

Novel therapies for inborn errors of fatty acid oxidation: A personalized medicine approach

Jerry Vockley, M.D., Ph.D.

University of Pittsburgh

Cleveland Family Endowed Chair in Pediatric Research

Children's Hospital of Pittsburgh

Chief of Medical Genetics

Director of the Center for Rare Disease Therapy



Center for Rare Disease Therapy

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HOSPITAL OF PITTSBURGH

Monthly Mito

EXPERT SERIES



WELCOME!



*Fatty Acid Oxidation
Disorders: the Other
Mitochondrial Energy Diseases*

Dr. Jerry Vockley, MD, PhD

- University of Pittsburgh Children's Hospital
- International Network for Fatty Acid Oxidation Research and Management (INFORM)



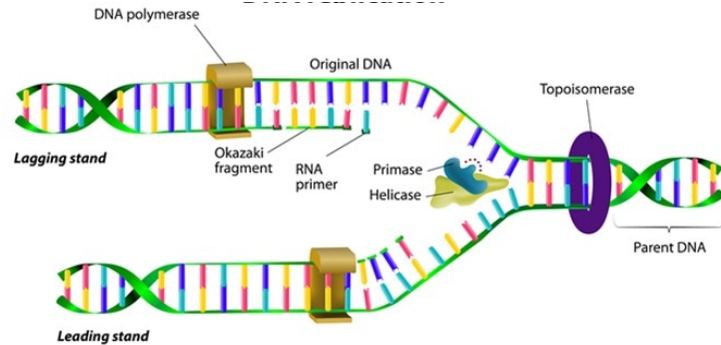
Conflicts of Interest

- Research funding
 - NIH
 - Ultragenyx Pharmaceuticals
 - Reneo Pharmaceuticals
 - Reata Pharmaceuticals
 - Moderna Pharmaceuticals
 - Biomarin Pharmaceuticals
- Consulting
 - American Gene Technologies
 - Moderna Pharmaceuticals
 - Cobalt, Inc
 - DNARx
 - Rand Corporation

