FAOD Updates

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Disclosures

Research funding

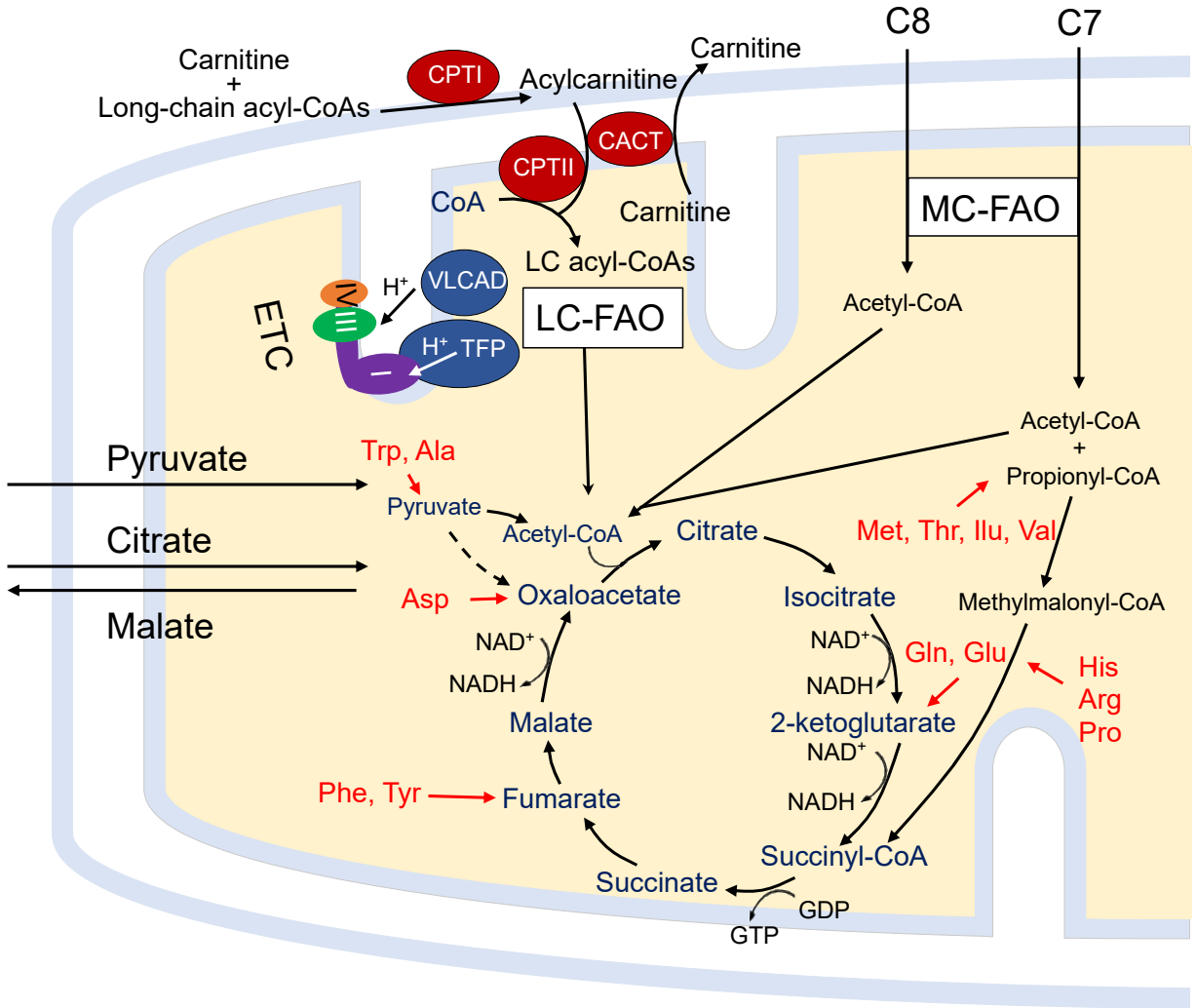
- NIH
- Ultragenyx
- Biomarin
- Takeda
- Acadia
- Alexion
- Reynolds family
- Wilson family
- Burch family

- CHP Foundation
- Moderna
- Stealth
- PTC Therapeutics
- Synlogic
- jnana
- Nestle
- Sanofi
- Amicus

Consulting

- BioMarin
- BioLogic
- Synlogic
- JNANA
- Sanofi
- Axcella Health
- Homology
- Agios
- Applied Therapeutics

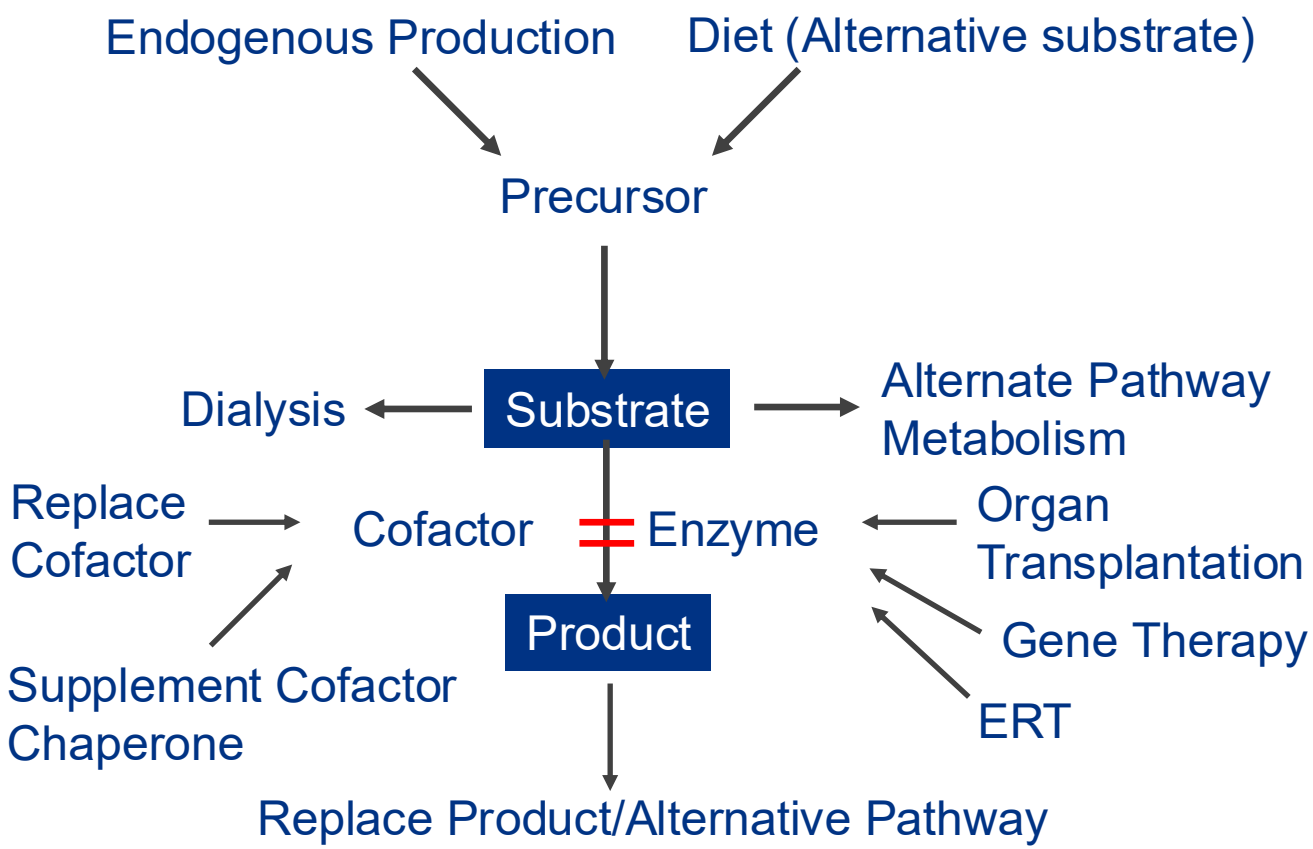
VLCAD and energy metabolism interactions



- FAO and ETC functionally and physically interact
- VLCADD major clinical events (MCEs)
  - Hypoglycemia +/- hyperammonemia
  - Recurrent rhabdomyolysis
  - Cardiomyopathy

Options for therapy

- Replace/substitute/stabilize enzyme
- Replace product
- Reduce substrate
- Remove toxin
- Supplement cofactor
- Activate alternative pathways for metabolism
- Provide alternative substrates



FAOD development update

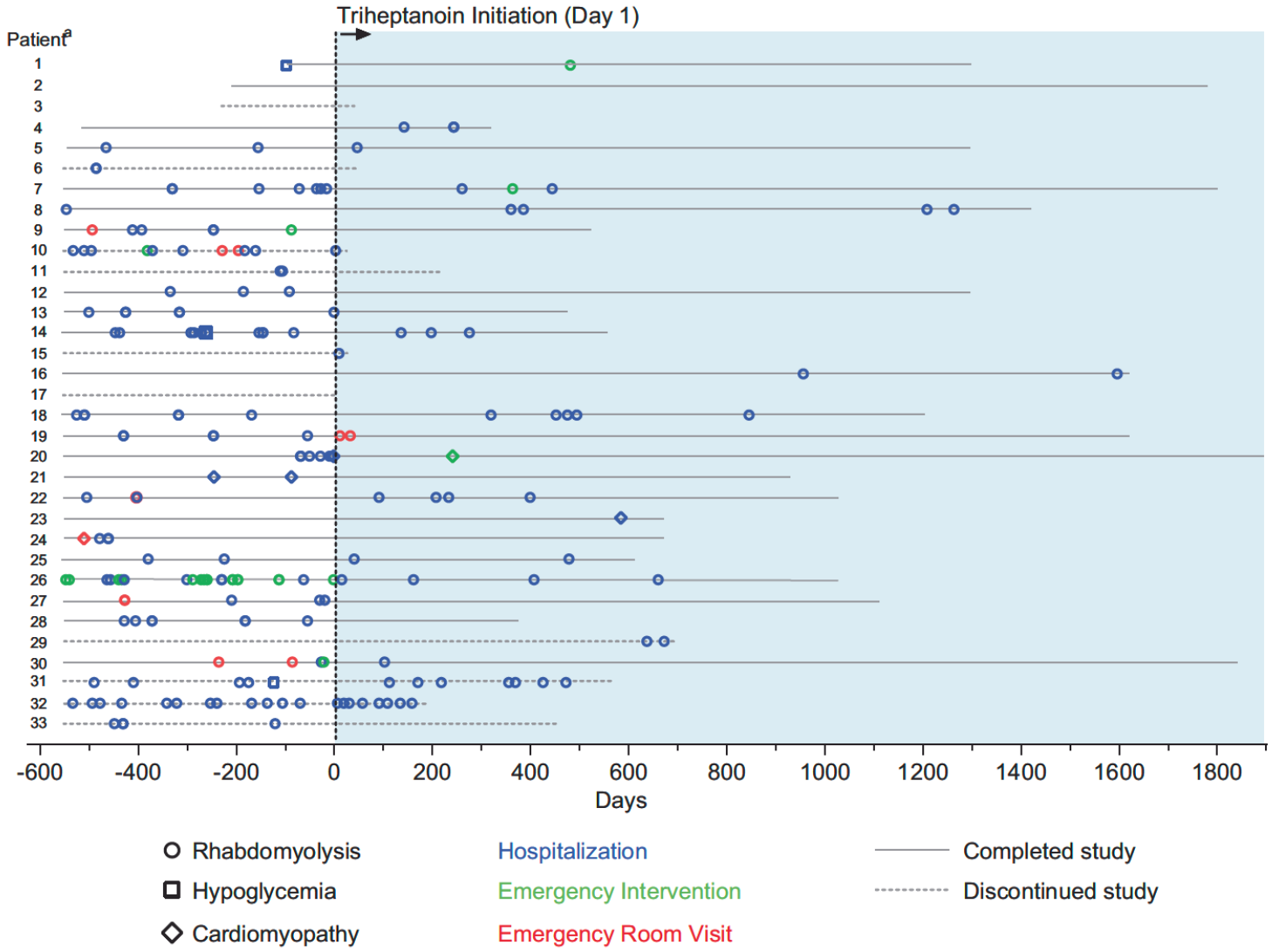
- Long chain FAODs
  - Nucleic acid therapy
    - Gene therapy VLCAD
    - mRNA therapy VLCAD
  - Alternative anaplerotic therapy
  - Mitochondrial targeted antioxidants
  - Cardiolipin binding peptide
  - PPARδ agonists
  - Endogenous chaperone therapy
  - 3-Hydroxybutyrate
- MCAD deficiency
  - Phenylbutyrate chaperone therapy
  - Alternative substrate
  - mRNA therapy

CPK Meter!

First in class

- Approved in USA in 2020
- Long term F/U still in progress
- Active clinical trials in EU

MCEs


Triheptanoin Initiation (Day 1)
Patient[a]
1
2
3
4
5
6
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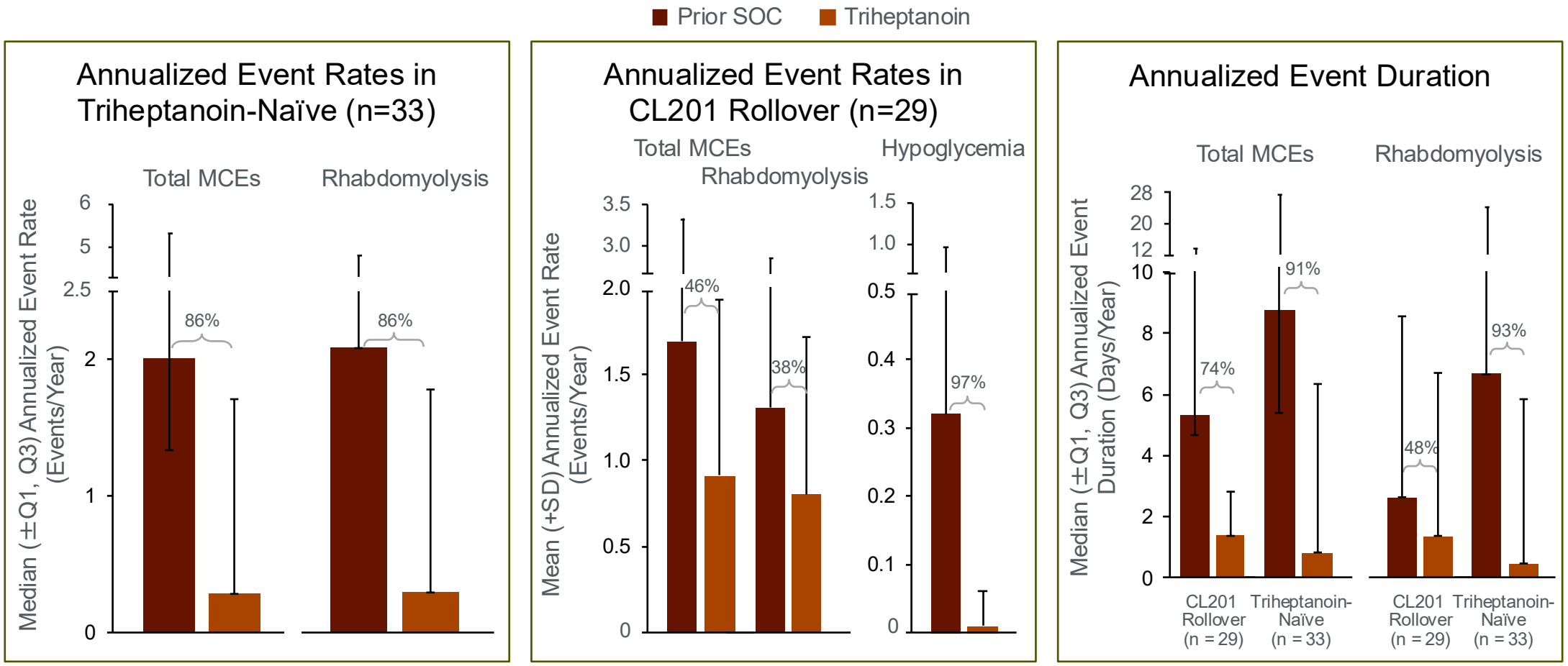
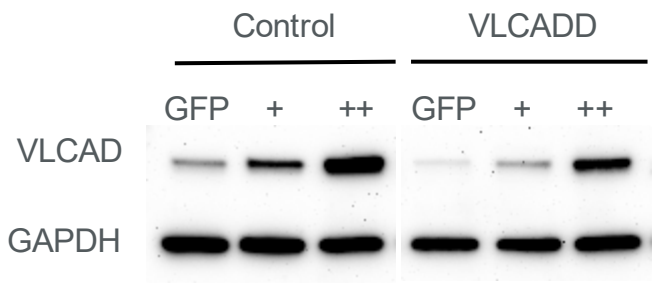
13
14
15
16
17
18
19
20
21
22
23
24
25
26
27
28
29
30
31
32
33
-600
-400
-200
0
200
400
600
800
1000
1200
1400
1600
1800
Days
Rhabdomyolysis
Hypoglycemia
Cardiomyopathy
Hospitalization
Emergency Intervention
Emergency Room Visit
Completed study
Discontinued study

