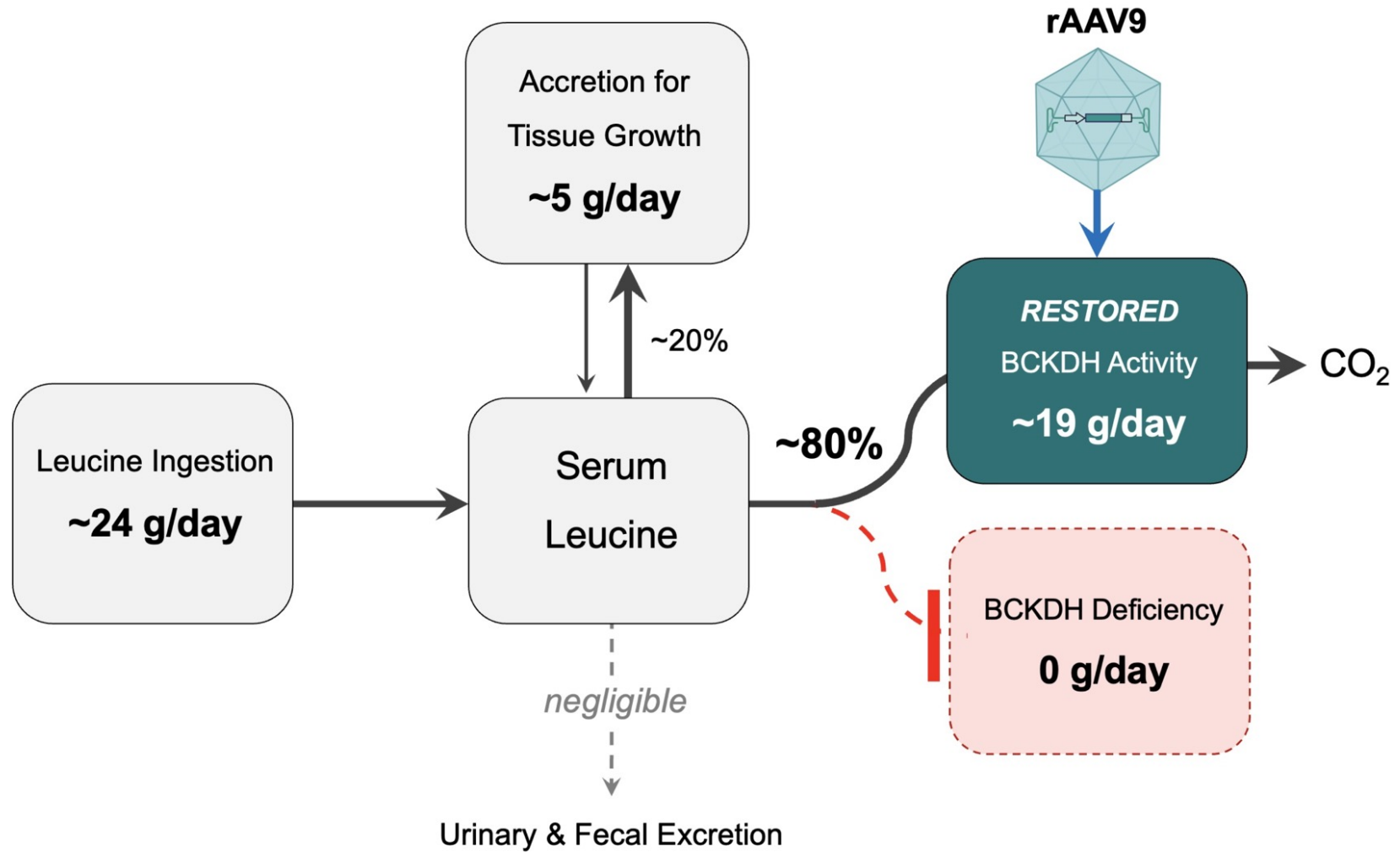
Normal



MSUD: Leucinosi

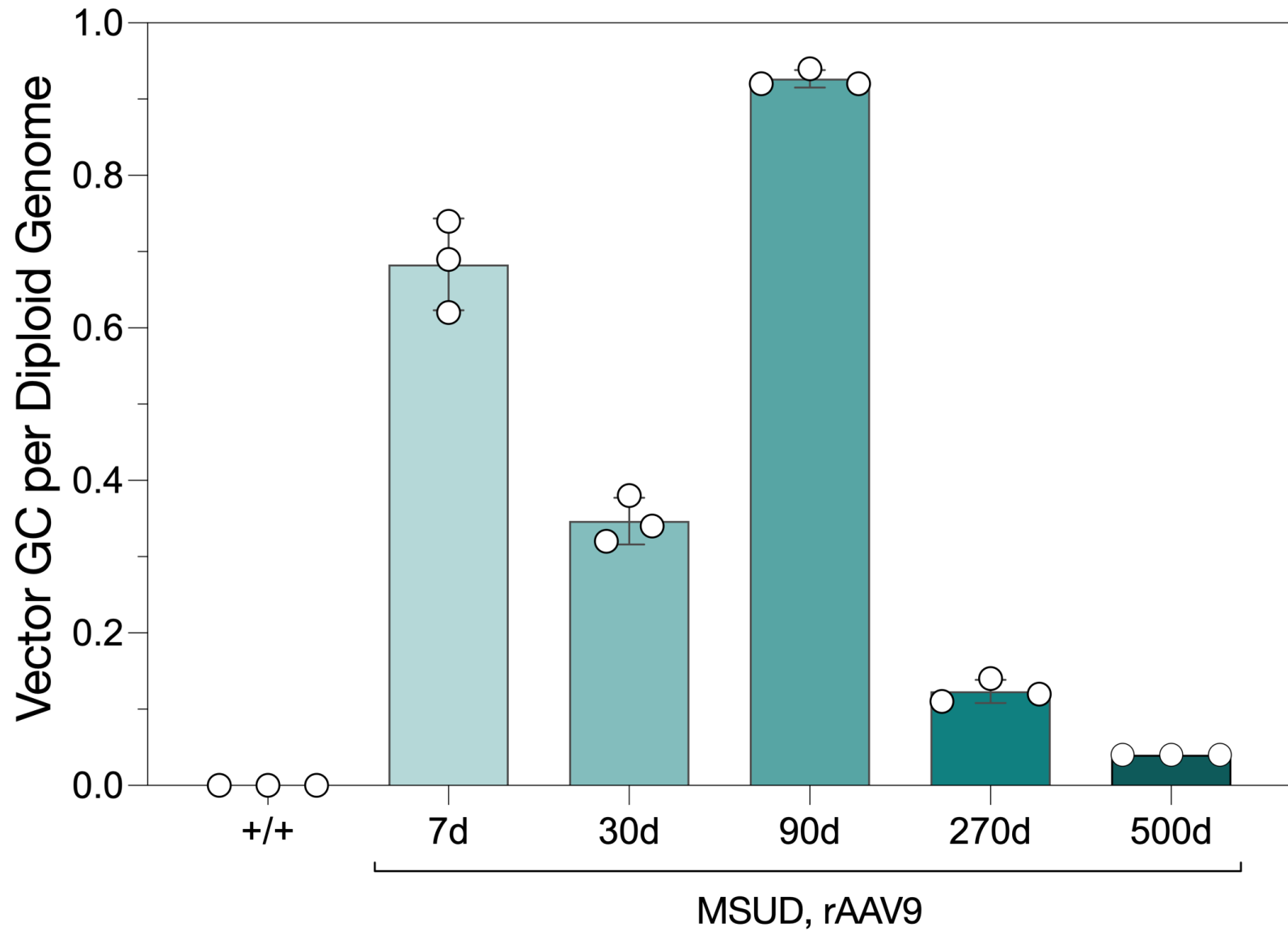