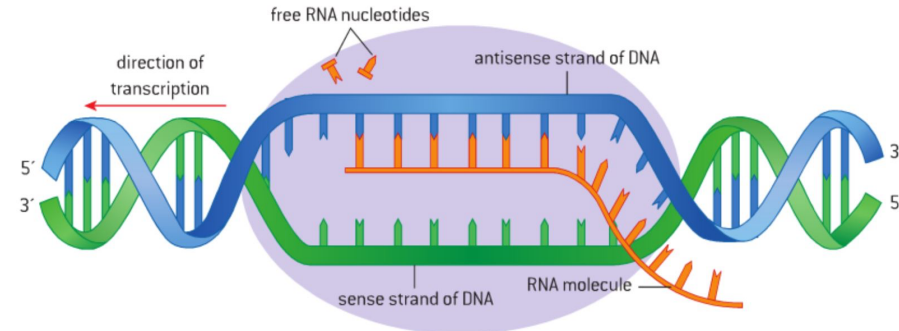


The central dogma

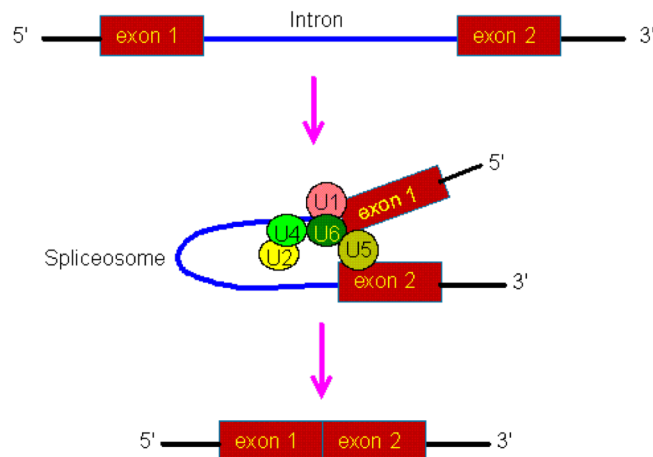
DNA replication



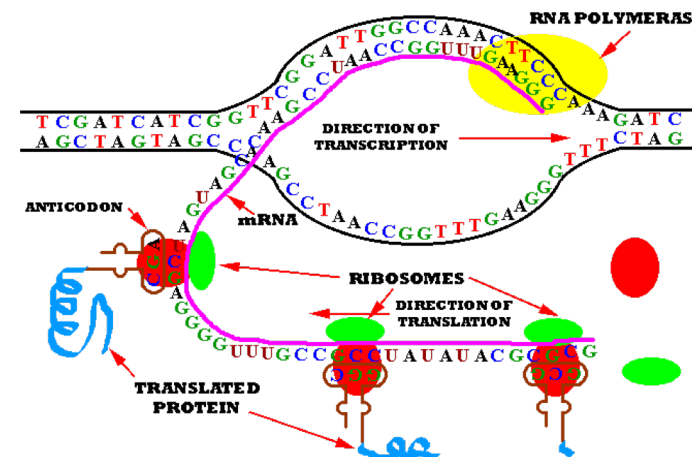
DNA transcription



RNA Splicing

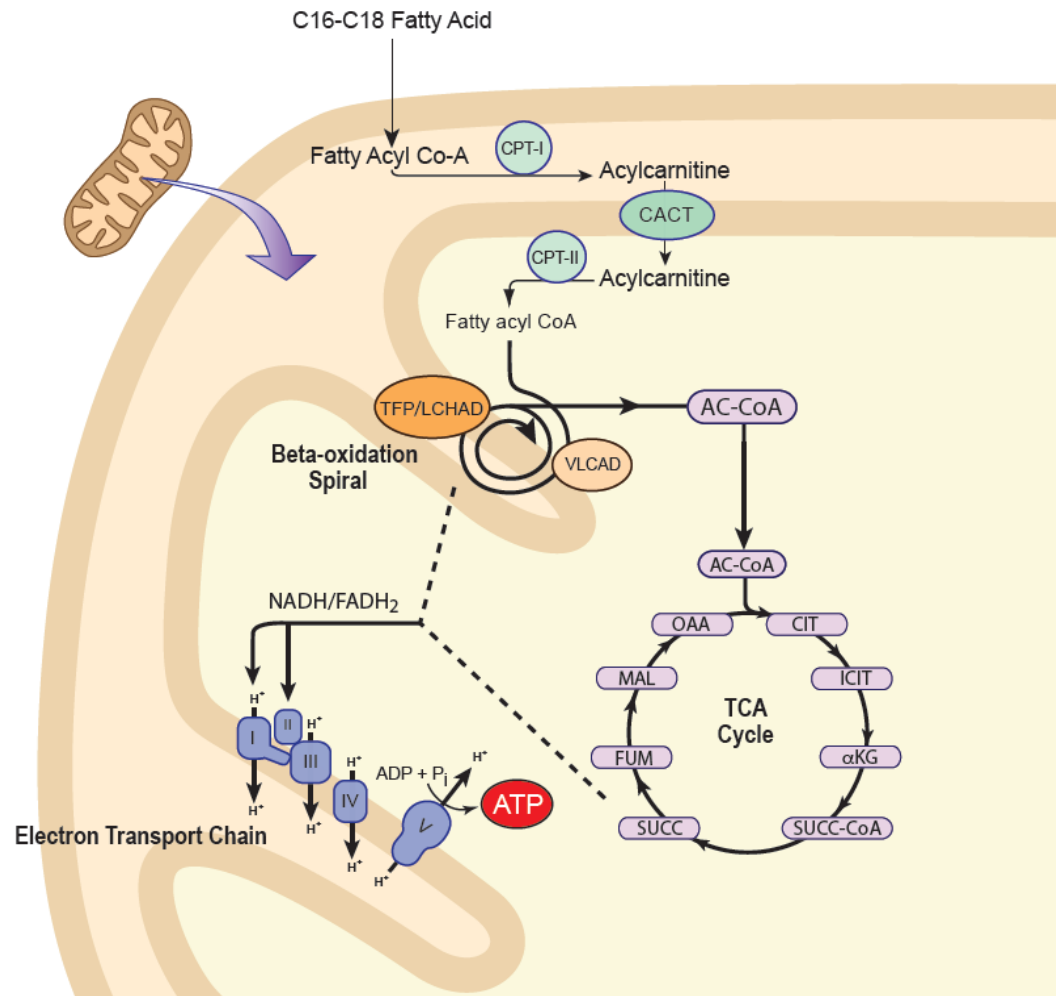


mRNA translation





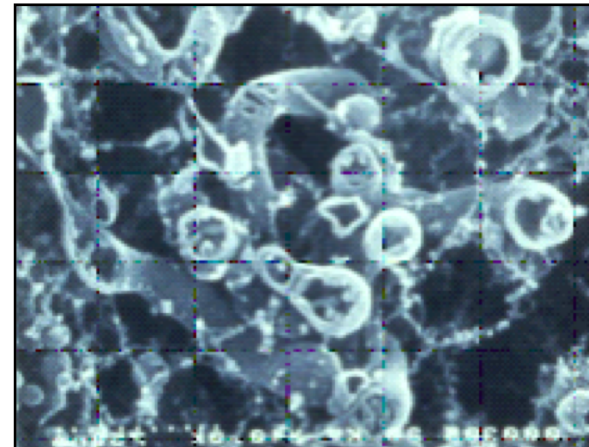
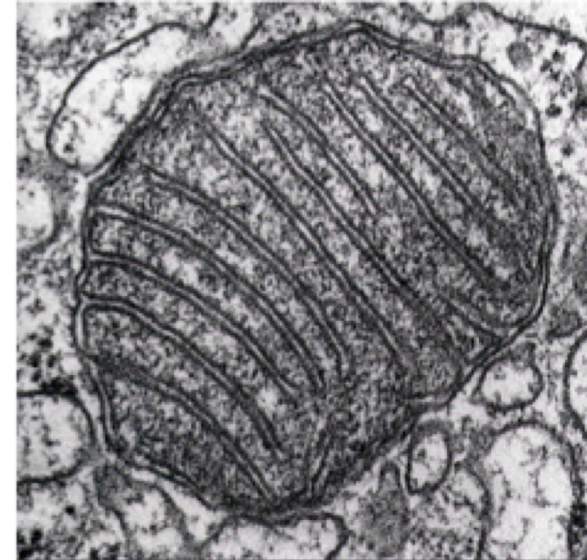
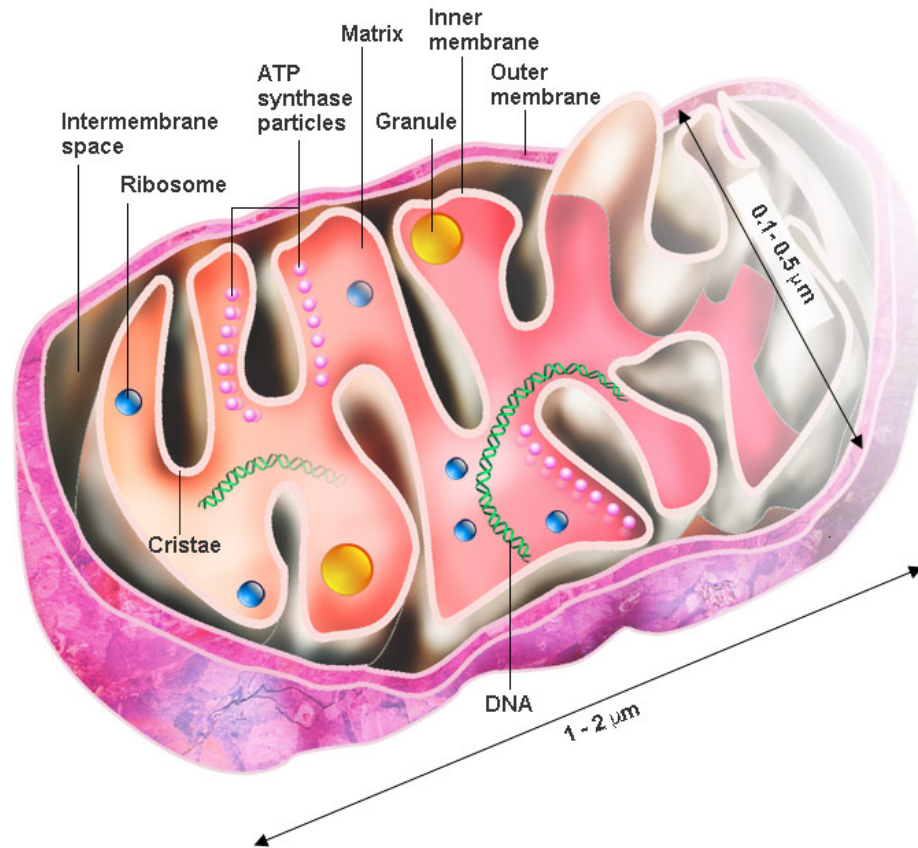
Energy metabolism interactions



- Multiple pathways
- Functionally and physically interact
- Overlap in clinical symptoms
- Secondary symptoms may dominate clinical picture