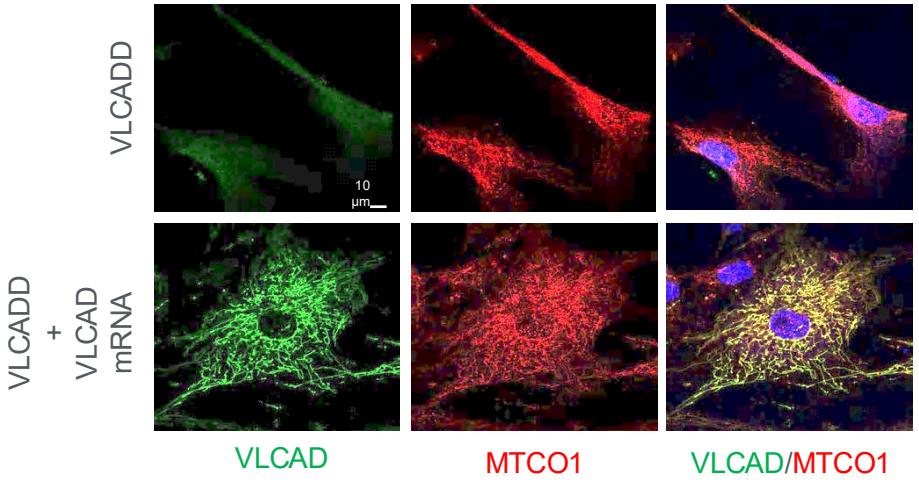
Reduction in major clinical events



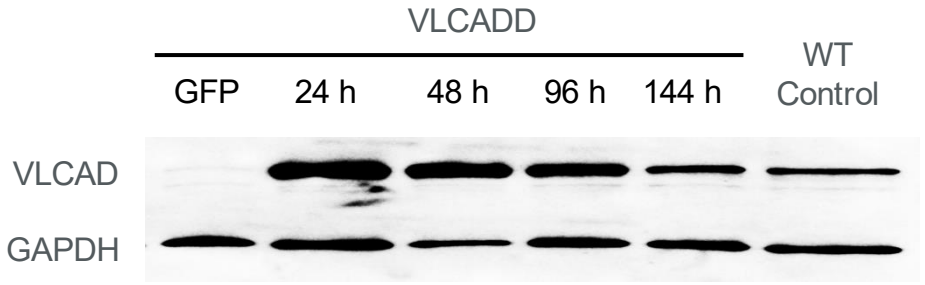
VLCAD mRNA therapy

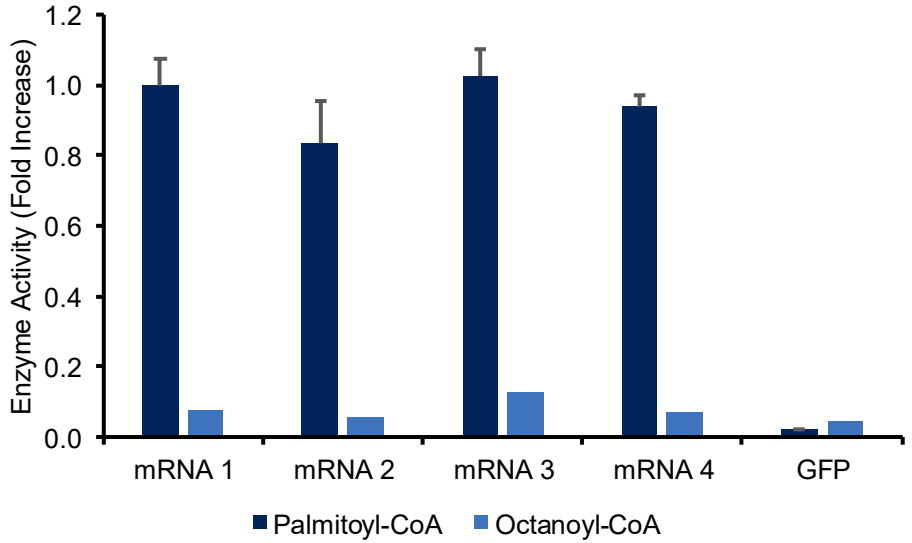
Patient fibroblasts





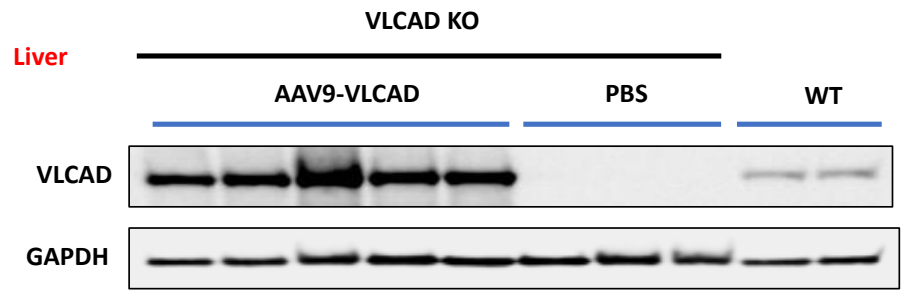
VLCAD KO Liver

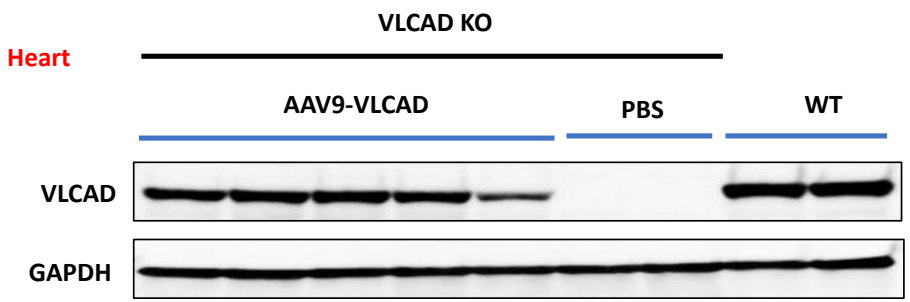


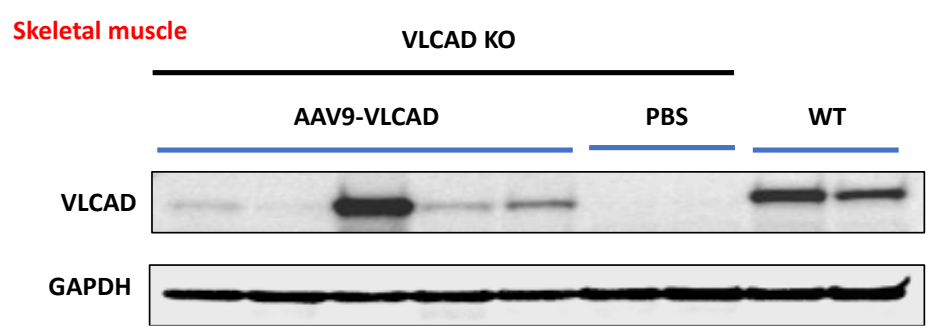


AAV-VLCAD KO gene therapy

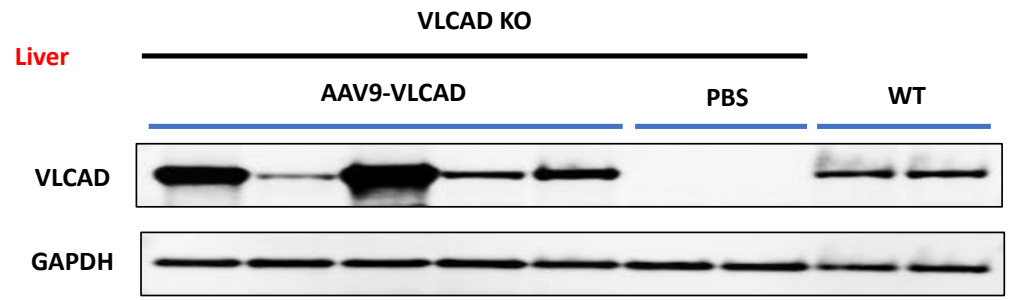
Male mice

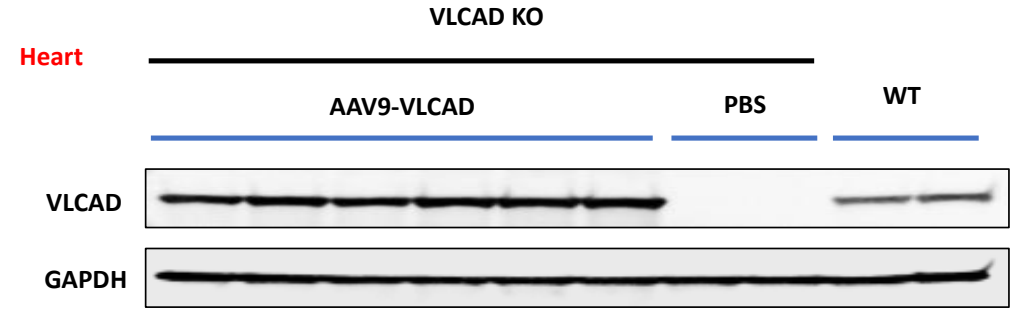


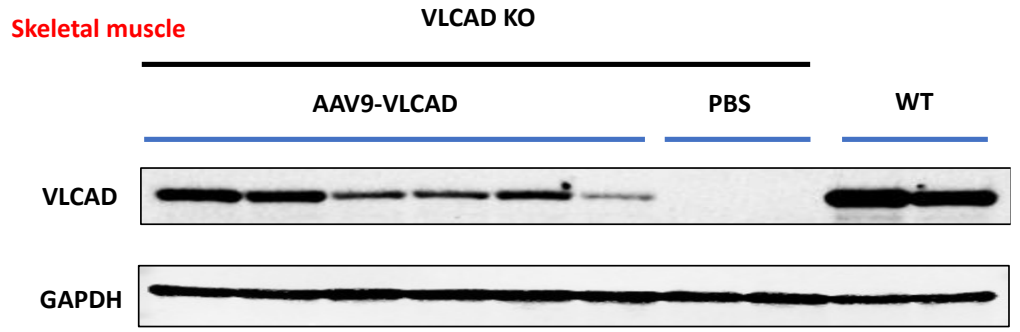




Female mice





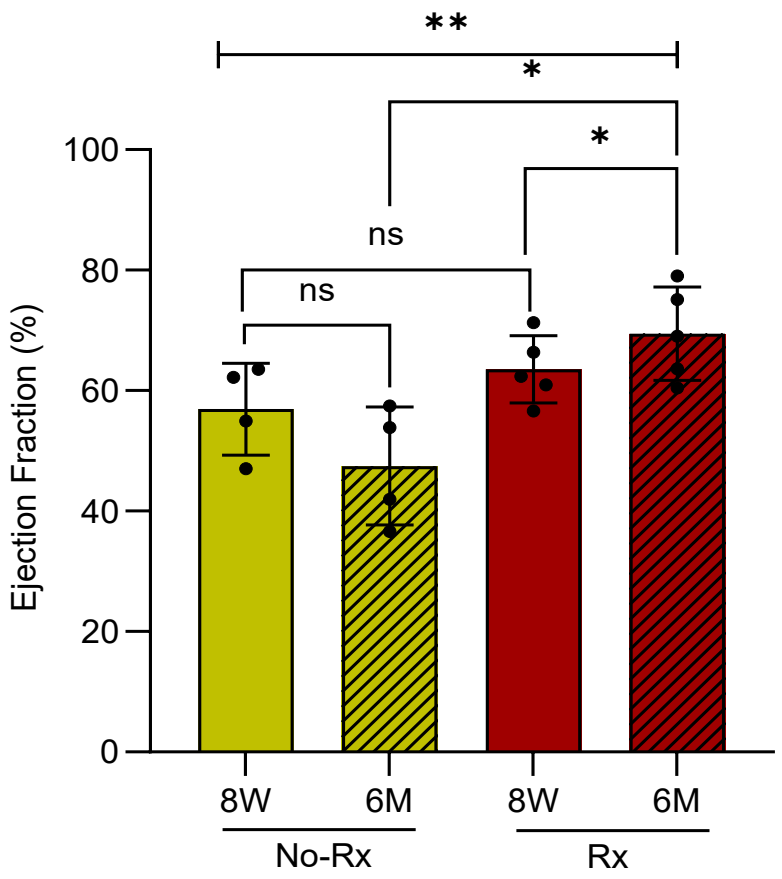


Mouse model summary

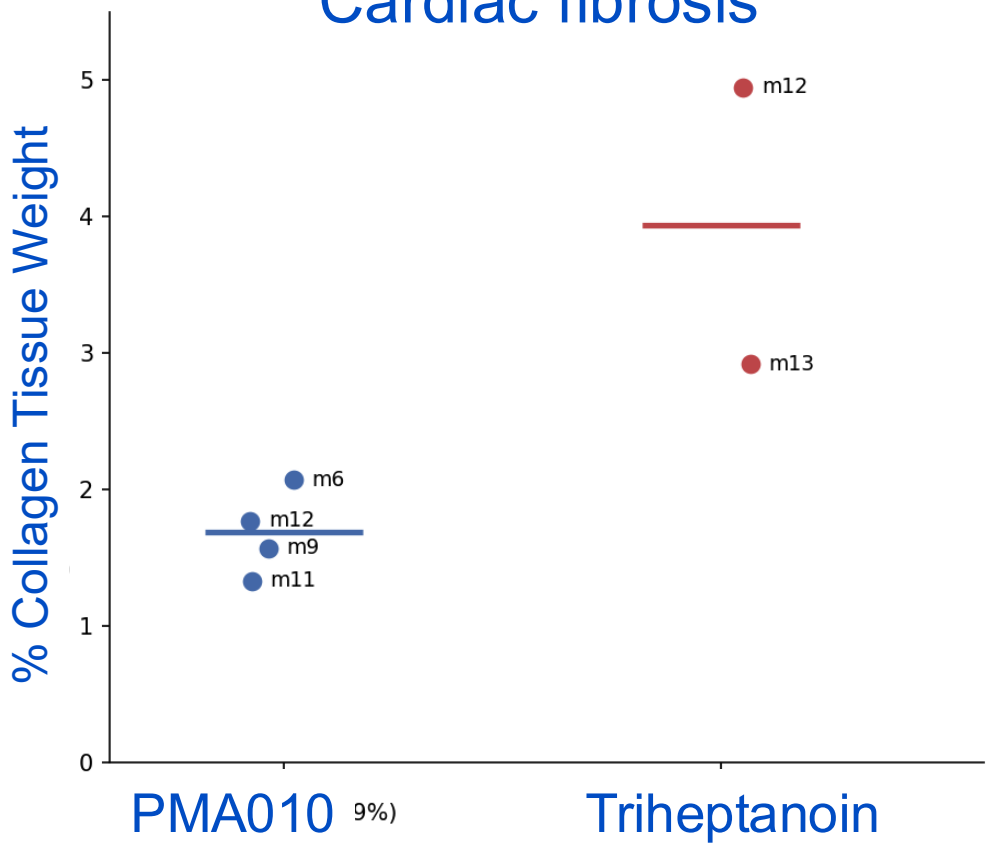
Characteristic	Wild type	VLCADD	DMKO
			
Exercise	↑↑↑	↑↑	↑
Cold tolerance	↑↑↑	↑	–
Rhabdomyolysis	–	–	↑↑
Exercise rhabdo	–	↑	↑↑↑
Lactic acidosis	–	↑	↑↑↑
Cardiomyopathy	–	–	↑↑↑