MSUD: Gene Therapy

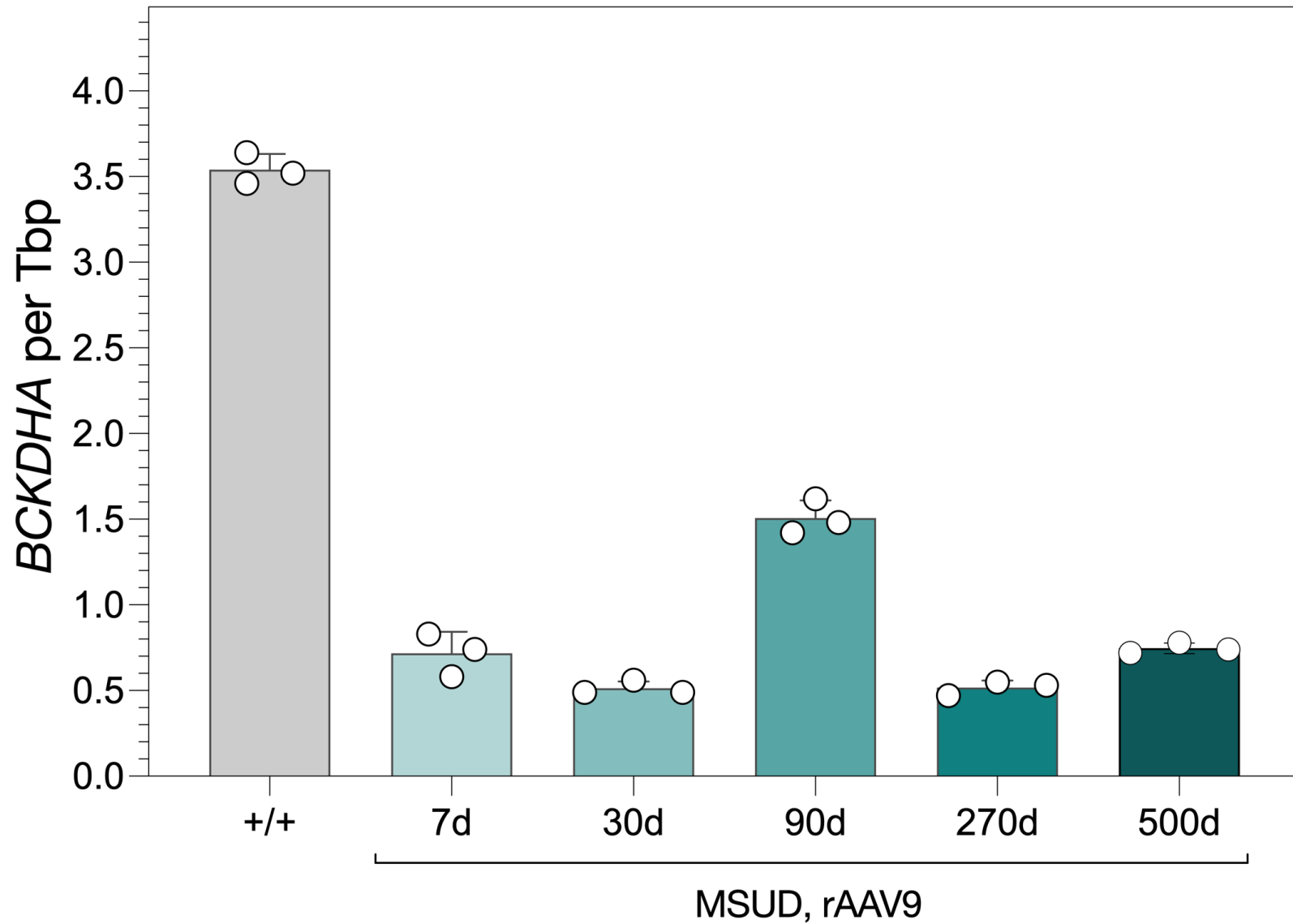


Limitations & Challenges

Vector Genomes in Muscle



BCKDHA mRNA in Muscle





And, as you travel life's highway, don't forget to stop and eat the roses.