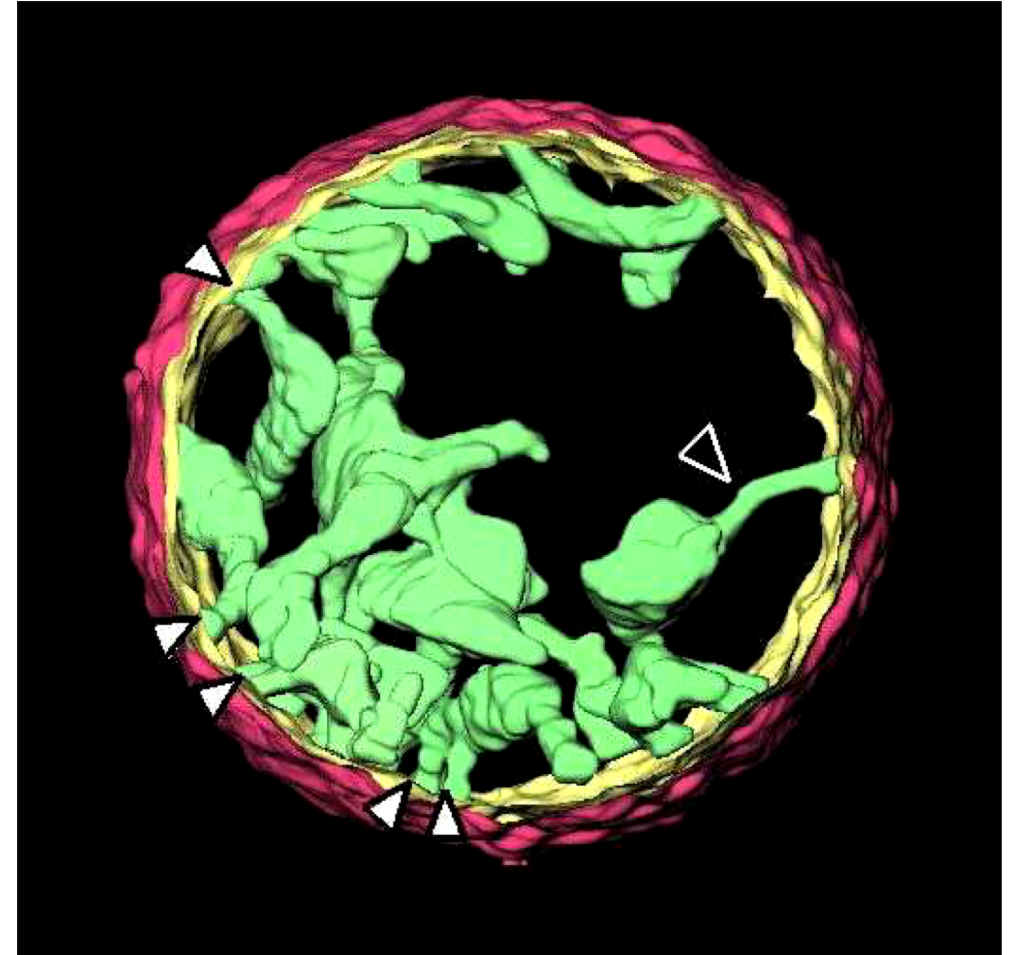
The mitochondrion





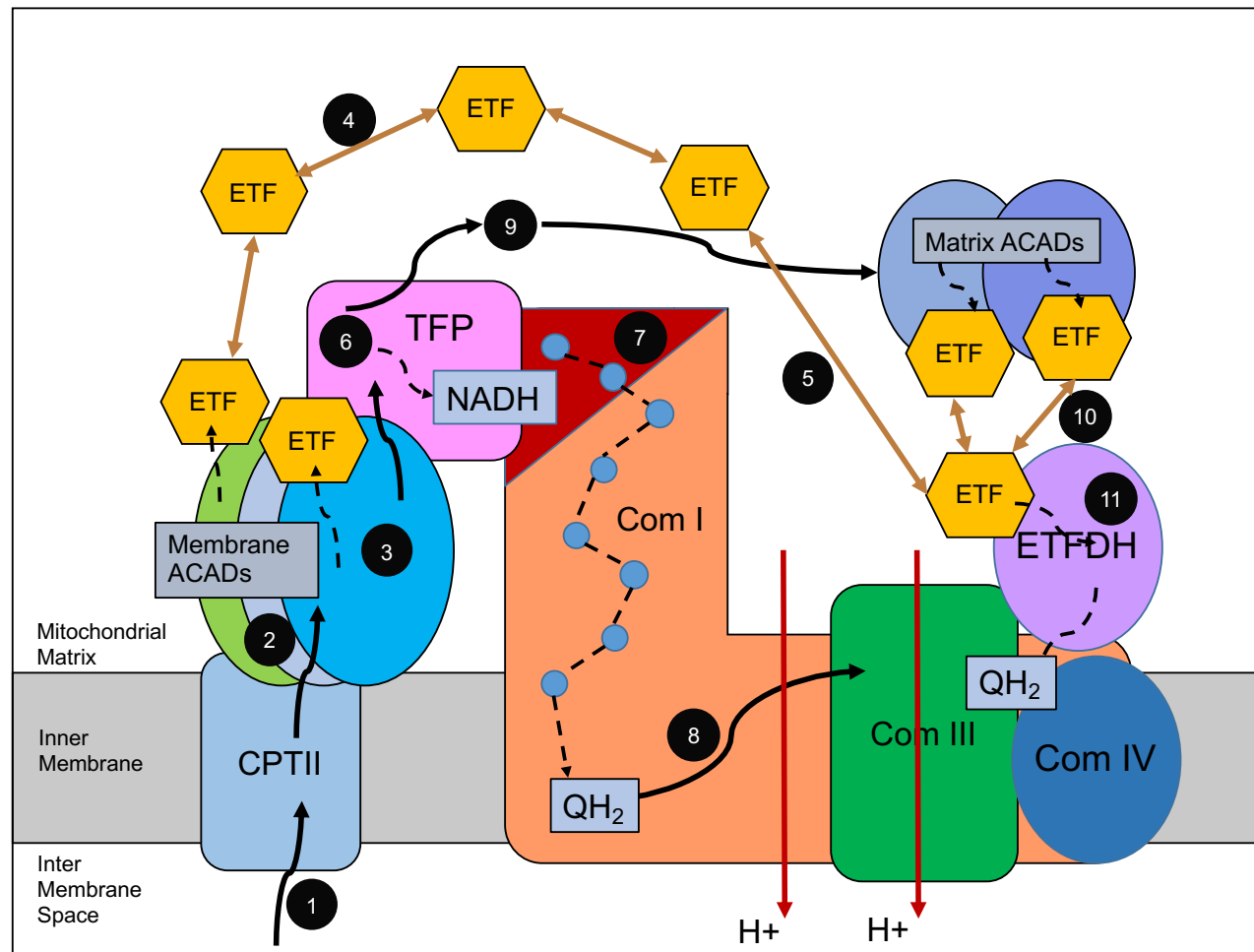
Mitochondria

- 100s-1000s per cell
- Bacterial origins
- Cytoplasmic
- Subcellular organelles
- Dynamic, pleomorphic, motile