Cardiac function with gene therapy

Ejection fraction

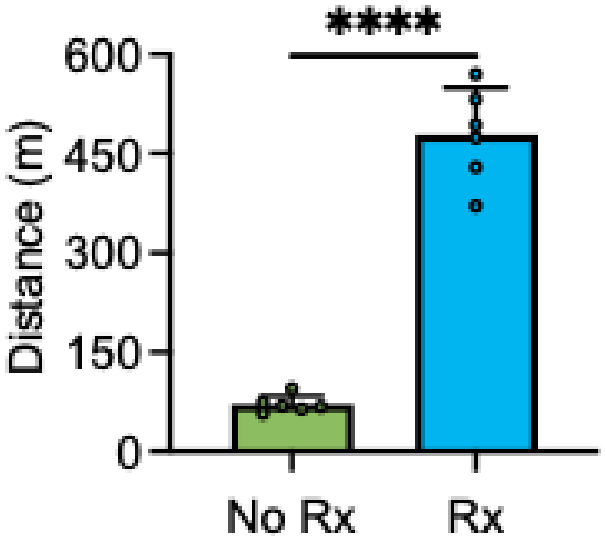


Cardiac fibrosis

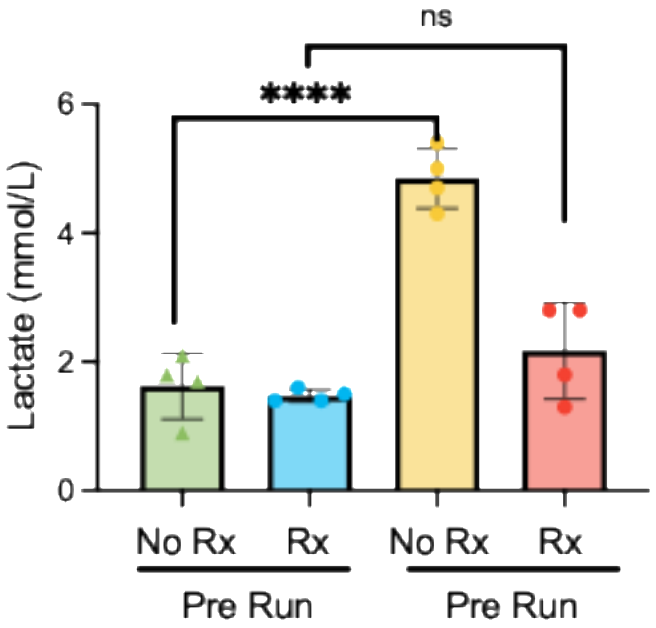


C8-carnitine improves MDKO performance

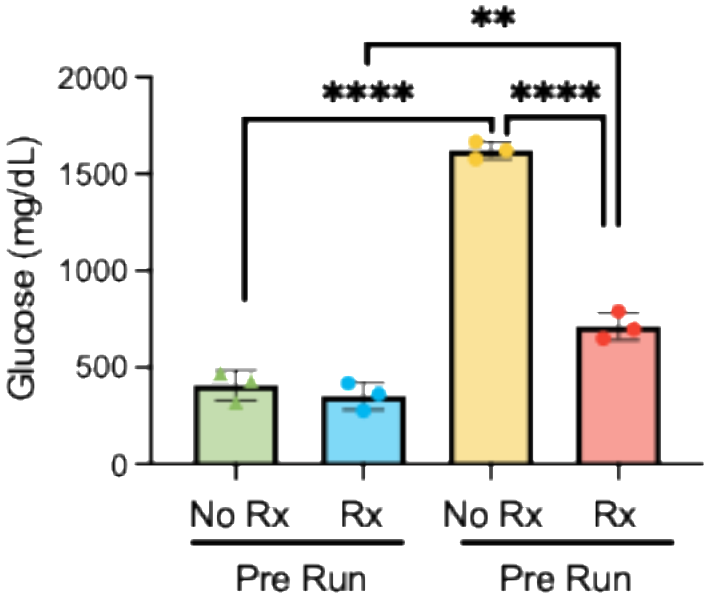
Distance



Lactate



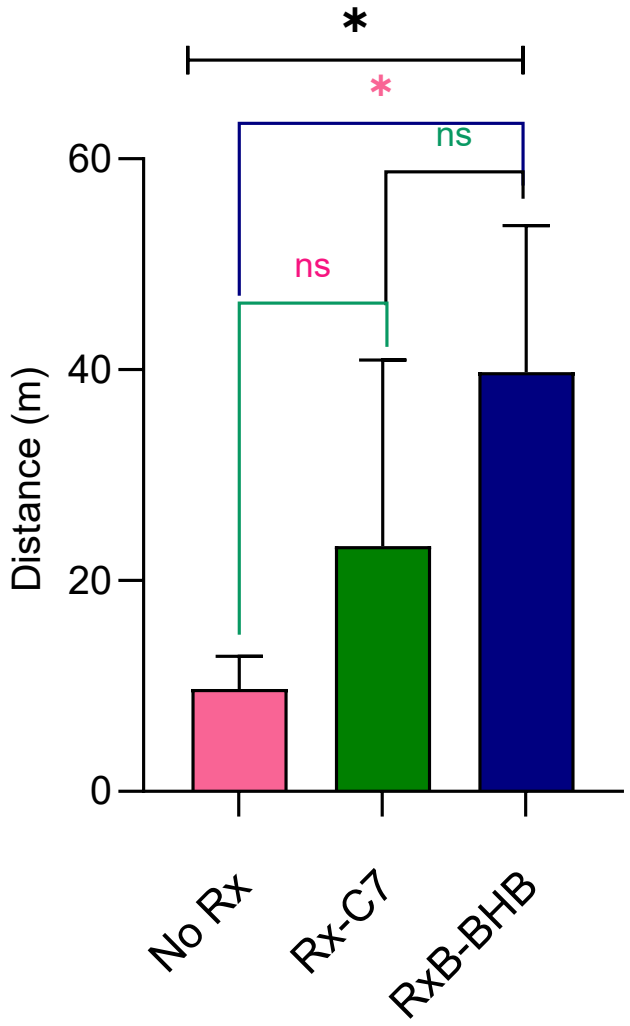
CPK



Eric Goetzman/Keaton Solo

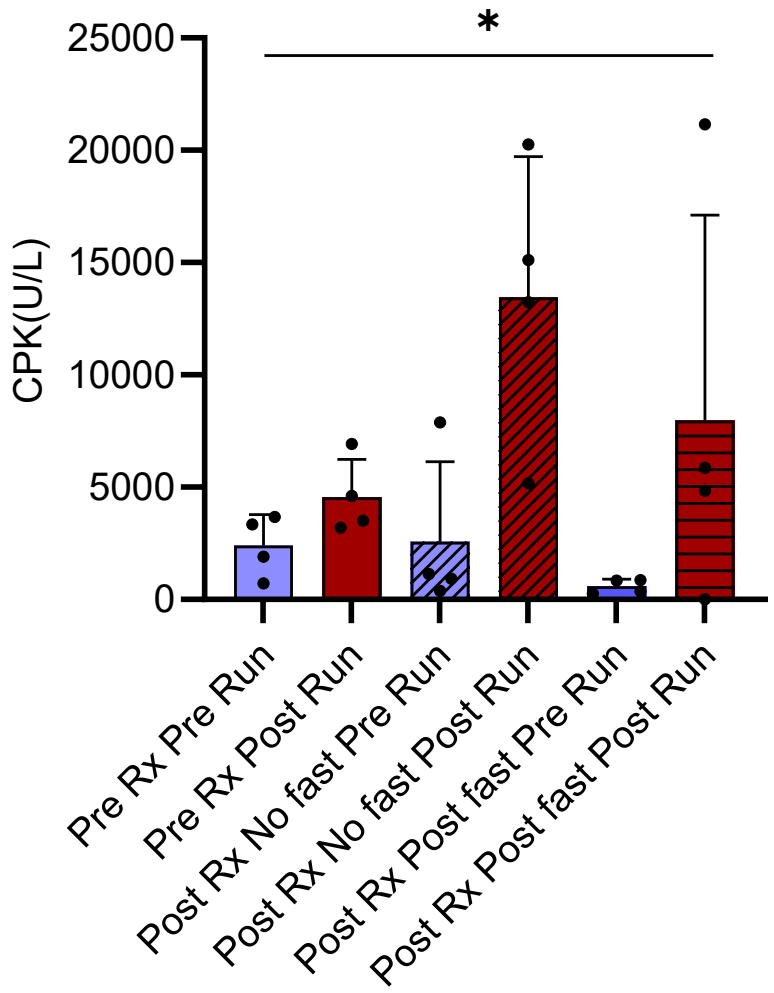
Treatments with ketones

- Arg-BHB/Na-BHB
- Developed by Nestle
- Treatment for 1 month
- Treadmill test

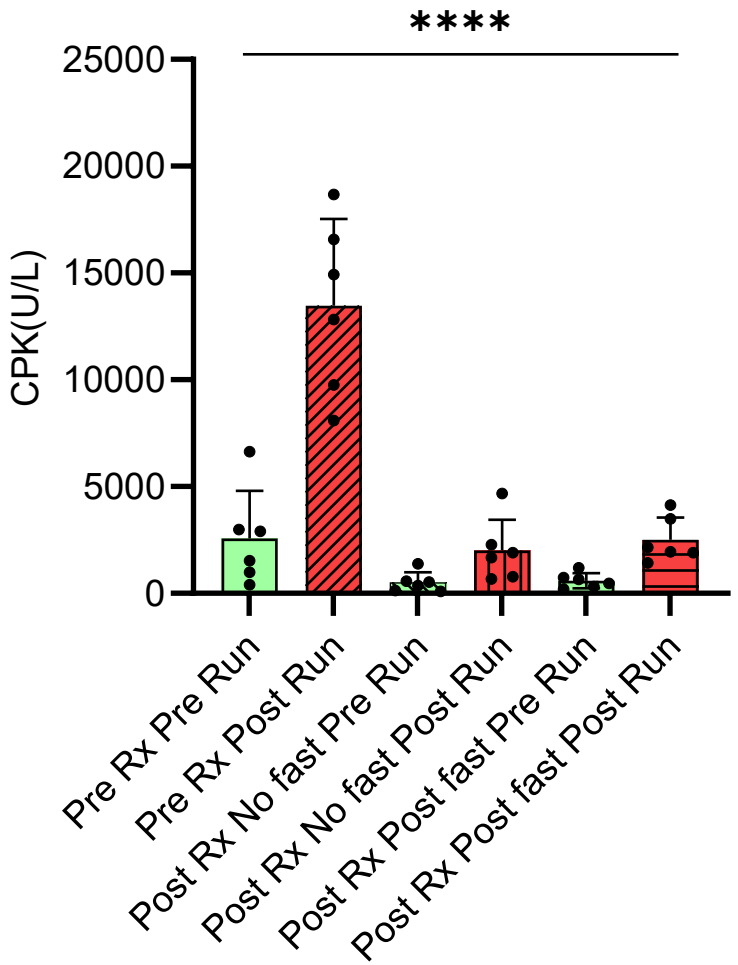


Triheptanoin vs ketones: CPK

Triheptanoin



Arg-BHB/Na-BHB

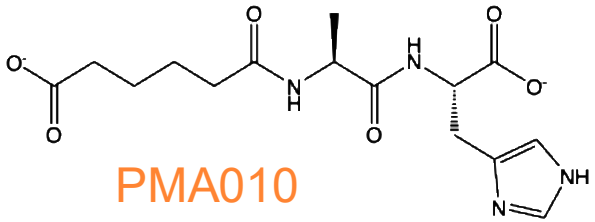


A new class of anaplerotic agents

Active Compound	Fatty Acyl Moiety	Dipeptide Moiety	Anaplerotic Input	Additional Reducing Equivalents*	Potential Ketone Intermediate*
PMA010	Adipyl	*D*-Ala-*D*-His	2 Acetyl-CoA 2 Succinyl-CoA	1 $NADPH^+ H^+$ 3 $NADH^+ H^+$ 1 $FADH_2$	
PMA019	Methyl-malonyl	*D*-Leu-*D*-His	3 Acetyl-CoA 2 Succinyl-CoA	1 $NADPH^+ H^+$ 2 $NADH^+ H^+$ 1 $FADH_2$	1 Acetoacetate
PMA020	Methyl-malonyl	*D*-Lys-*D*-His	2 Acetyl-CoA 2 Succinyl-CoA	1 $NADPH^+ H^+$ 3 $NADH^+ H^+$ 1 $FADH_2$	1 Acetoacetate
PMA023	Methyl-malonyl	*D*-Ile-*D*-His	1 Acetyl-CoA 3 Succinyl-CoA	1 $NADPH^+ H^+$ 3 $NADH^+ H^+$ 1 $FADH_2$	
Heptanoate**	Heptanoyl	---	2 Acetyl-CoA 1 Succinyl-CoA	2 $NADH^+ H^+$ 2 $FADH_2$	1 β-Ketovalerate

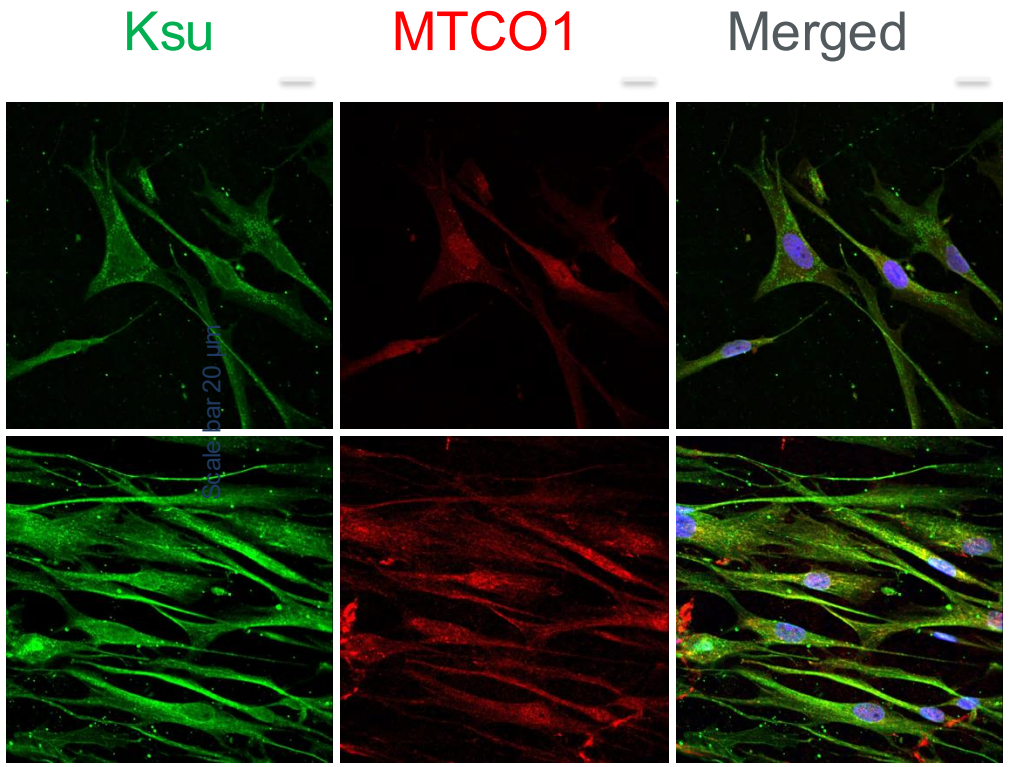
*Produced in mitochondria
**Released by lipase

PMA010 improves function in VLCADD cells



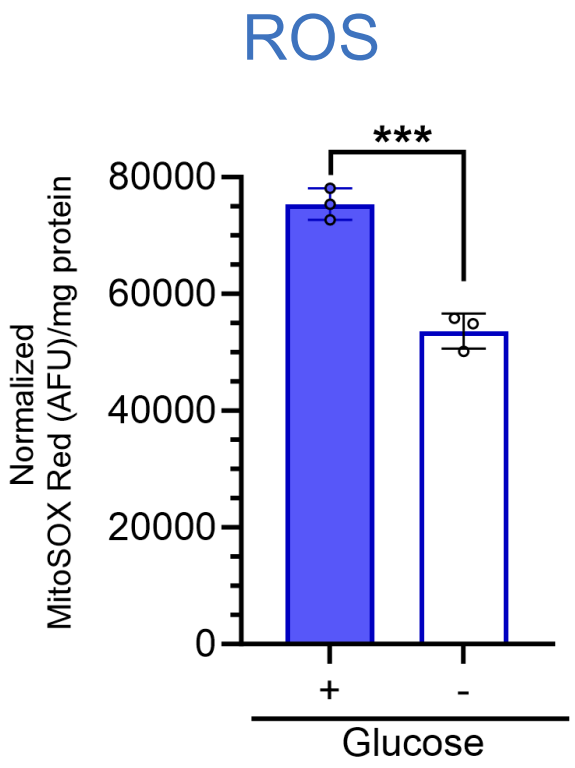
PMA010

Adipyl-*D*-alaninyl-*D*-histidine



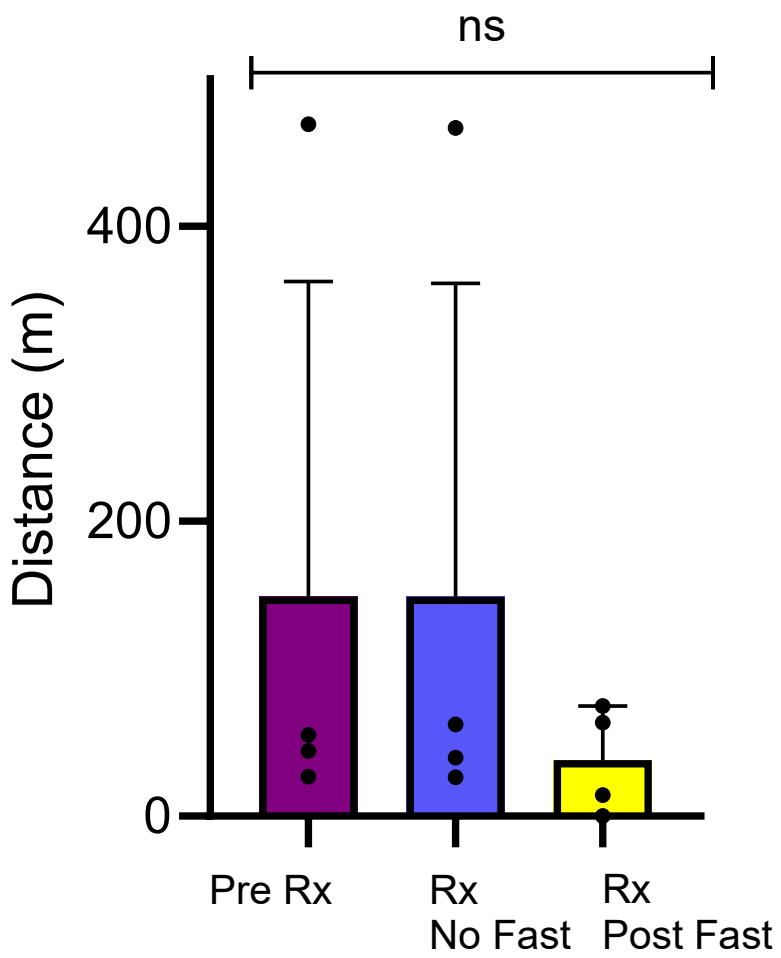
No Glucose
Untreated

No Glucose
[PMA10]

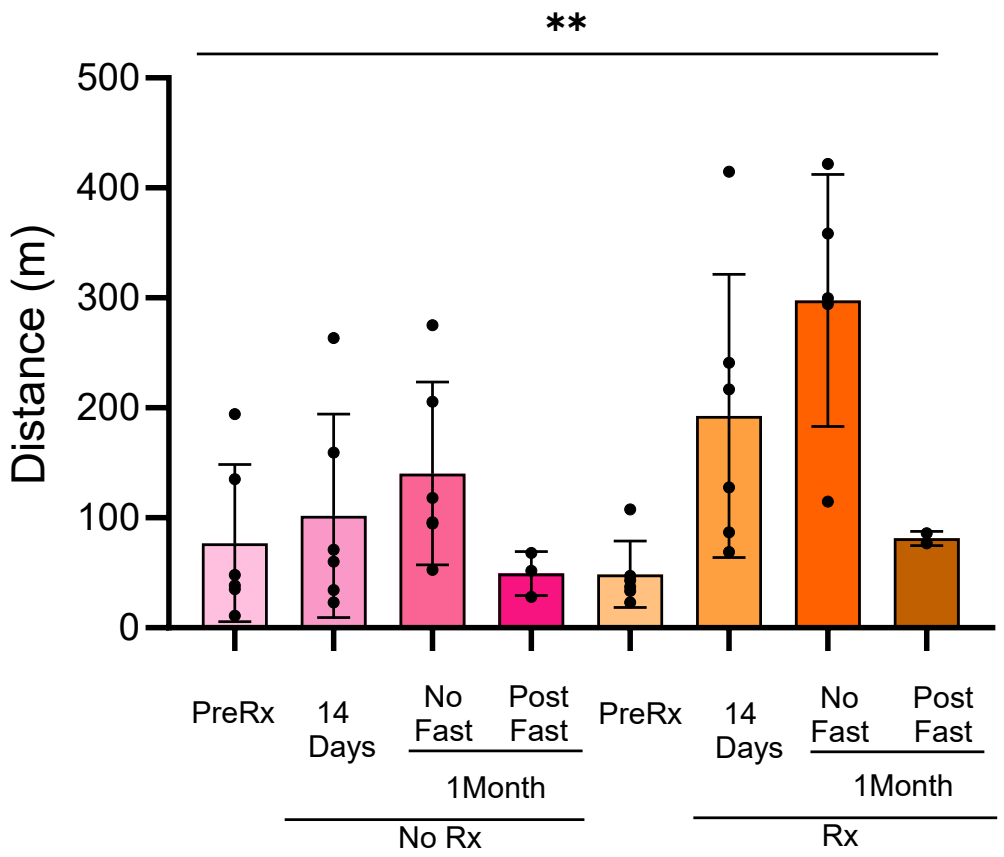


Triheptanoin vs PMA010: Distance run

Triheptanoin (14 days)