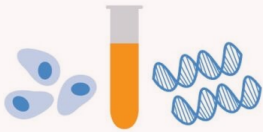
Gene Therapy by the Numbers (2024)

30
MILLION
U.S. PATIENTS
with 7,000 known rare/ultra-rare diseases



85% 
of rare/ultra-rare diseases are monogenic

\$2
BILLION
to bring a new cell or gene therapy to market




33 
FDA-approved cell and gene therapies

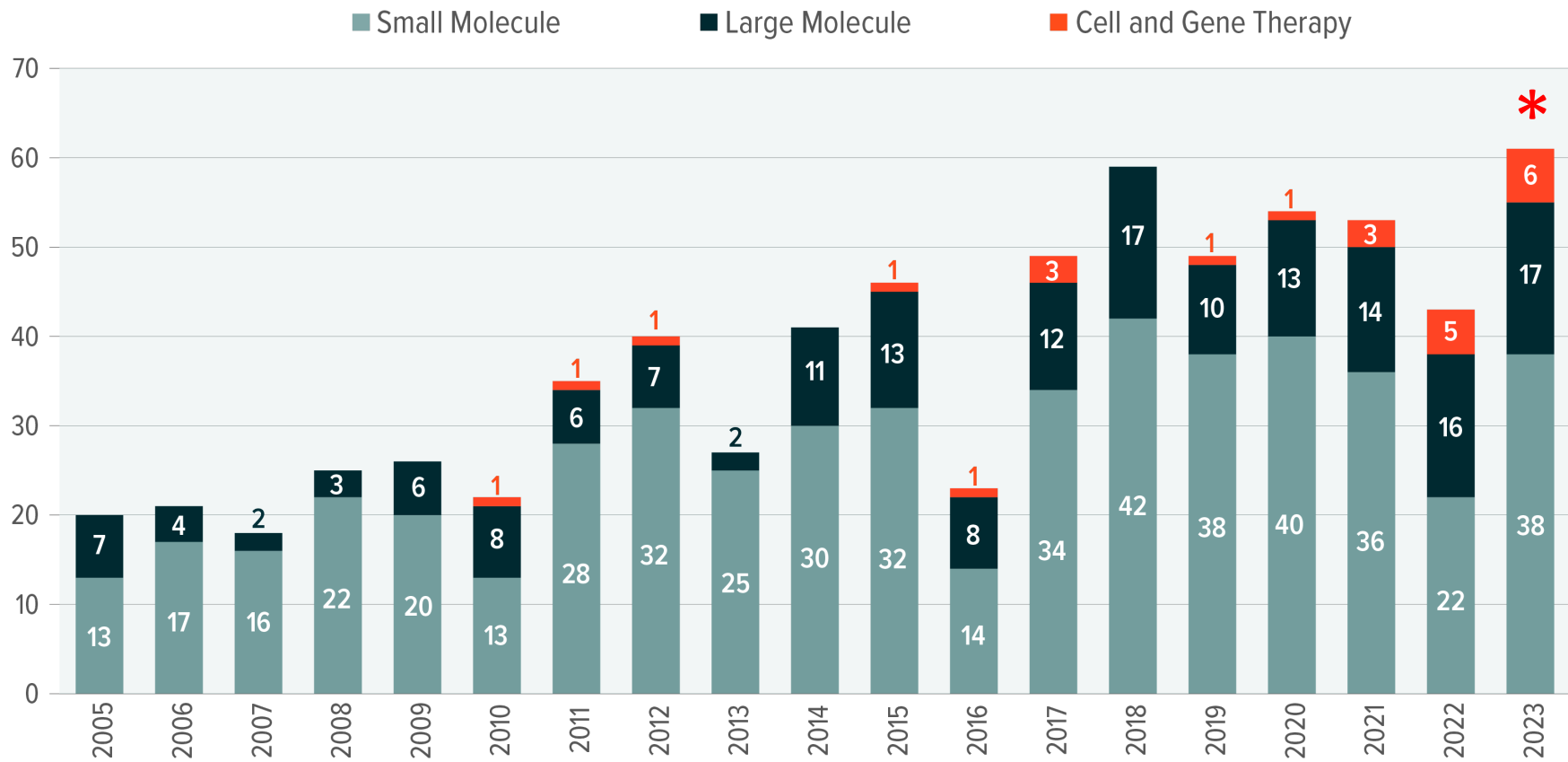
10-20 / year
expected cell and gene therapy product approvals by **2025**