Energy protein complex model





Clinical implications



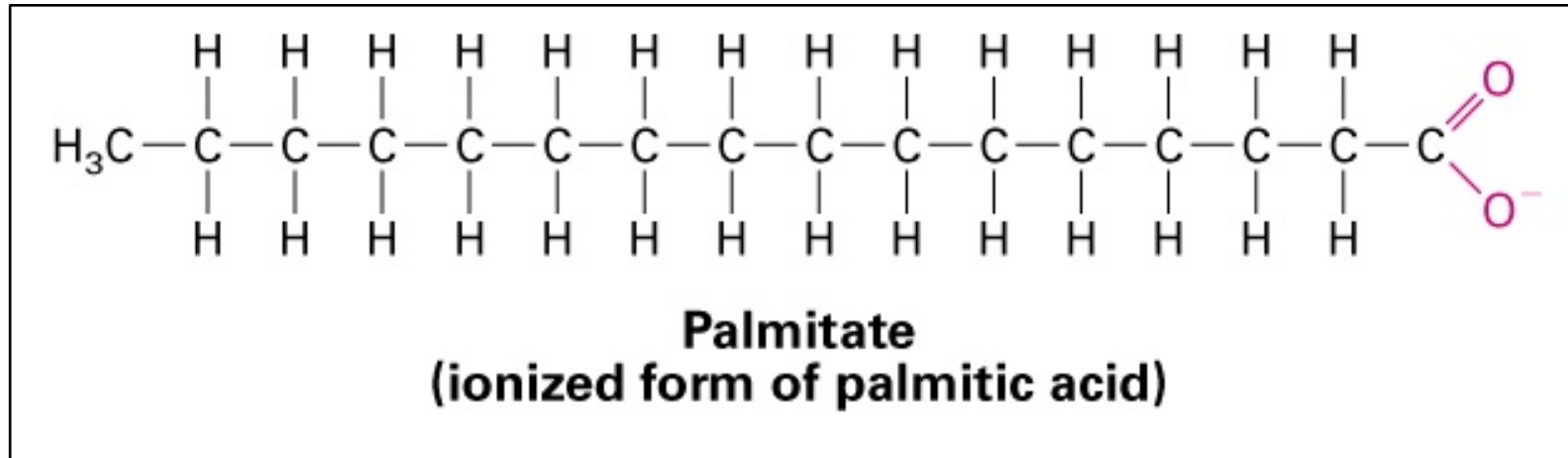


A house of cards





Harvesting energy

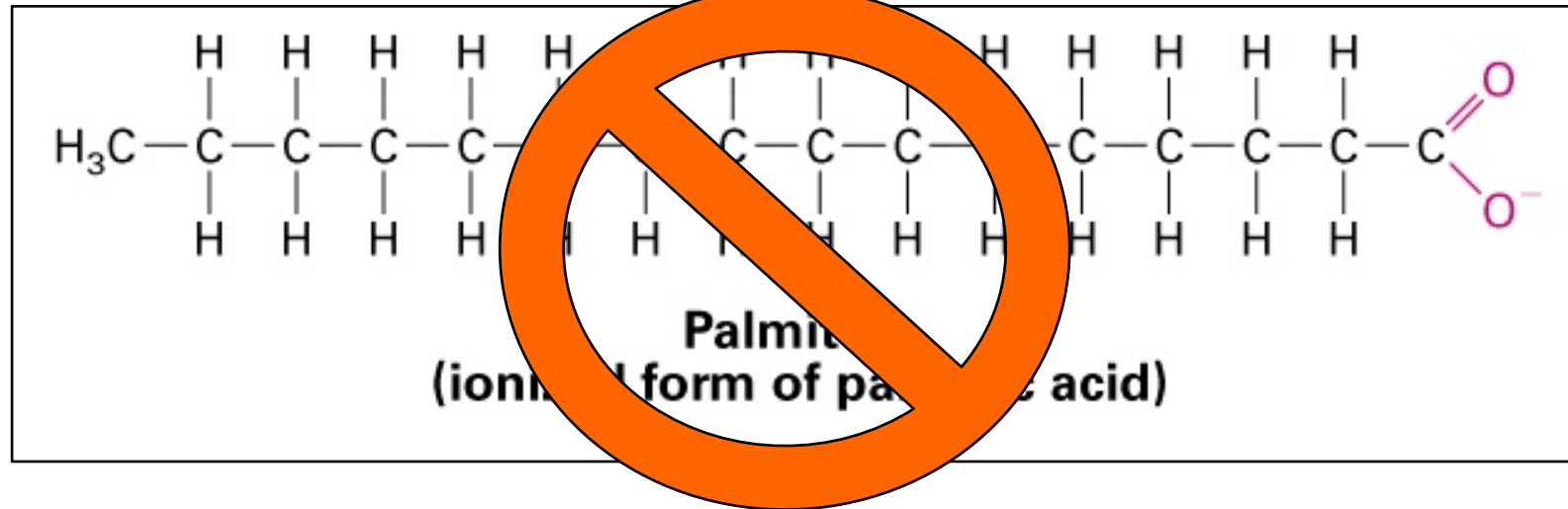


Complete oxidation to CO₂ and H₂O

Source	ATP/molecule	Total ATP
7 FADH ₂	2	14
7 NADH	3	21
8 Acetyl-CoA	10	80
Activation	-2	-2
NET		123



Energy in long chain FAODs

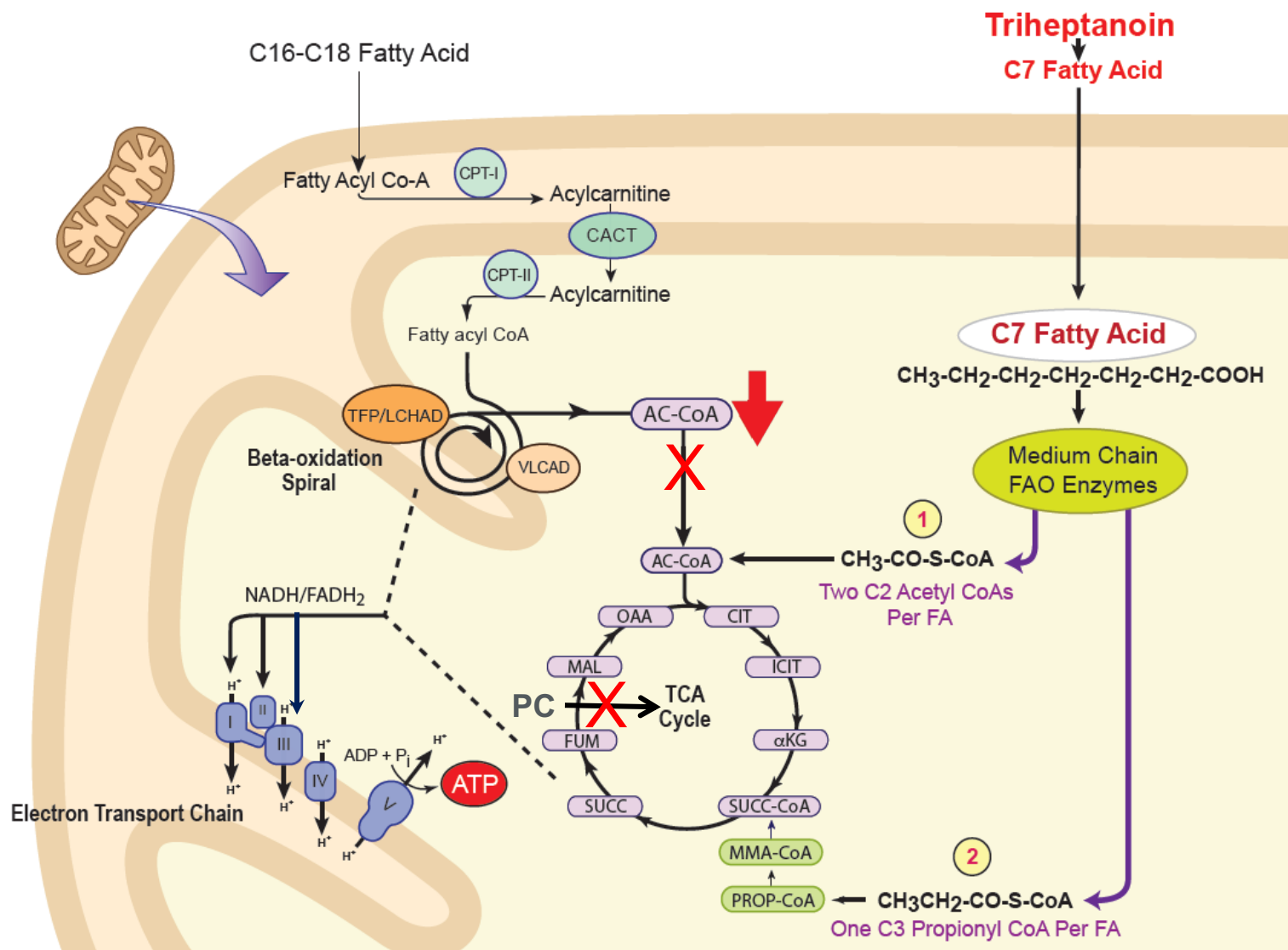


Interrupted oxidation to CO₂ and H₂O

Source	ATP/molecule	Total ATP
7 FADH ₂	0	0
7 NADH	0	0
8 Acetyl-CoA	0	0
Activation	-2	-2
NET		-2