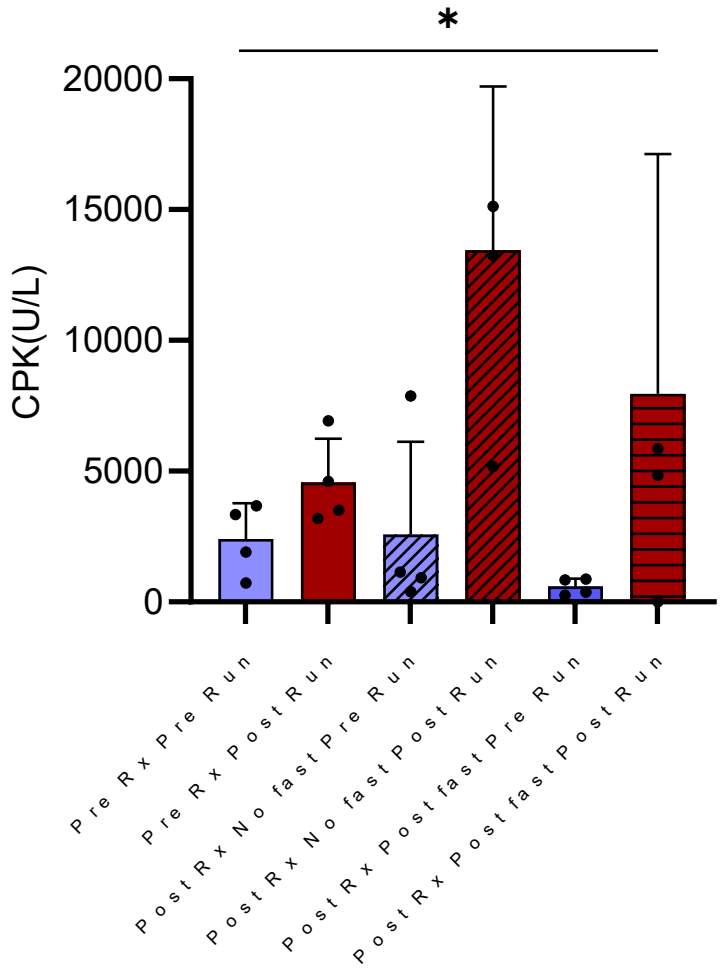


PMA010

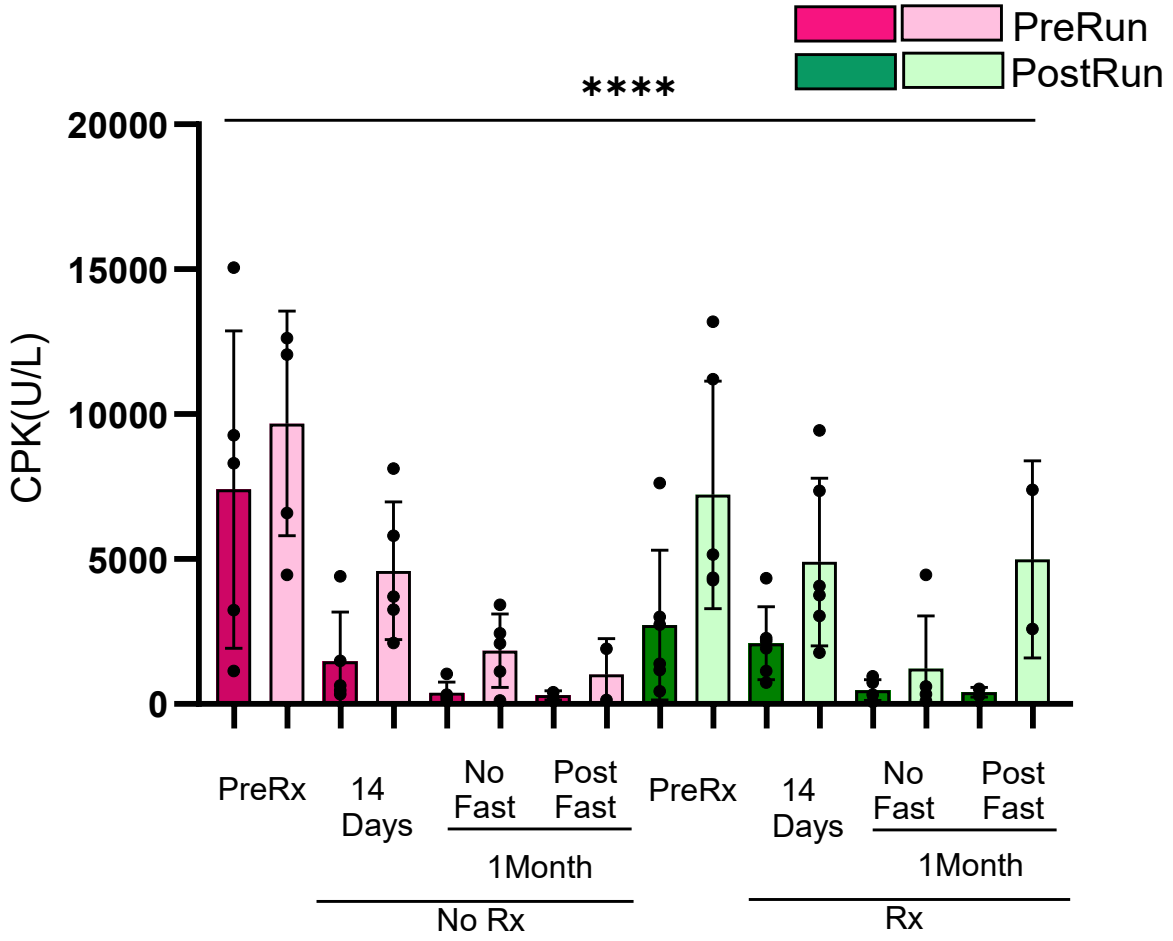


Triheptanoin vs PMA010: CPK

Triheptanoin (14 days)

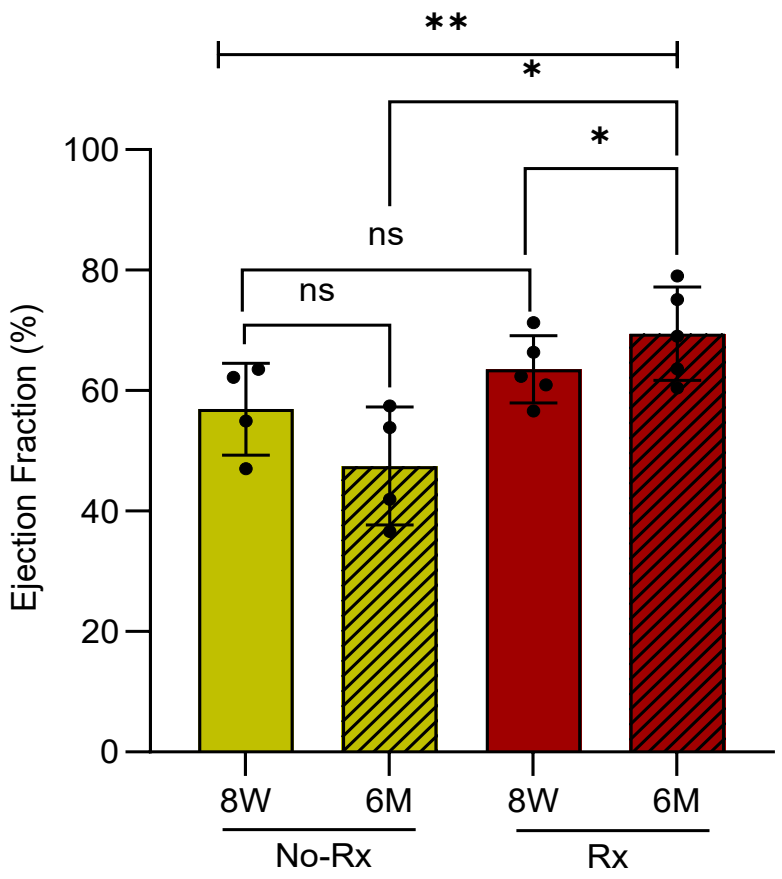


PMA010

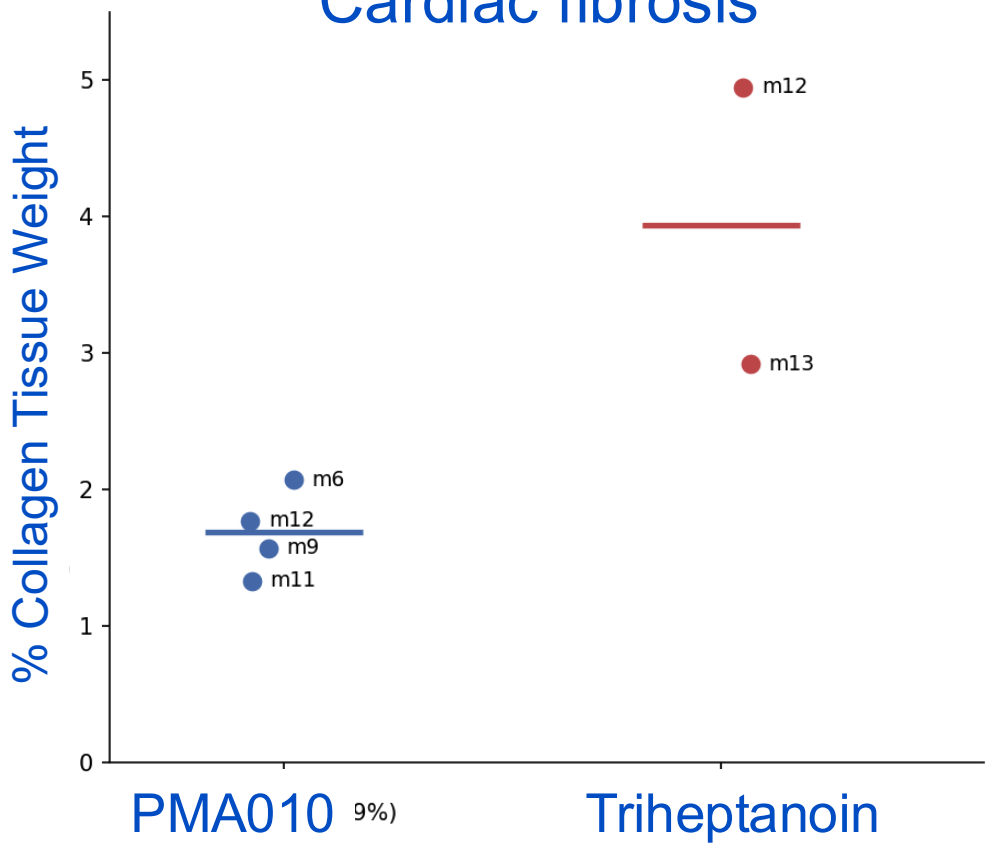


Cardiac function

Ejection fraction

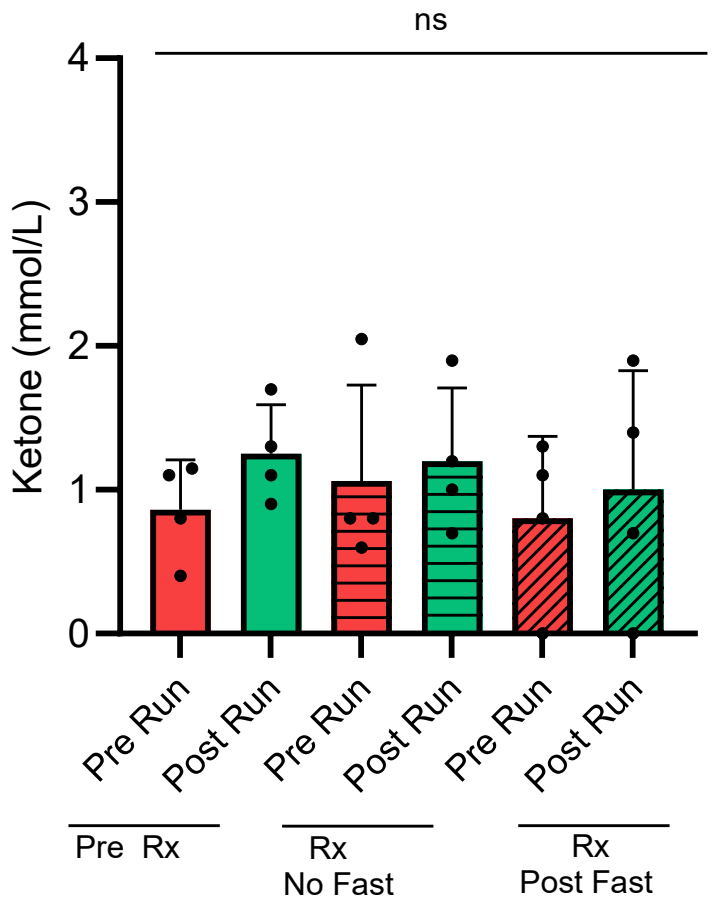


Cardiac fibrosis

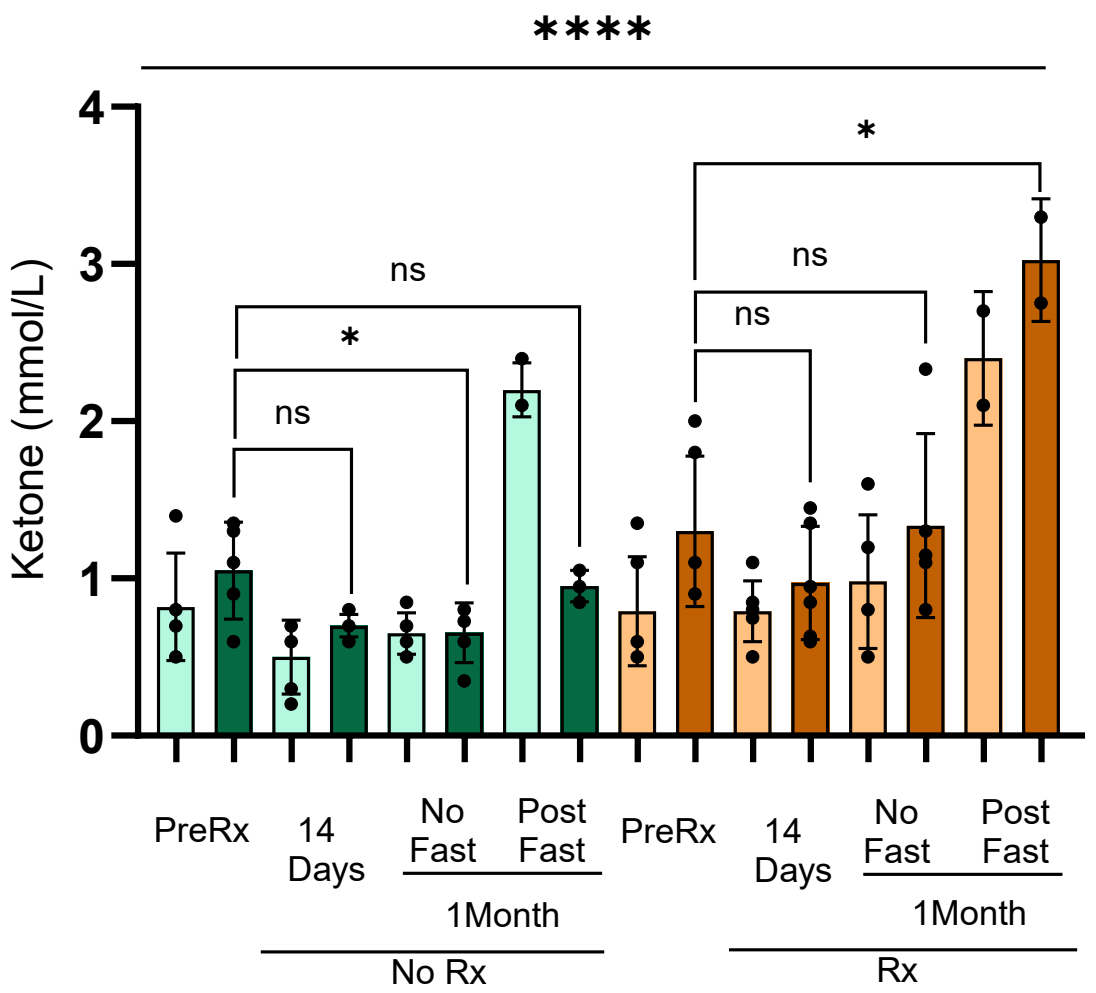


Triheptanoin vs PMA010: Ketones

Triheptanoin (14 days)



PMA010



Inflammation in VLCAD deficiency

- 18 Patients
- Age12 mo-31 years
- Stored well samples
- Multiple samples on 3 patients

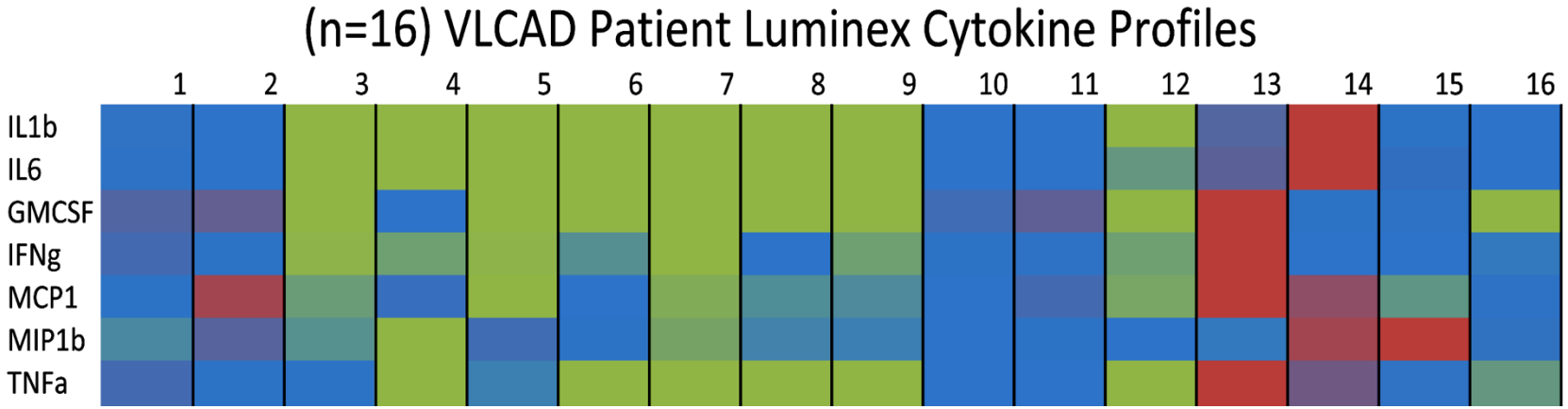
Table 1. Demographic and clinical characteristics of VLCADD patients

Patient #	Sex	Race/Ethnicity	*ACADVL* mutation	Age at 1st visit	Average CPK, outpatient[a]	Average CPK, admission
1	Female	Caucasian	T1372C (F548L); 1668 ACAG 1669 splice site	19 years	812.7	36 816
2	Female	Caucasian	c.1182+1G>A; c.566T>C (p.I189T)	15 months	122	31 570.5
3[b]	Female	Caucasian	T1619C and 9-bp insertion; duplication of bp 1707-1716 in exon 18, duplicates amino acids 530-532 DGA	4 years (new diagnosis)	97.5	28 933.8
4	Female	Caucasian	848T>C (V283A); 1182(+3)G>T	12 months	79.7	2740
5	Male	Caucasian	1322G>A (p.G401D); 1837C>T (p.R573W)	31 years	244.1	8444.4
6	Female	Caucasian	Deletion 887-888 exon 10; G-6A intron proceeding exon 18	16 years	129	27 227.3
7	Male	Hispanic	N/A[c]	16 years	N/A	16 474
8	Male	Caucasian	A770Del; G1613C	13 years	441.5	25 054.5
9	Male	Caucasian	N/A[c]	12 years	893	31 325
11	Male	Caucasian	A770Del; G1613C	9 years	247.3	5417.5
12	Female	Caucasian	G1406A (R429Q); splice site mutation exon 11, G +1A	13 years		52 293
13	Male	Caucasian	605T>C; 1837C>T	9 years	266.0	72 743
14	Female	African American	*Not done*			76 615
15	Female	Caucasian	1316G>A (G439D); 1328T>G (M443R)	21 months	306	35 542
16	Male	Caucasian	c.343delG p.Glu115LysfsX2; c.1198G>A, p.Val400Met	7 years	163.5	N/A
17	Female	Caucasian	c.343delG p.Glu115LysfsX2; c.1198G>A, p.Val400Met	10 years	265.5	N/A
18	Female	Caucasian	N/A[c]	17 years	252	N/A

[a]Creatine phosphokinase (CPK) values (μg L^{-1}); normal range = 10–120 μg L^{-1}.
[b]Patient with highly recurrent rhabdomyolysis, data on multiple samples shown in Figures 2 and 4.
[c]N/A, not available.