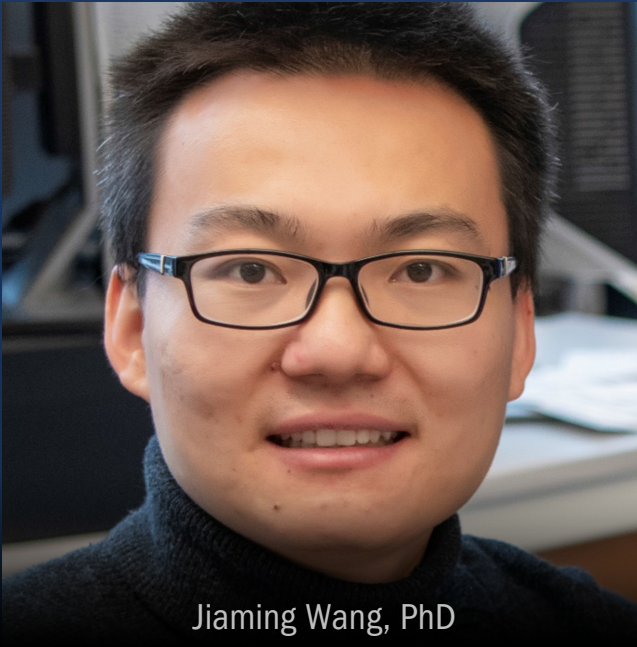


\$20.4
BILLION
projected average annual spending on gene therapies, 2023-2024



FDA Approvals by Class (2024)





Jiaming Wang, PhD



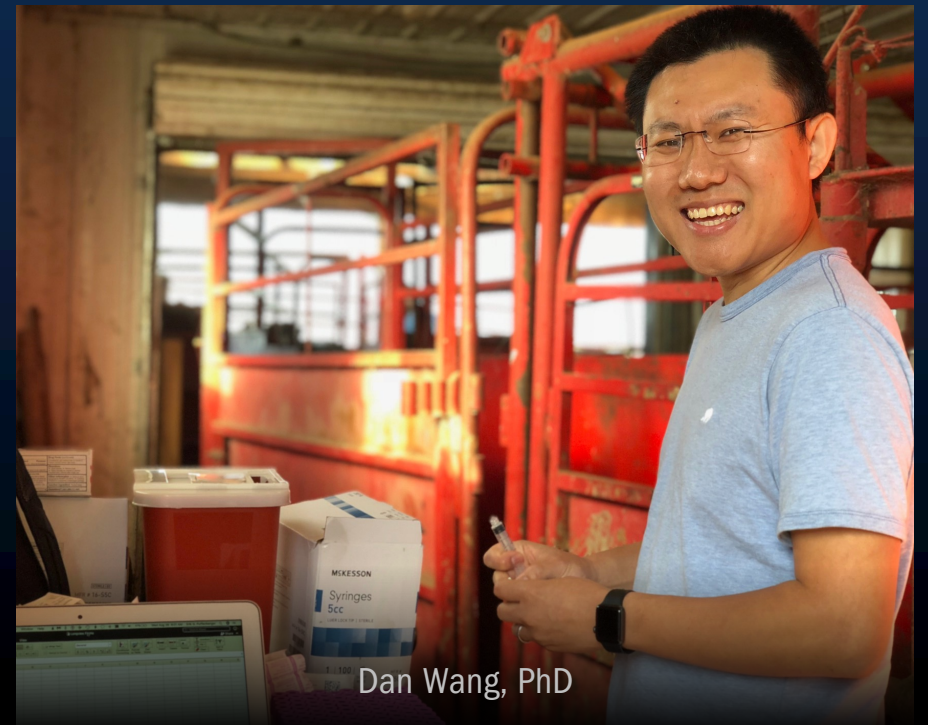
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Heather Gray-Edwards, DVM PhD



Guangping Gao, PhD



Dan Wang, PhD

Few burdens are heavy if everyone lifts."

Amish Proverb