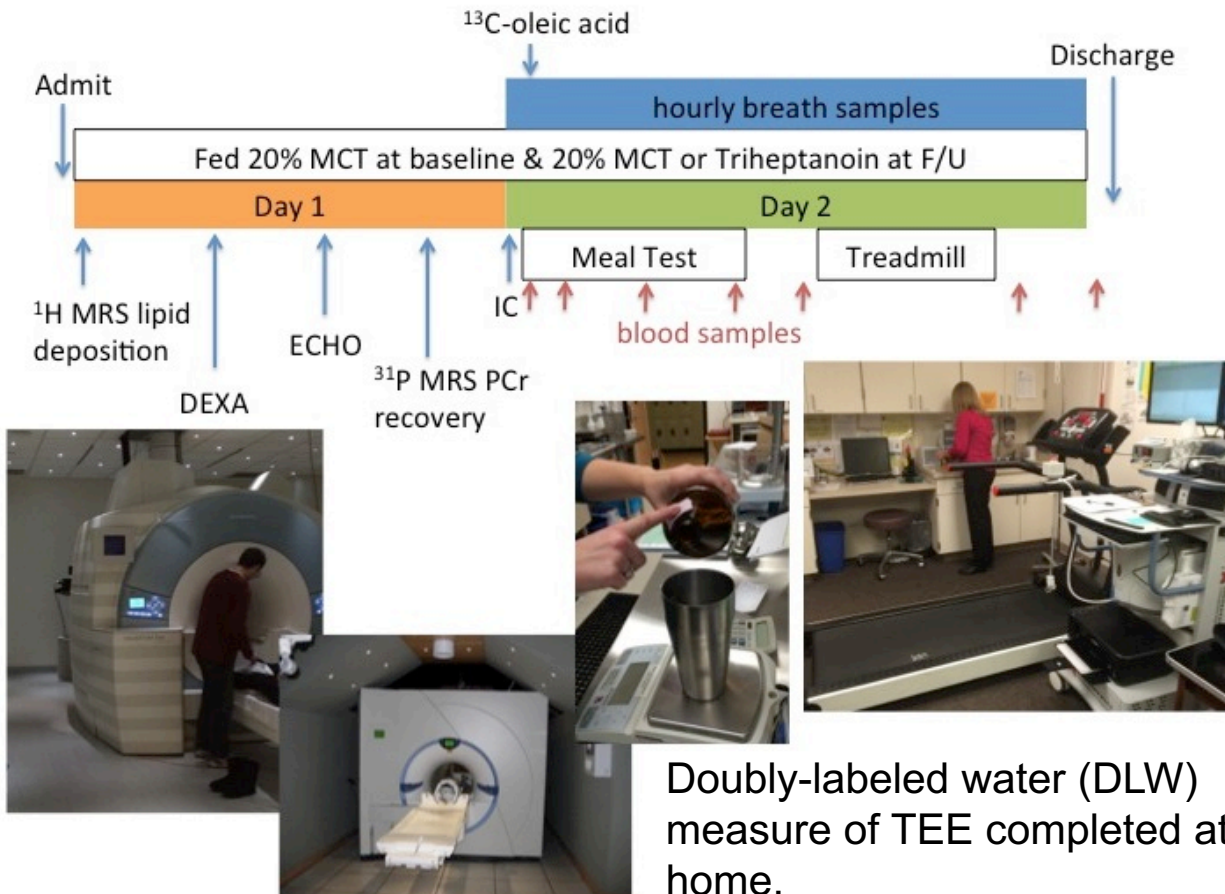


Anaplerotic therapy





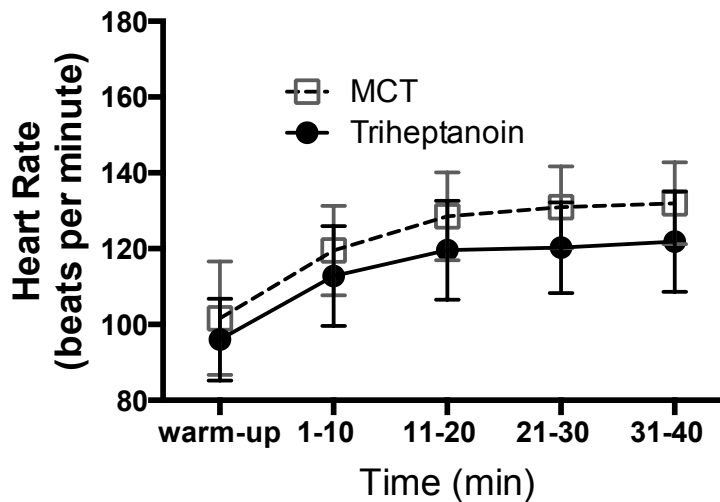
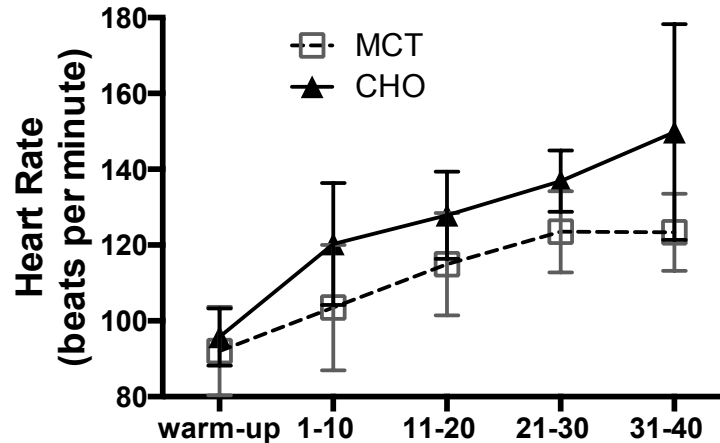
FDA triheptanoin trial



- Double blind comparison of C7 vs C8
- 4 month treatment
- Functional and metabolite before and after treatment



Conclusions



- Triheptanoin similarly tolerated as MCT
- No observed skeletal muscle effect
- **Cardiac effect of triheptanoin**
 - Improved LV ejection fraction
 - Lower HR for same work performed
- Similar CPK, acylcarnitines & ketones



Ultragenyx clinical trial

Characteristic	n (%)
Prior treatment with MCT	27 (93)
Clinical Manifestations	
Skeletal Myopathy	25 (86)
Hepatic Disease	3 (10)
Cardiac Disease	2 (7)
Disease History ^a	
Rhabdomyolysis	26 (90)
Muscle Pain	22 (76)
Exercise Intolerance	21 (72)
Hypoglycemia	18 (62)
Muscle Weakness	16 (55)
Cardiomyopathy	13 (45)

^aOccurring in >32% of subjects.



78 Week outcomes

Major Clinical Event	Mean (SD) Annualized Event/Year			
	Pre-treatment	Post-treatment	% Change	P Value ^b
Overall MCEs	1.69 (1.61)	0.88 (1.14)	-48.1	0.021
Rhabdomyolysis Events	1.30 (1.50)	0.83 (1.15)	-36.1	0.119
Hypoglycemia Events	0.32 (0.91)	0.02 (0.12)	-92.8	0.068
Cardiac Events	0.07 (0.27)	0.02 (0.12)	-69.6	0.309
Hospitalizations ^a	1.39 (1.35)	0.65 (1.01)	-53.1	0.016
Rhabdomyolysis	1.03 (1.90)	0.63 (1.00)	-38.7	0.104
Hypoglycemia	0.30 (0.83)	0	-100.0	0.067
Cardiomyopathy	0.07 (0.27)	0.02 (0.12)	-69.6	0.309