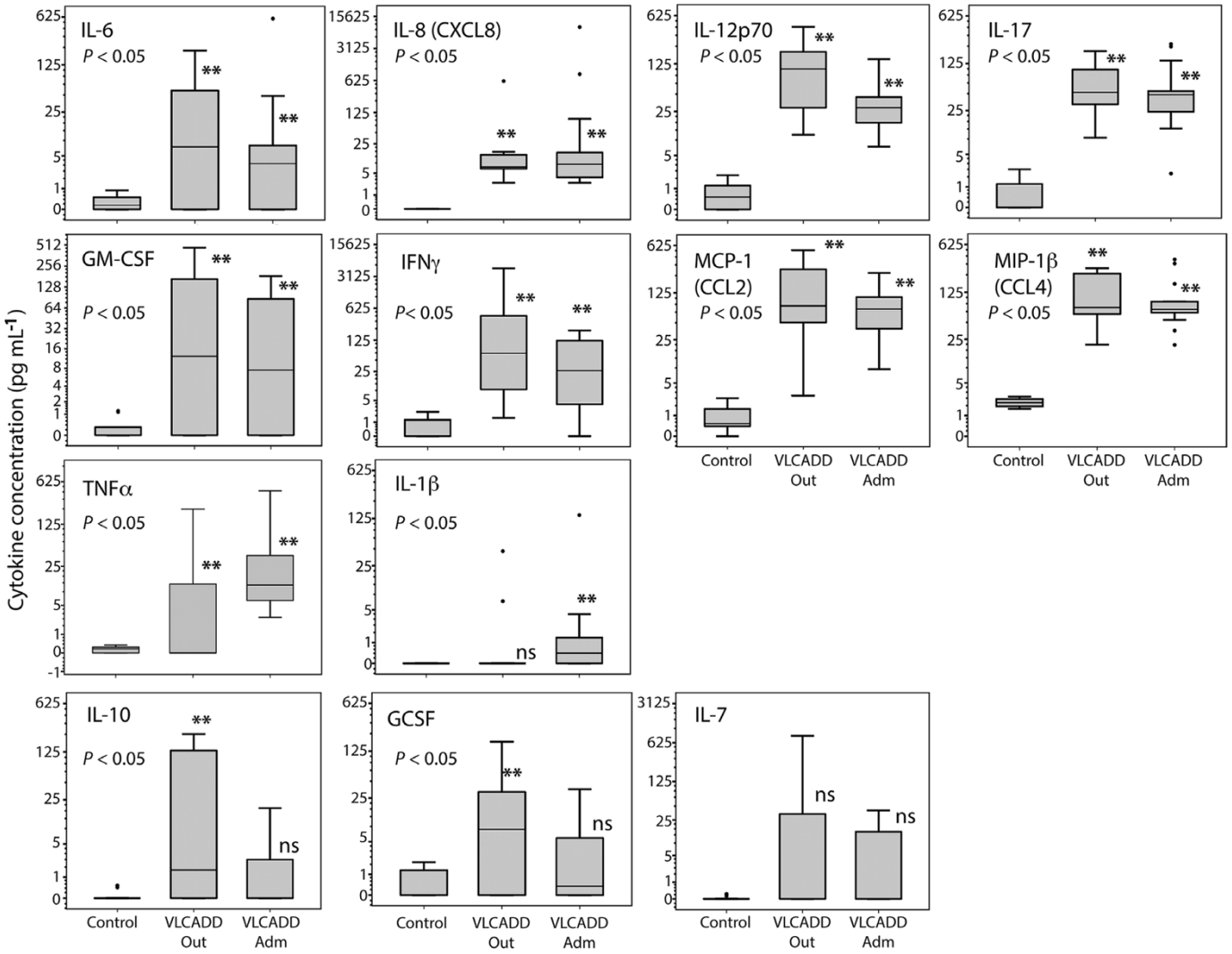
Cytokines in VLCAD patients

Inflammation is unrecognized in LC-FAODs

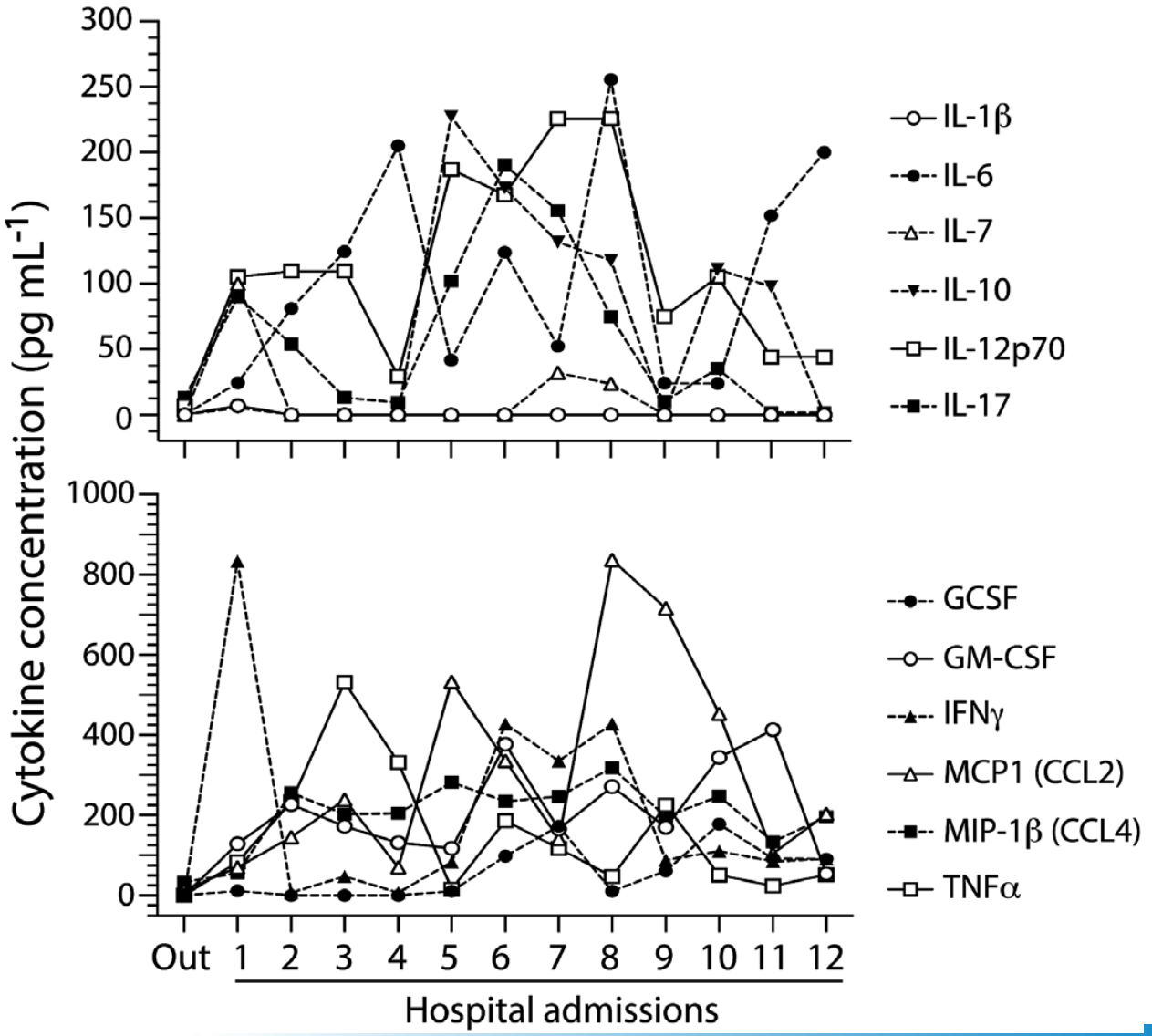


Key:			
IL1b (pg/ml)	0	-	141
IL6 (pg/ml)	0	-	591
GMCSF (pg/ml)	0	-	468
IFNg (pg/ml)	0	-	4657
MCP1 (pg/ml)	0	-	278
MIP1b (pg/ml)	0	-	378
TNFa (pg/ml)	0	-	442

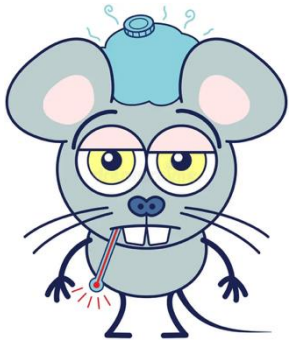
Cytokine measurements



Multiple hospitalizations over 2 years

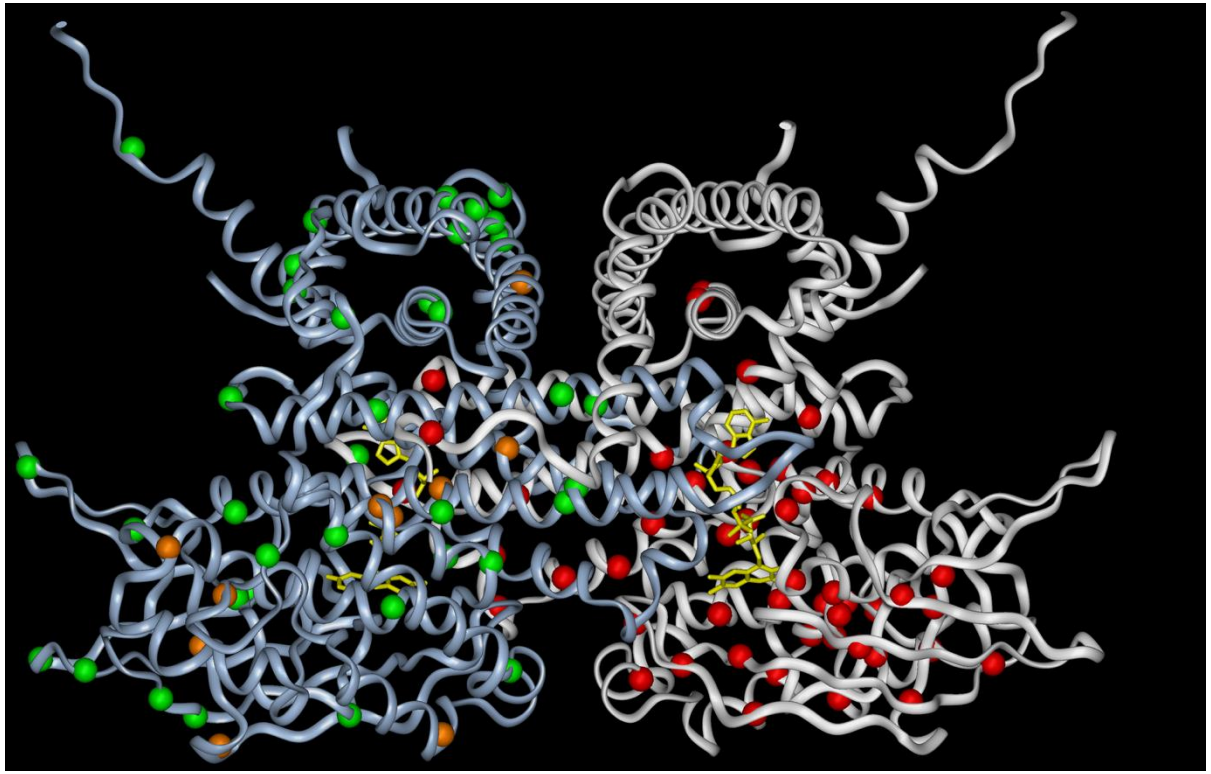


A look ahead for treatment

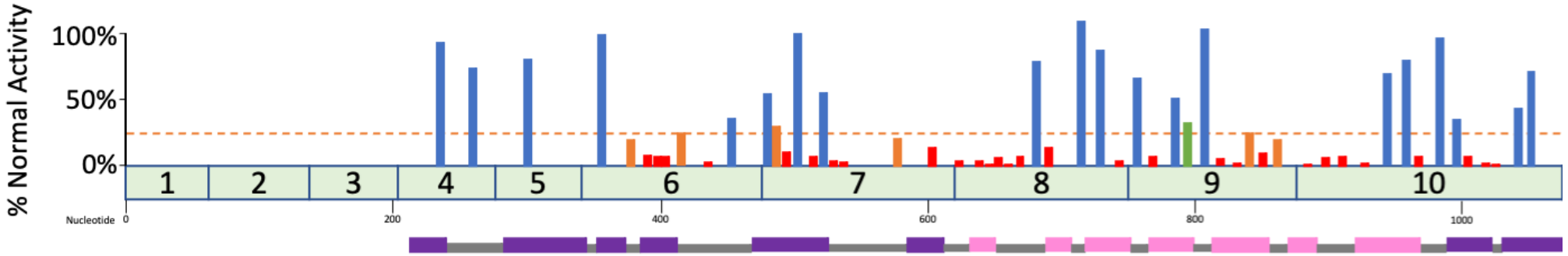
Identified by NBS	Start treatment	Acute episodes	Older patients?
			
Genotype	Severe: Anaplerosis Mild: Follow	Intermittent or routine mRNA Anti-inflammatories Anaplerosis	Gene therapy

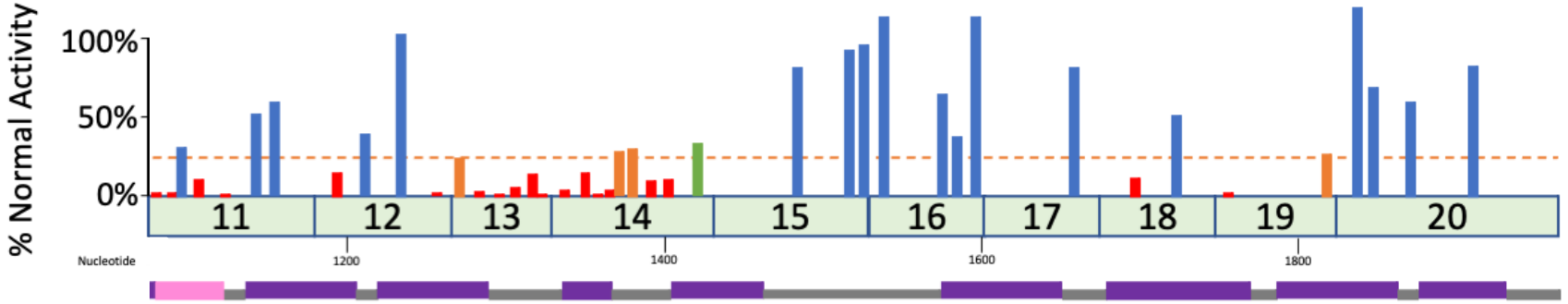
VLCAD and NBS

- NBS results aren't always clear
  - Mild vs severe vaiants
  - Variants of unknown significance
- Characterize single gene variants in a cell line
- >100 variants characterized to date
- Fibroblast testing as needed for non-coding alleles



Enzyme Activity of Exon Variants





Blue = benign
Green = continued VUS
Orange = pathogenic (mild)
Red = pathogenic (severe)

= α–helix
= β–sheet
= random coil

Variant amino acid characterizations

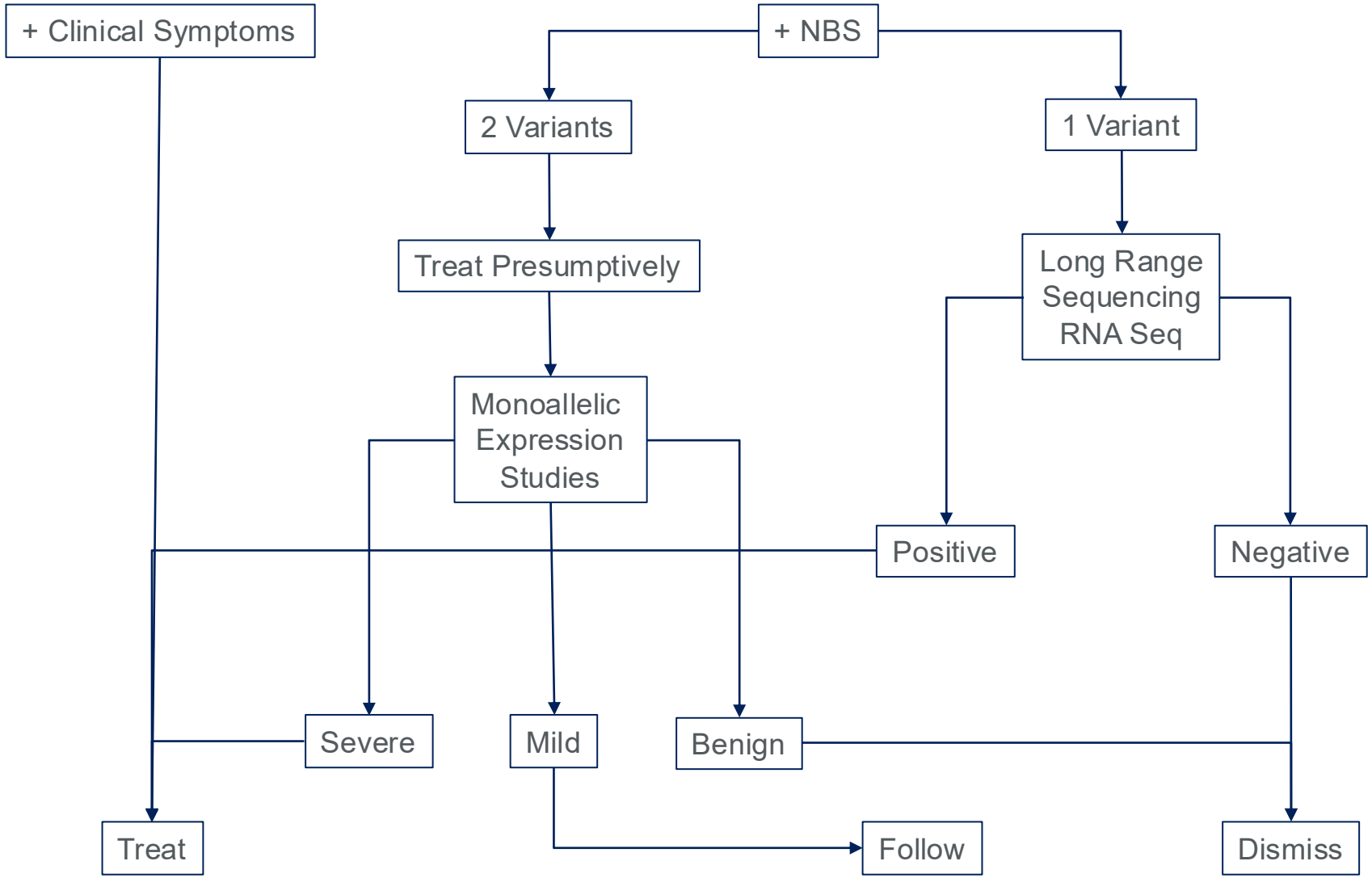
	NP to NP, P to P	NP to P, P to NP	NP to C, C to NP	P to C, C to P	C to C (same)	C to C (opposite)	Totals
Benign	12	7	5	7	3	3	37
Continued VUS		3					3
Pathogenic (mild)	2	4	1	1		2	10
Pathogenic (severe)	15	10	13	6	3	2	49

NP = nonpolar
P = polar
C = charged

Recurrent splice variants

Variant (NM_000018.4)	Effect
c.277+59_277+72del	Intron 4 retention
c.343delG	Exon 6 skipping
c.957G>A, p.Ser319=	Exon 10 skipping
c.1077+1G>A	Exon 10 skipping
c.1077+1delinsCAC	Exon 10 skipping
c.1182+2dupT	Exon 11 skipping
c.1287G>A, p.Val429=	Exon 13 cryptic splicing

NBS algorithm

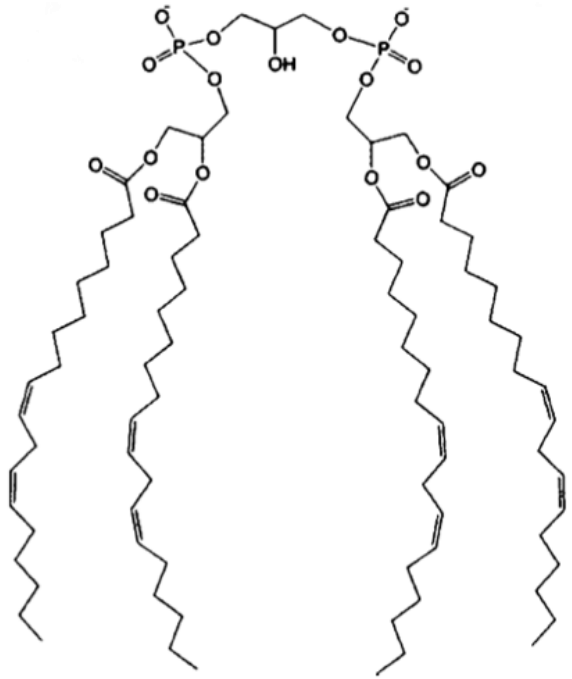


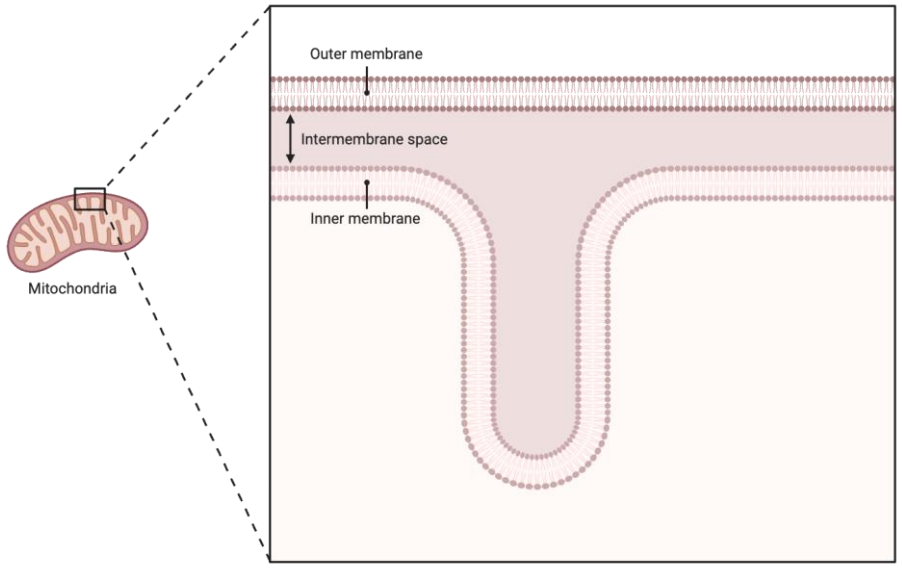
Expanding Expanding Therapeutic Targets in TFP Deficiency: A Role for Cardiolipin Remodeling

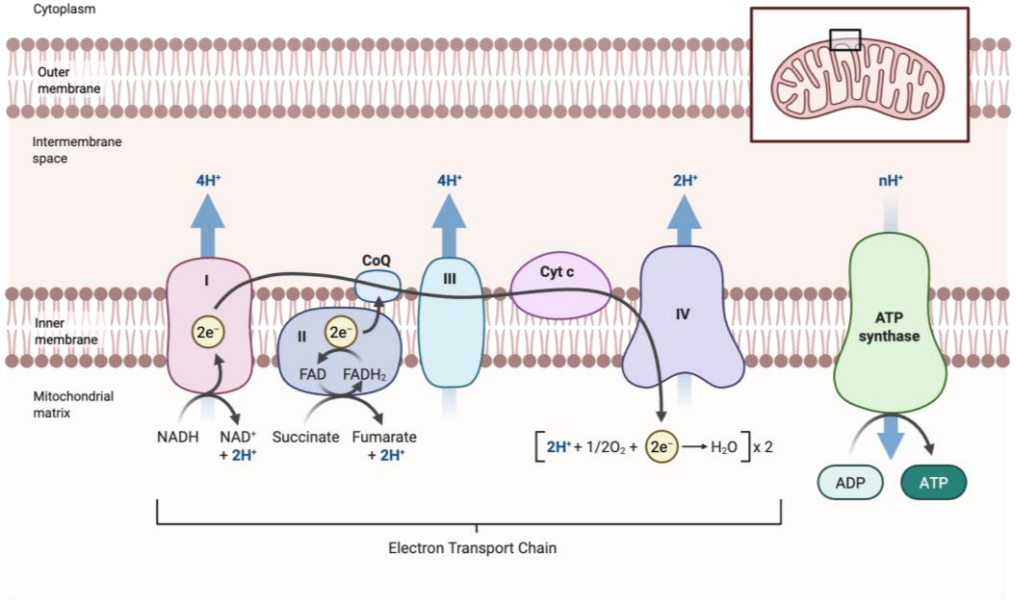
From mitochondrial bioenergetics to preclinical insights

Eduardo Vieira Neto, MD, PhD
Genetic and Genomic Medicine Division
Dept of Pediatrics, University of Pittsburgh

Cardiolipin

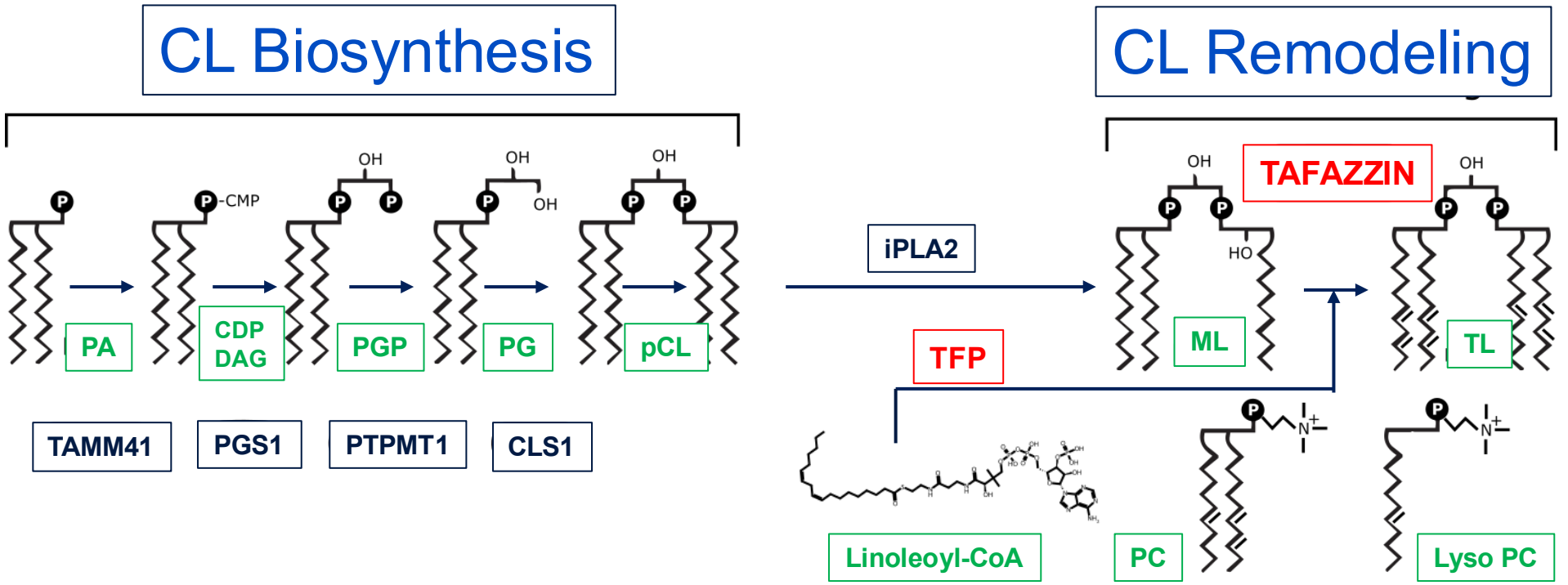




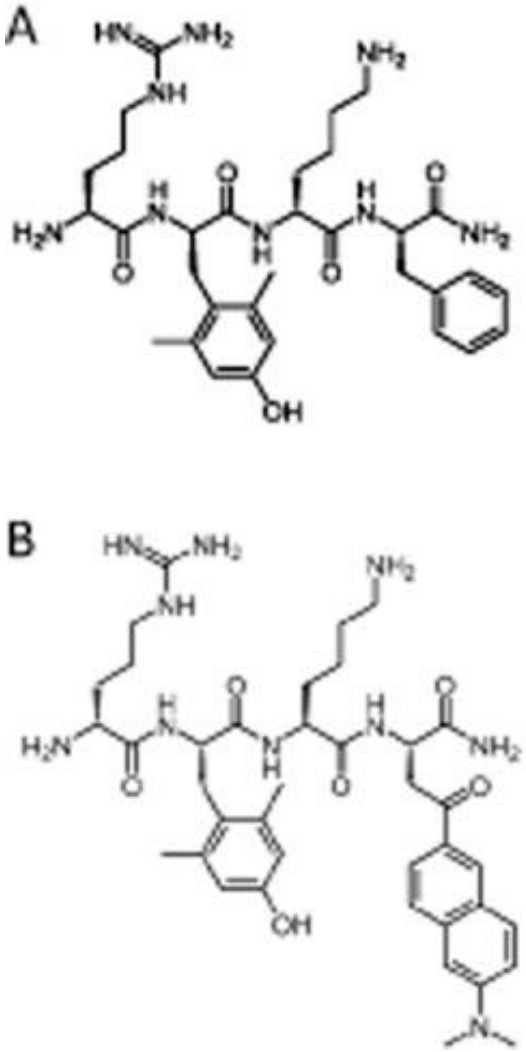


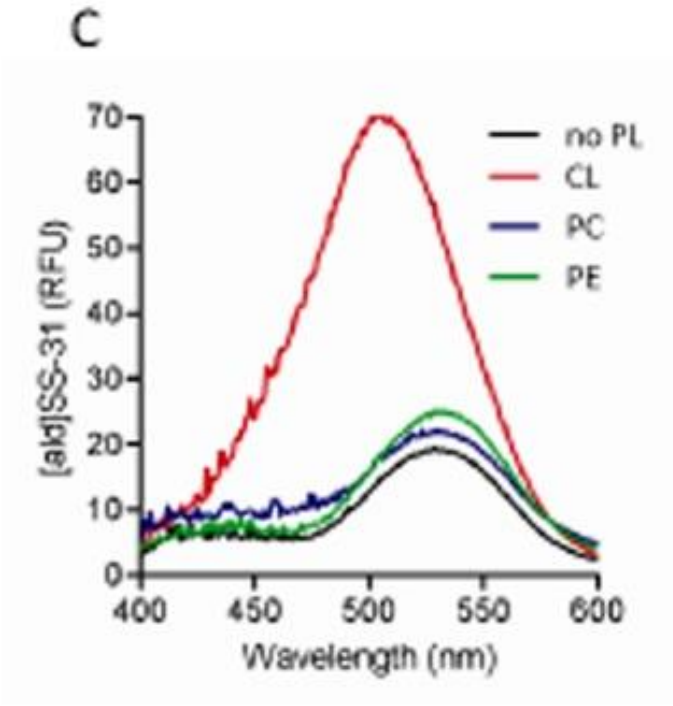
- Tetralinoleoyl cardiolipin
- Mature form of cardiolipin in tissues with extreme metabolic demands

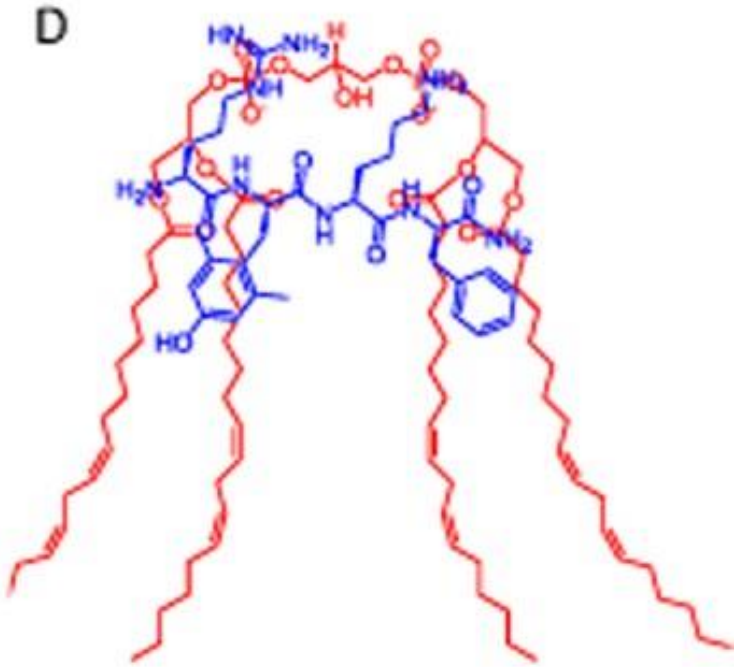
Electron transport chain (ETC) stabilization


CL Biosynthesis
CL Remodeling
PA
CDP DAG
PGP
PG
pCL
TAMM41
PGS1
PTPMT1
CLS1
iPLA2
TAFAZZIN
ML
TL
TFP
Linoleoyl-CoA
PC
Lyso PC