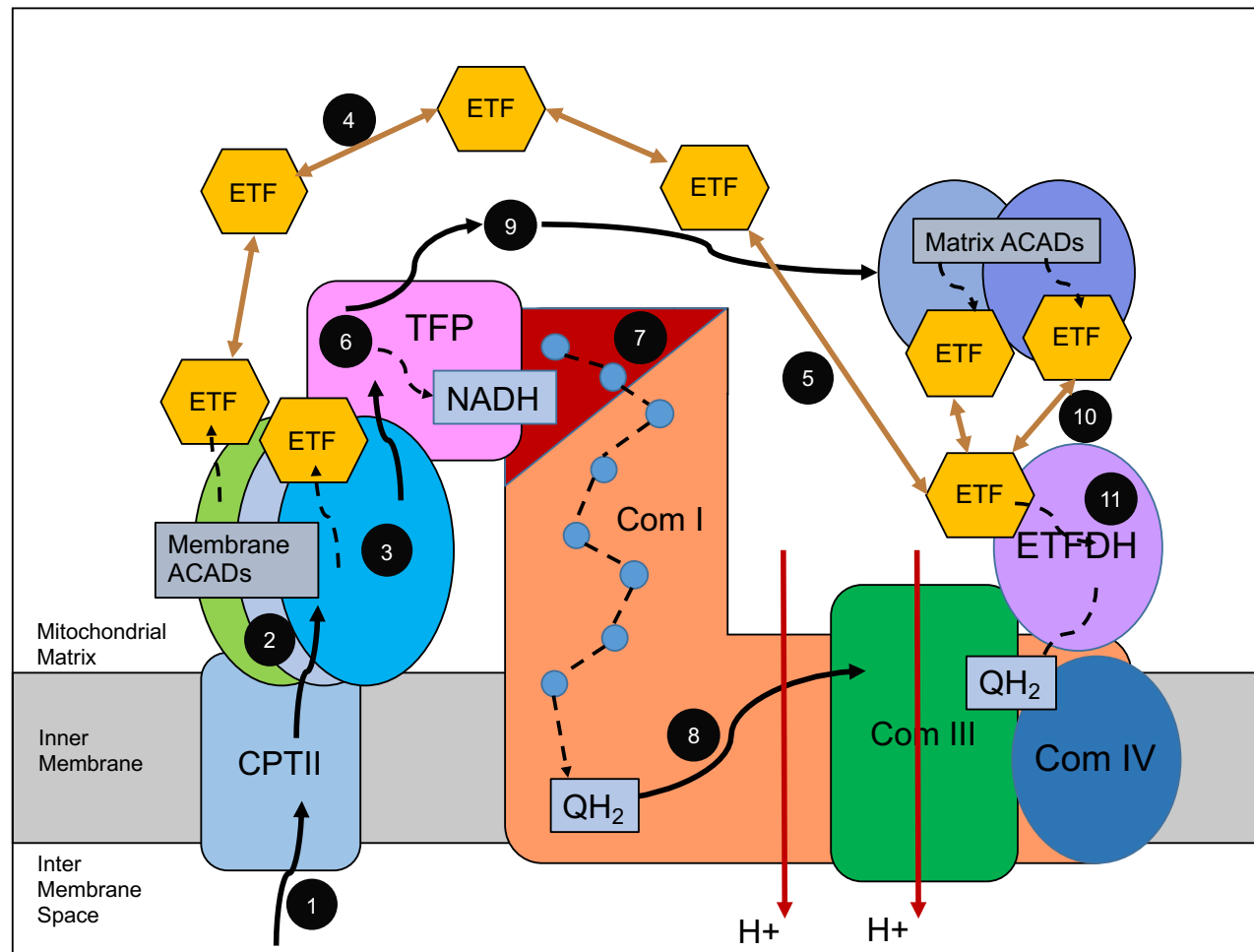
Safety

- 29 subjects (100%) with ≥ 1 treatment emergent adverse event (TEAE)
- 19/29 subjects (66%) had treatment-related AEs
- 19 subjects (66%) serious AEs
 - 1 SAE (gastroenteritis) was considered possibly related to study drug
- No subjects died
- 1 subject discontinued from study (moderate diarrhea)
- 3 subjects discontinued UX007 (unrelated to study drug)
 - Moderate myalgia
 - Mild GE reflux and vomiting
 - Mild pain

Most Frequent TEAEs	%
Diarrhea	55
Rhabdomyolysis	48
Vomiting	48
Upper respiratory tract infection	41
Viral gastroenteritis	34
Headache	31
Pyrexia	31
Abdominal pain	28
Gastroenteritis	21