Intervention: elamipretide

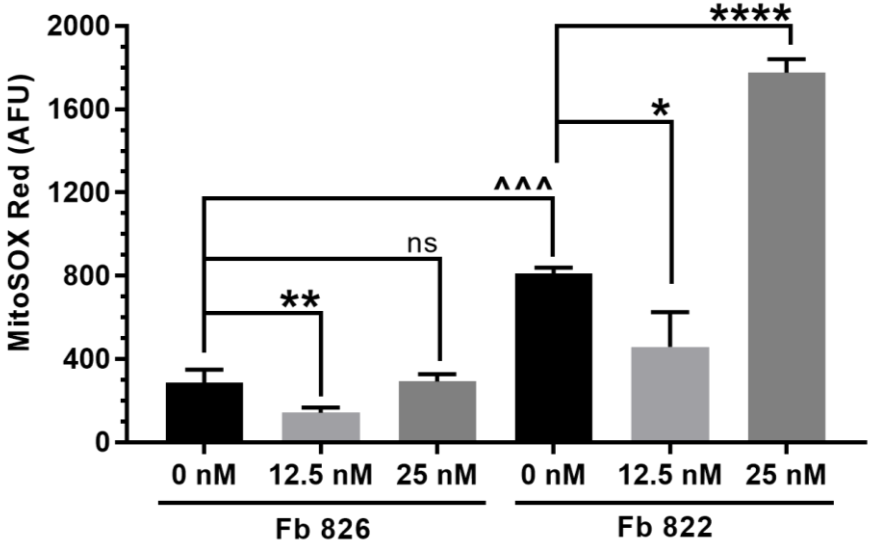


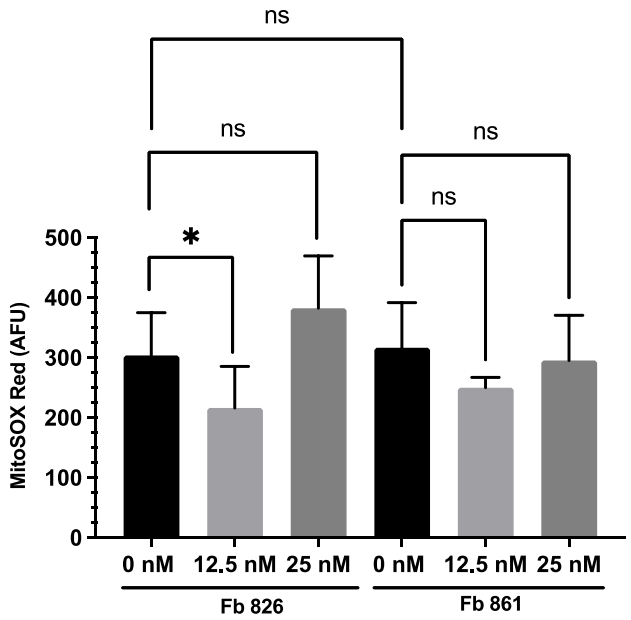


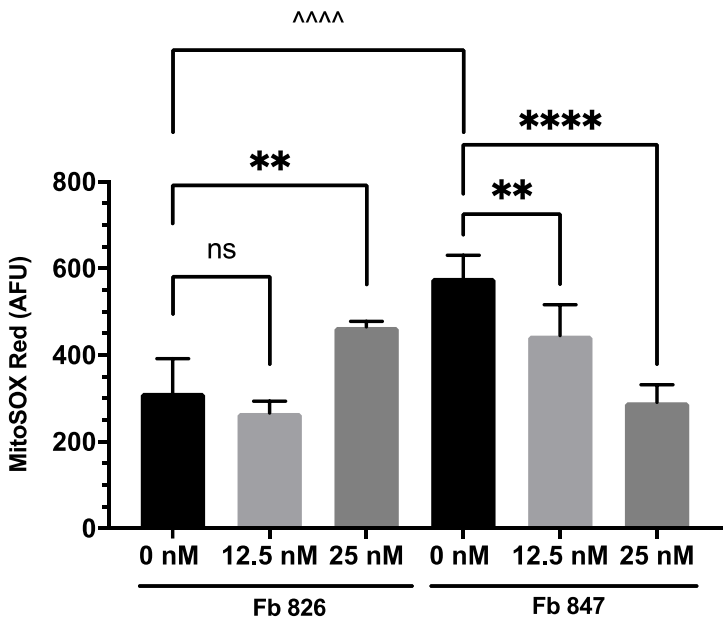


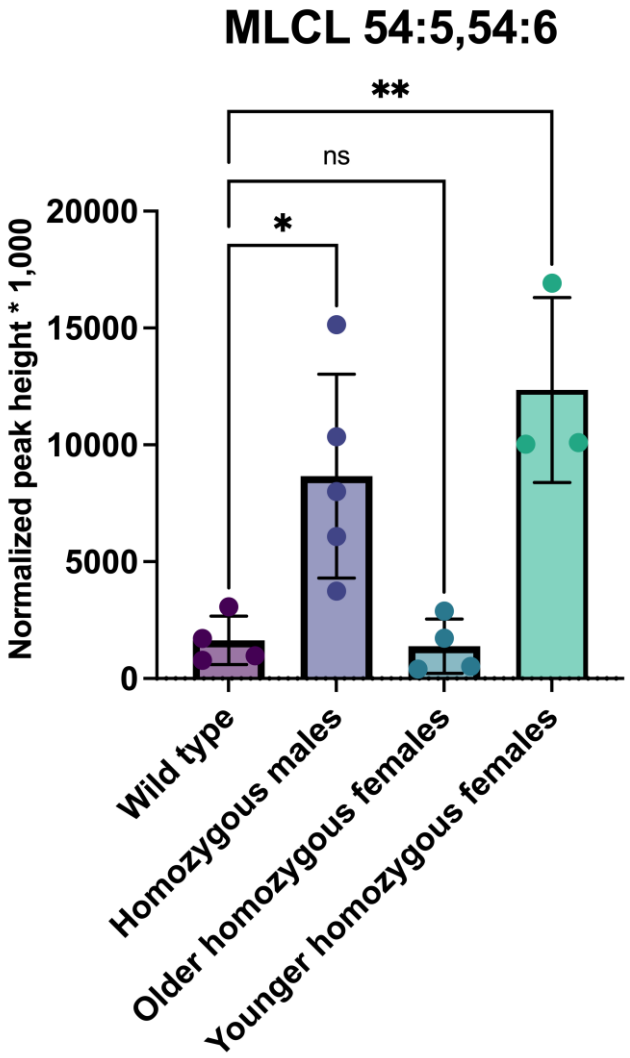
Reprinted from: Apr;171(8):2029-50; Figure 4; p. 2034

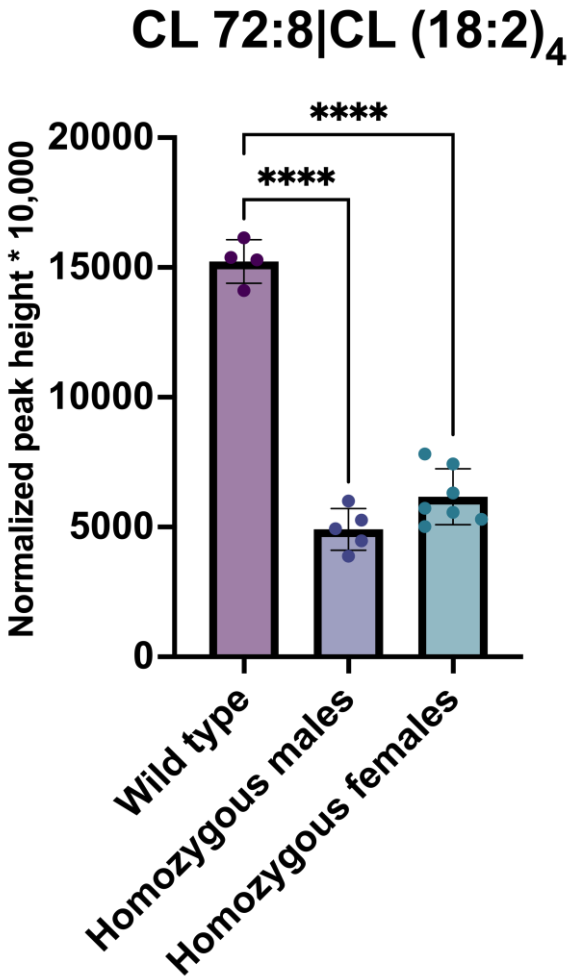
Elamipretide treatment of TFP cell lines





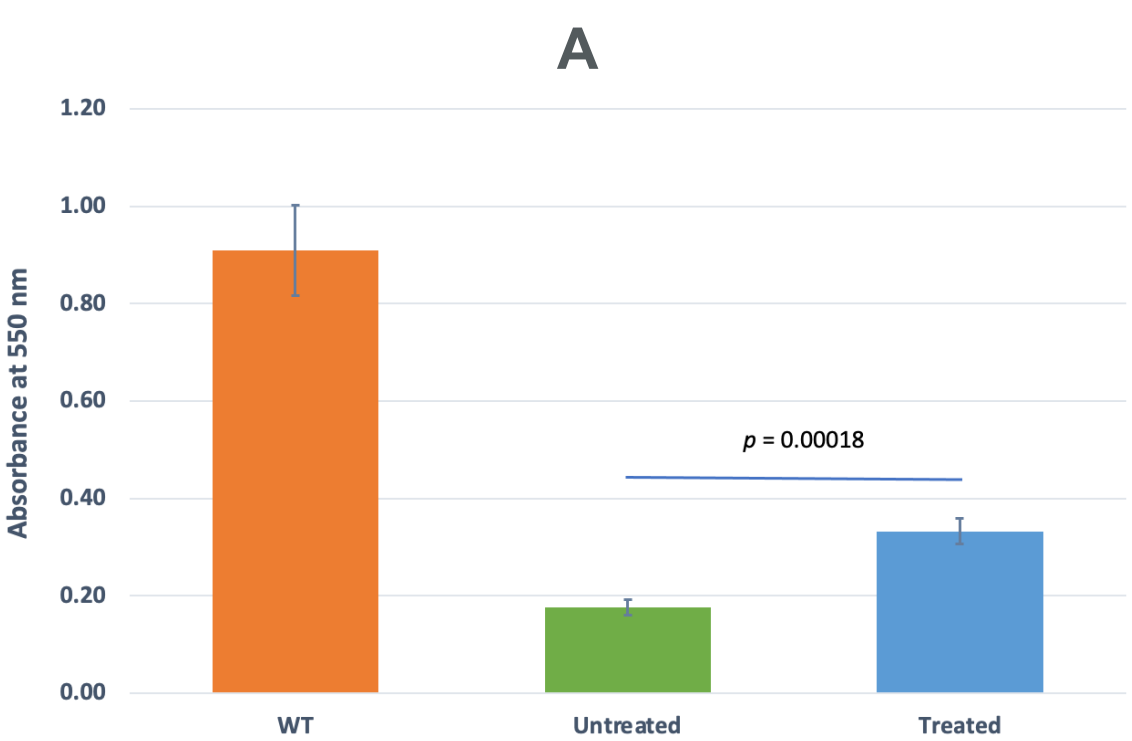


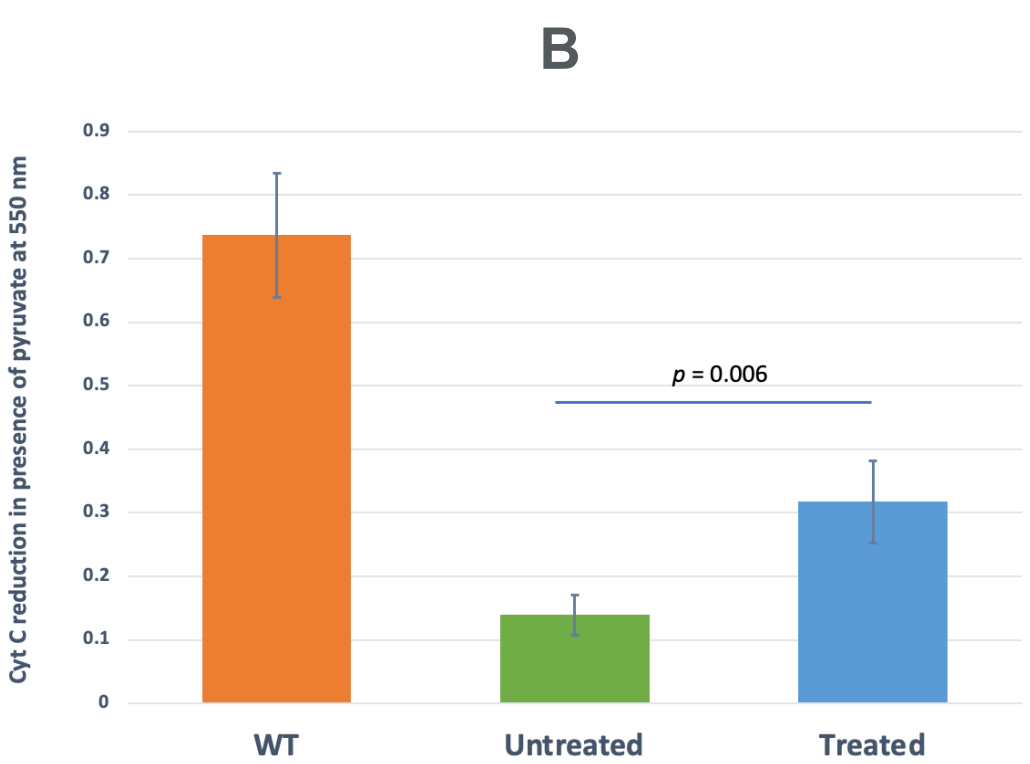




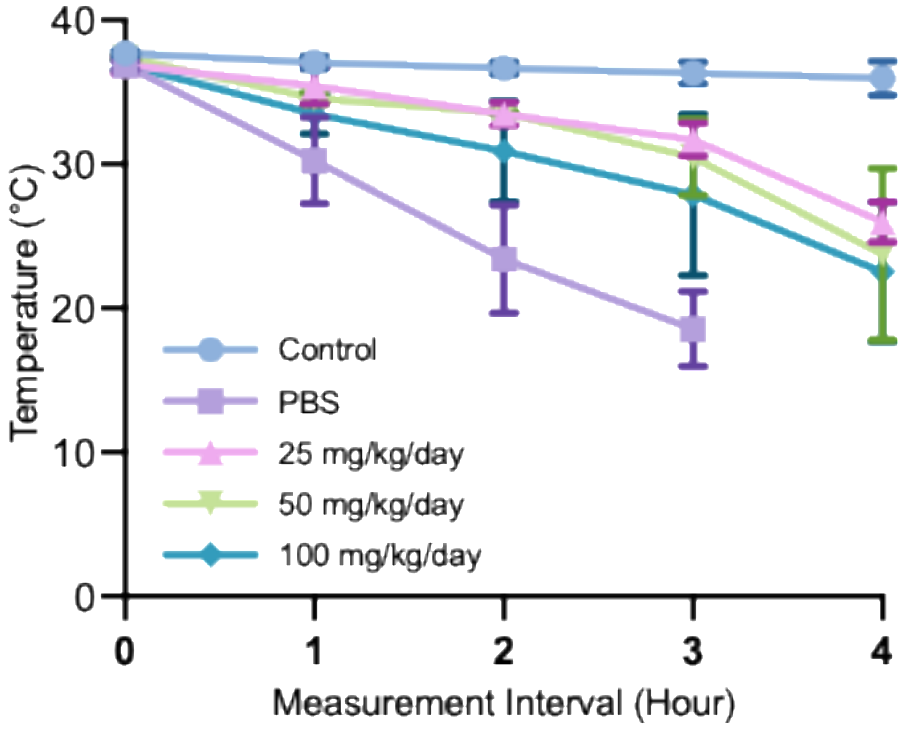
β-TFP mice have lower concentrations of tetralinoleoyl-cardiolipin, but the increase in monolysocardiolipins is sex and age dependent.

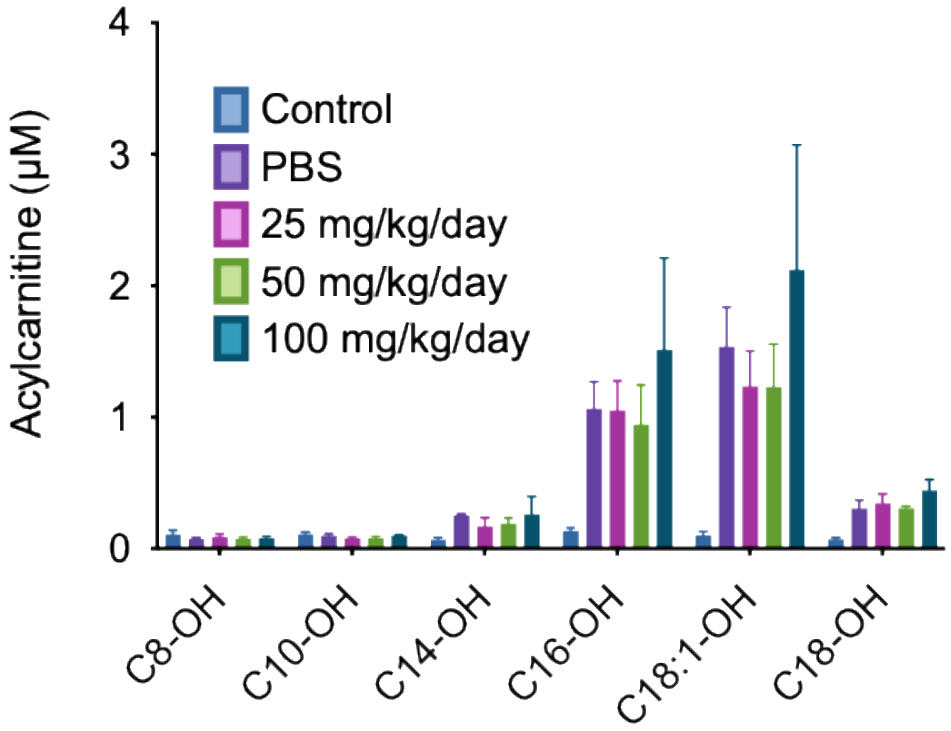
Elamipretide treatment of TFP mice





A new CL binding peptides

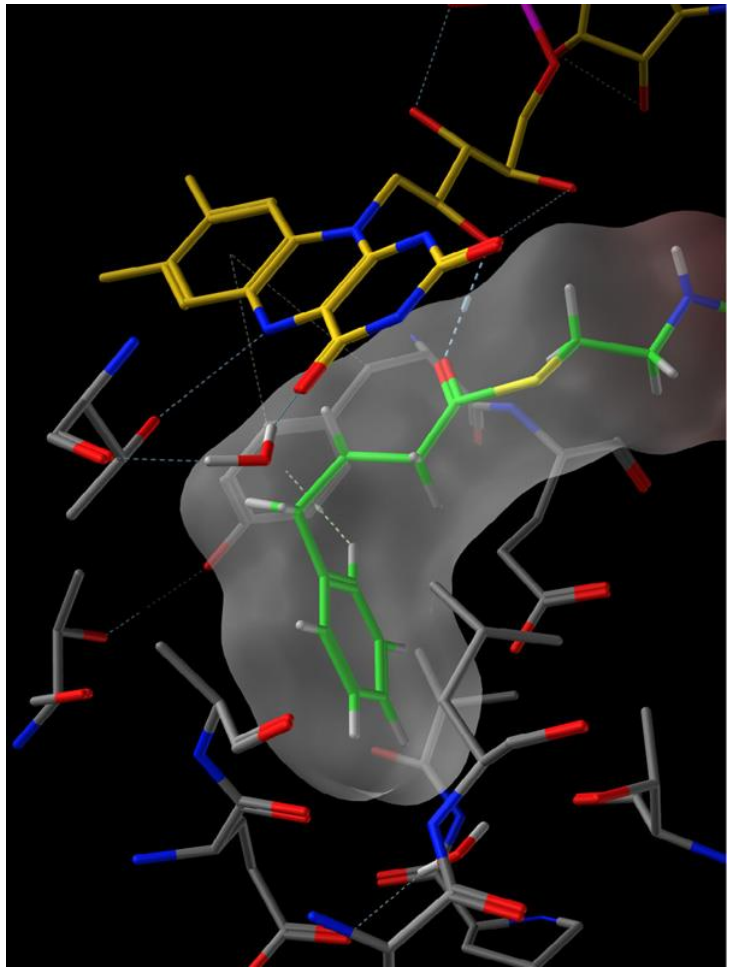




The CPK Holy Grail!