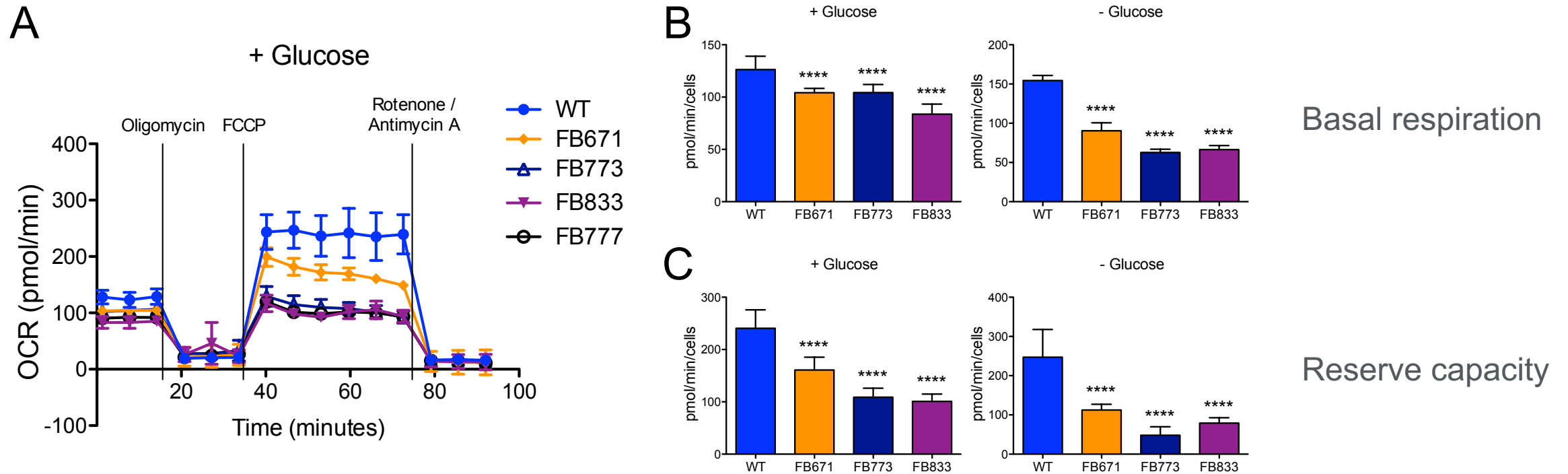


Energy protein complex model



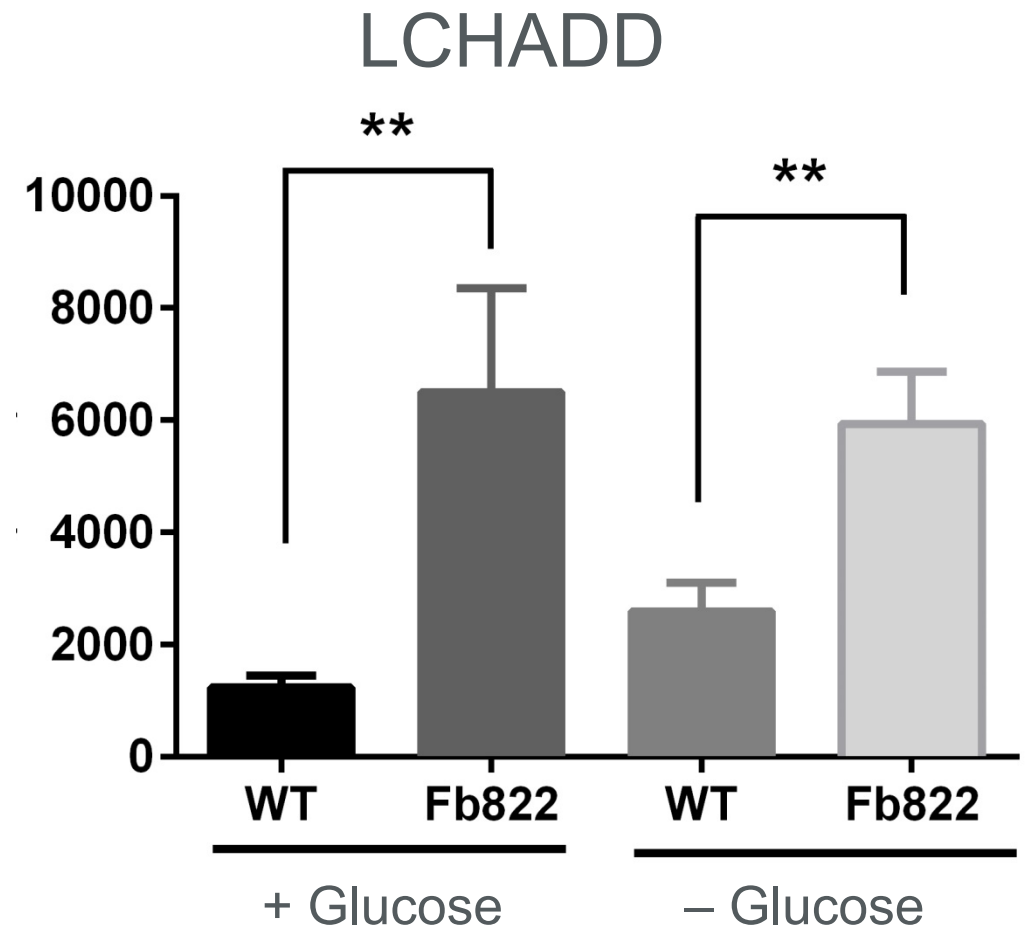
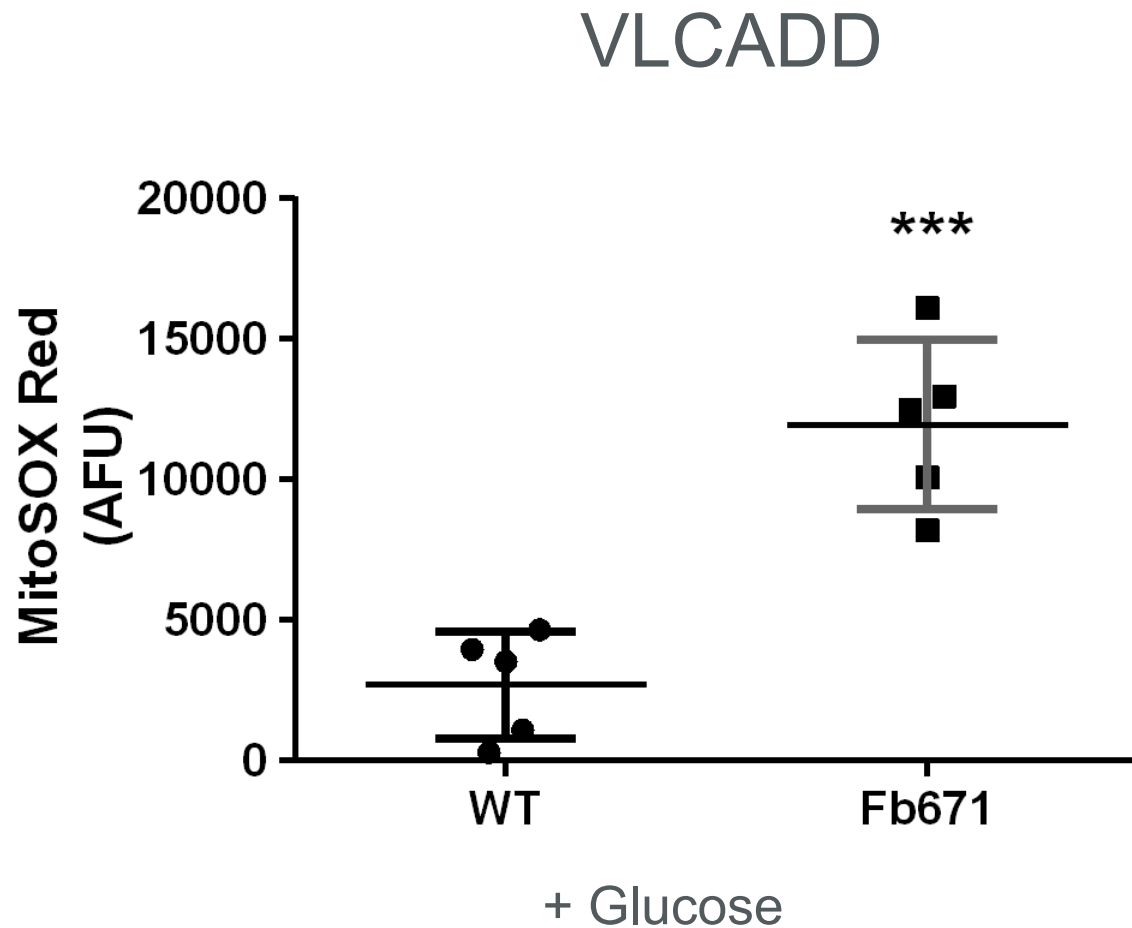


VLCADD oxygen consumption is impaired





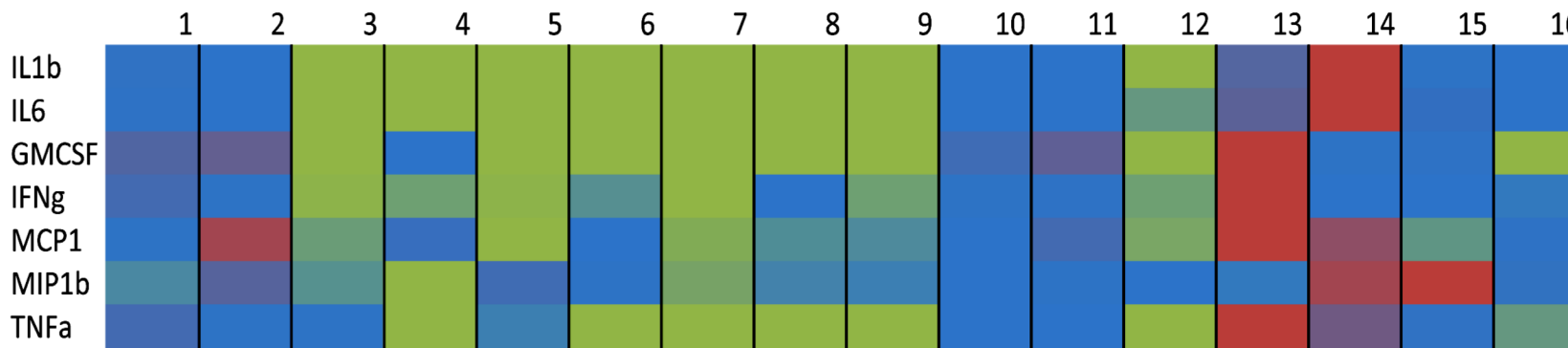
Superoxide production is increased in LC-FAODs