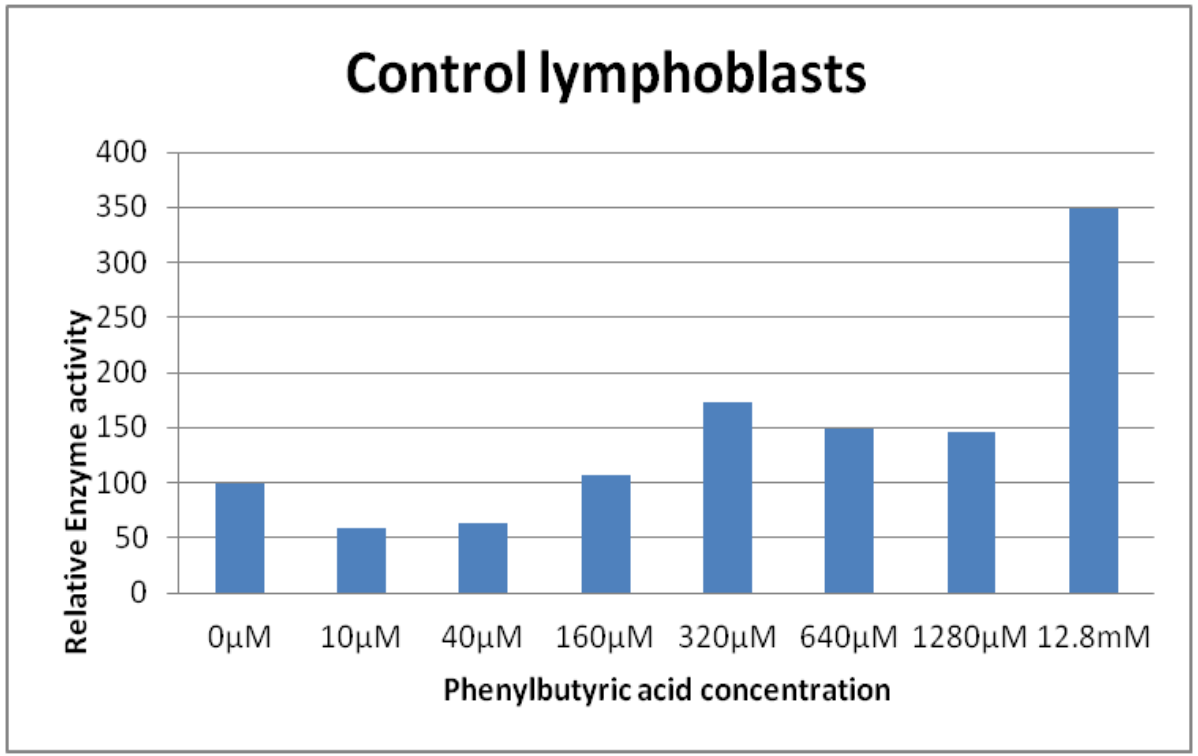
- Home CPK meter would reduce anxiety and improve management through acquisition of accurate data
- Current state of the market?
- Three current projects to develop one

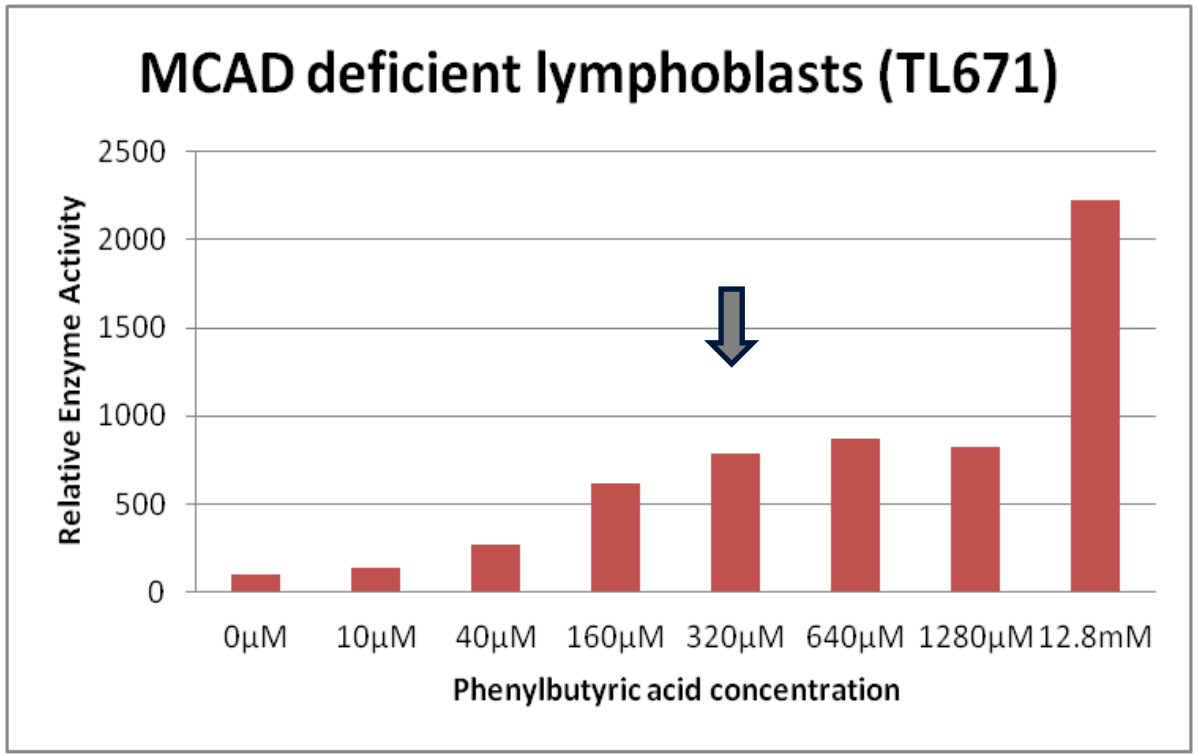
MCAD deficiency



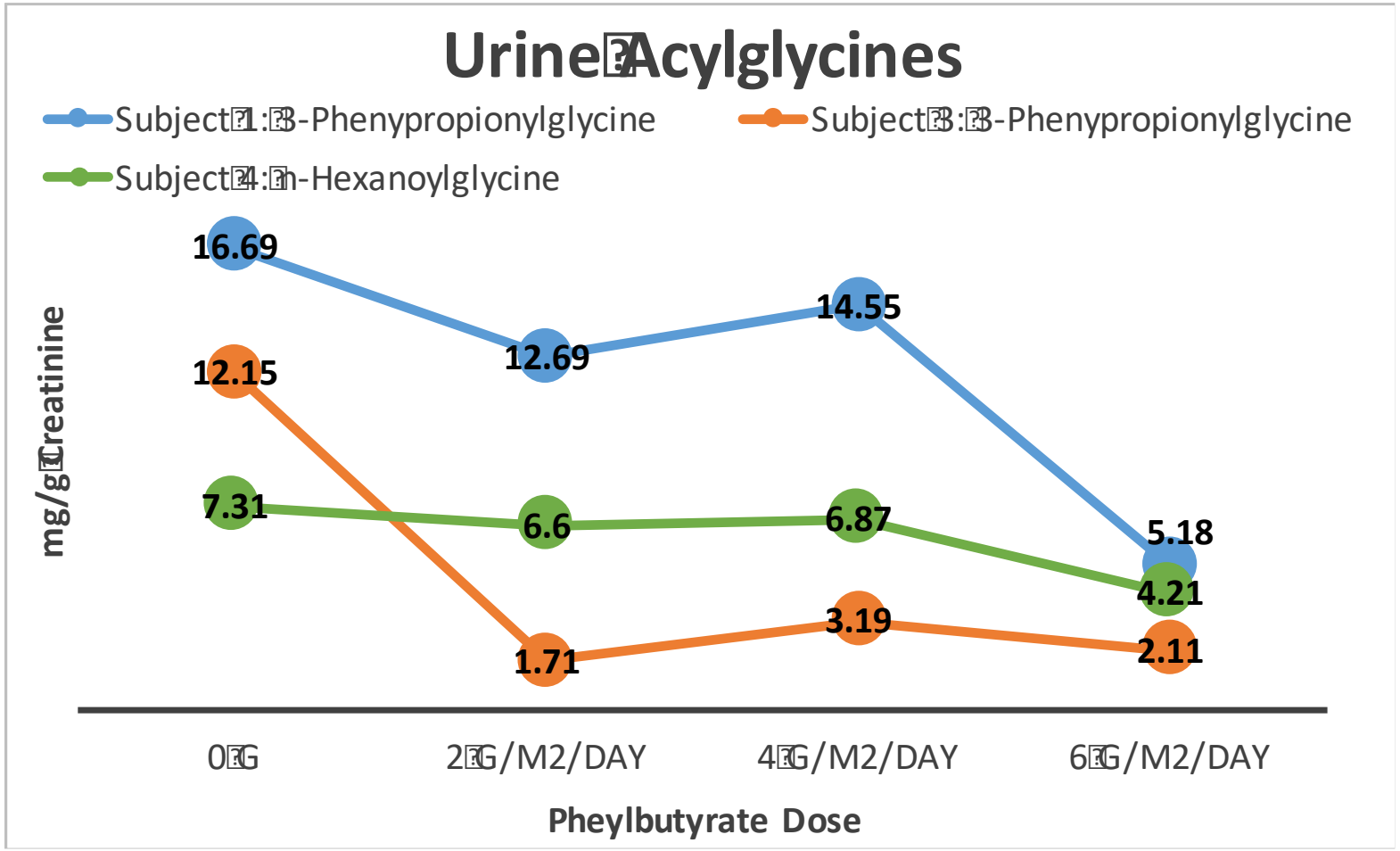
- K304E MCAD mutation is a folding defect
- MCAD metabolizes phenylbutyryl-CoA as substrate
- Binding pocket analogues are strong chaperonins
- Phenylbutyryl-CoA as a chaperonin therapy for MCAD deficiency

MCAD and phenylbutyrate



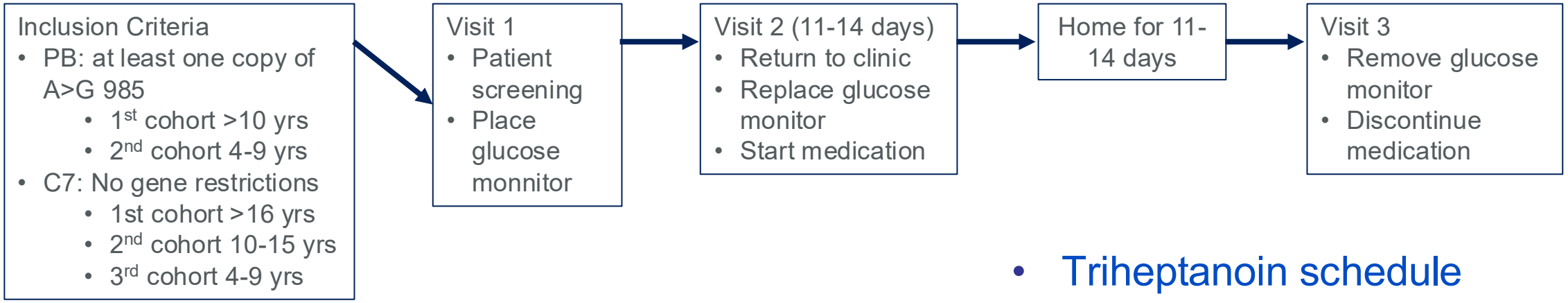


Clinical trial urine acylglycines



Jerry Bedoyan

MCADD rotocol designs



- Study end points
  - Prevention of hypoglycemia
  - Reduction of fatty acid oxidation intermediates
  - Improvement in patient wellbeing (PEDs SQL)

- Triheptanoin schedule
  - Days 1-4: 0.2 gm/kg
  - Days 5-8: 0.35 gm/kg
  - Days 9-12: 0.5 gm/kg triheptanoin
  - Days 13-16: 0.7 gm/kg
  - Days 17-20: 0.85 gm/kg triheptanoin
  - Days 21-24: 1.0 gm/kg

Results

Glucose level	Patient 1		Patient 2	
mg/dl	Pretreatment	Treatment	Pretreatment	Treatment
< 40	0	0	4	0
40-50	0	0	2	0
51-60	0	0	3	0
61-70	6	0	14	0
71-80	21	0	122	0
>80	All the rest			

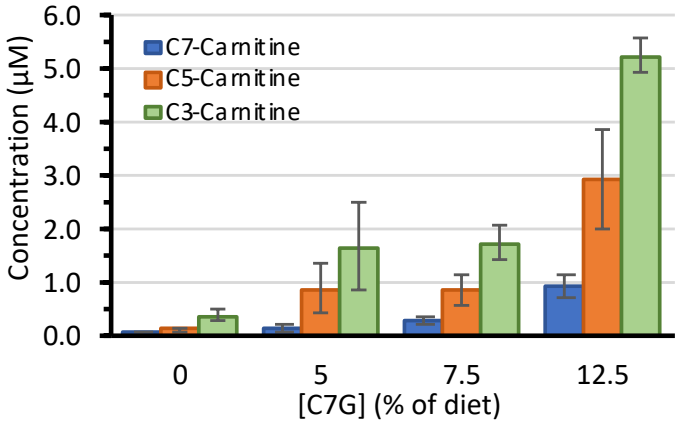
MCADD cells efficiently utilize C7-CoA as substrate

Fibroblast Cells	Specific Activity (nmol ETF_{red}·min^{-1}·mg^{-1}; mU/mg) ±SD*				C7/C4 (%)
	C4-CoA	C7-CoA	C8-CoA	C16-CoA	
Control	0.93 ±0.20	1.93 ±0.13	2.18 ±0.07	4.13 ±0.43	208
MCADD	1.00 ±0.16	0.51 ±0.03	Not Detectable	2.64 ±0.30	51
Enzyme	**Specific Activity (µmol ETF_{red}·min^{-1}·mg^{-1}; U/mg) ±SD***				
hSCAD	17.61 ±5.71	3.69 ±0.14	0.06 ±0.004	N/A	21

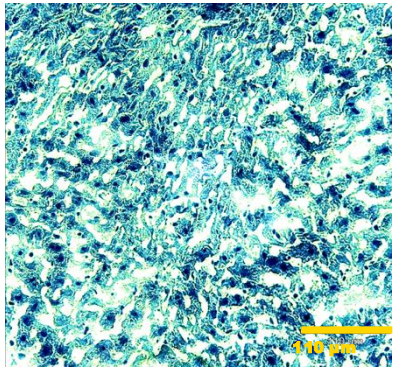
*n=3

Triheptanoin decreases steatosis in MCADD liver

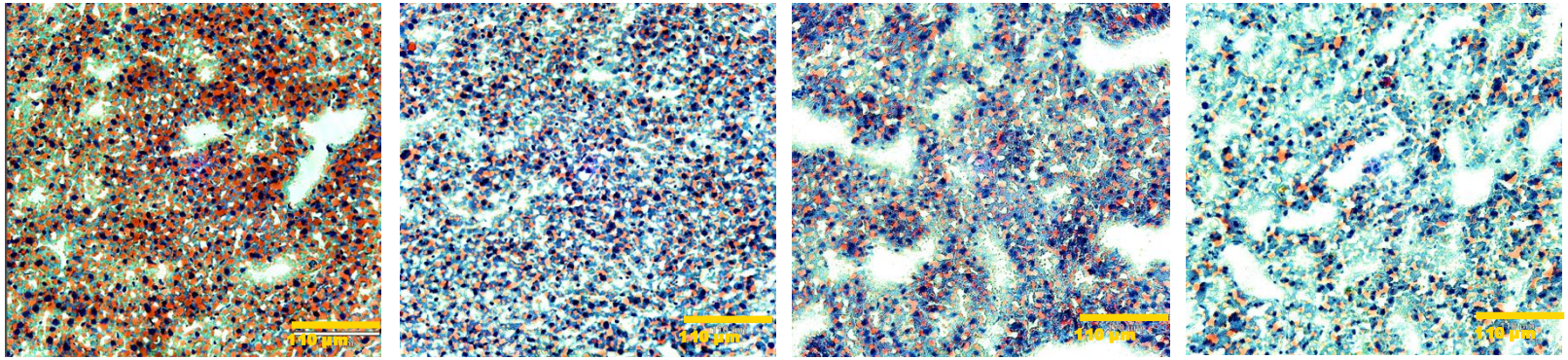
Plasma acylcarnitines



(Oil Red O stain)



Wild Type
(Untreated)



Acadm$^{-/-}$
(Treated)

0% 5% 7.5% 12.5%*

*C7 percent of diet weight

Thanks to my lab and collaborators

Walid Mohsen
Eric Goetzman

Questions