Cytokines in VLCAD patients

(n=16) VLCAD Patient Luminex Cytokine Profiles

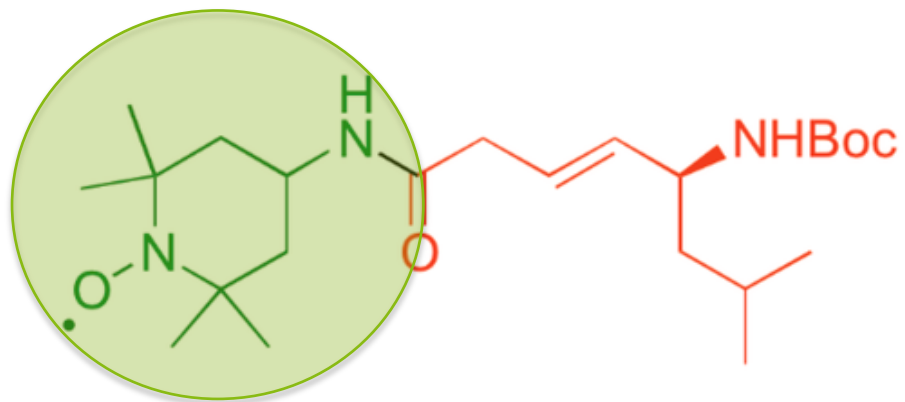


Key:

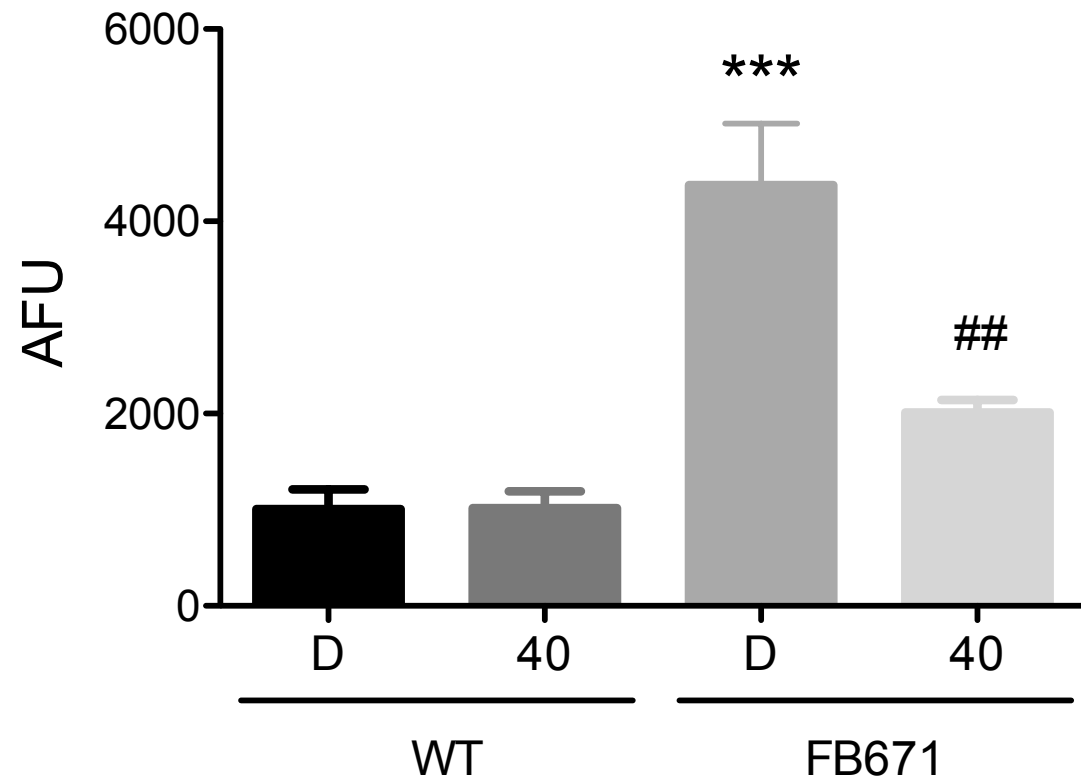
	0	-	141
IL1b (pg/ml)	0	-	141
IL6 (pg/ml)	0	-	591
GMCSF (pg/ml)	0	-	468
IFNg (pg/ml)	0	-	4657
MCP1 (pg/ml)	0	-	278
MIP1b (pg/ml)	0	-	378
TNFa (pg/ml)	0	-	442



Antioxidant treatment of VLCADD

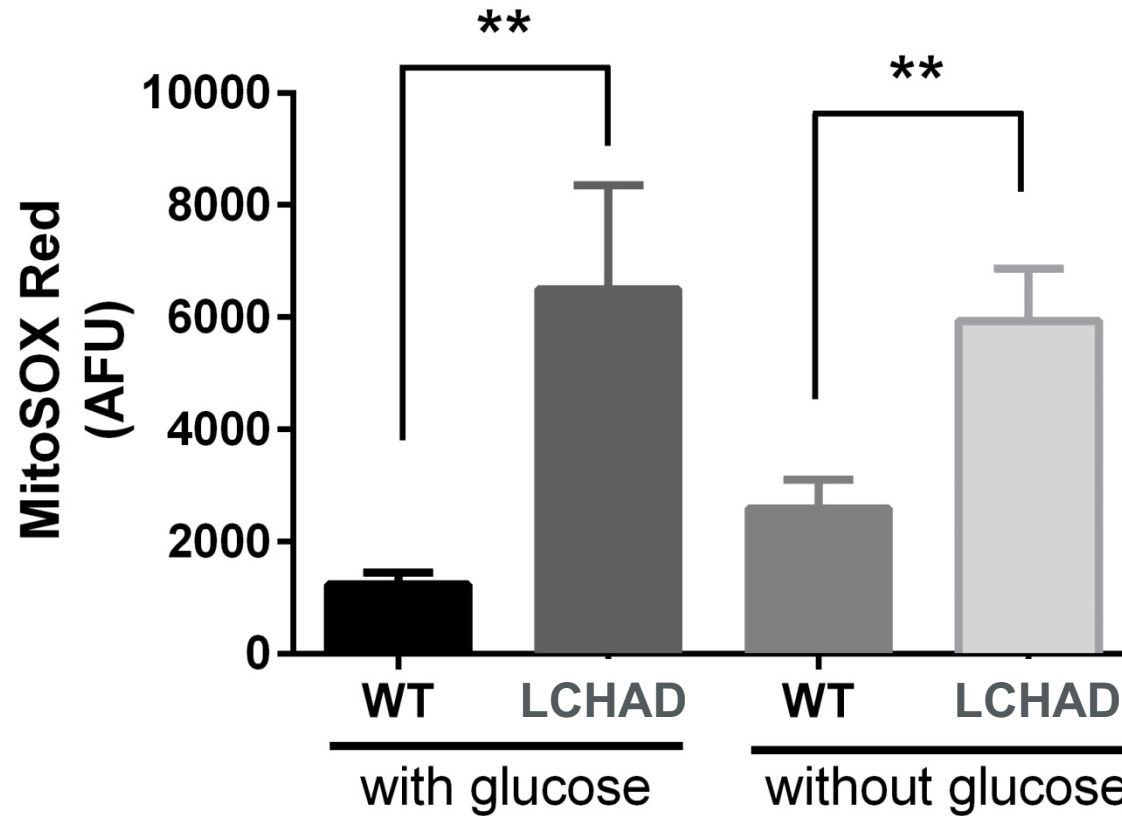


JP4-039





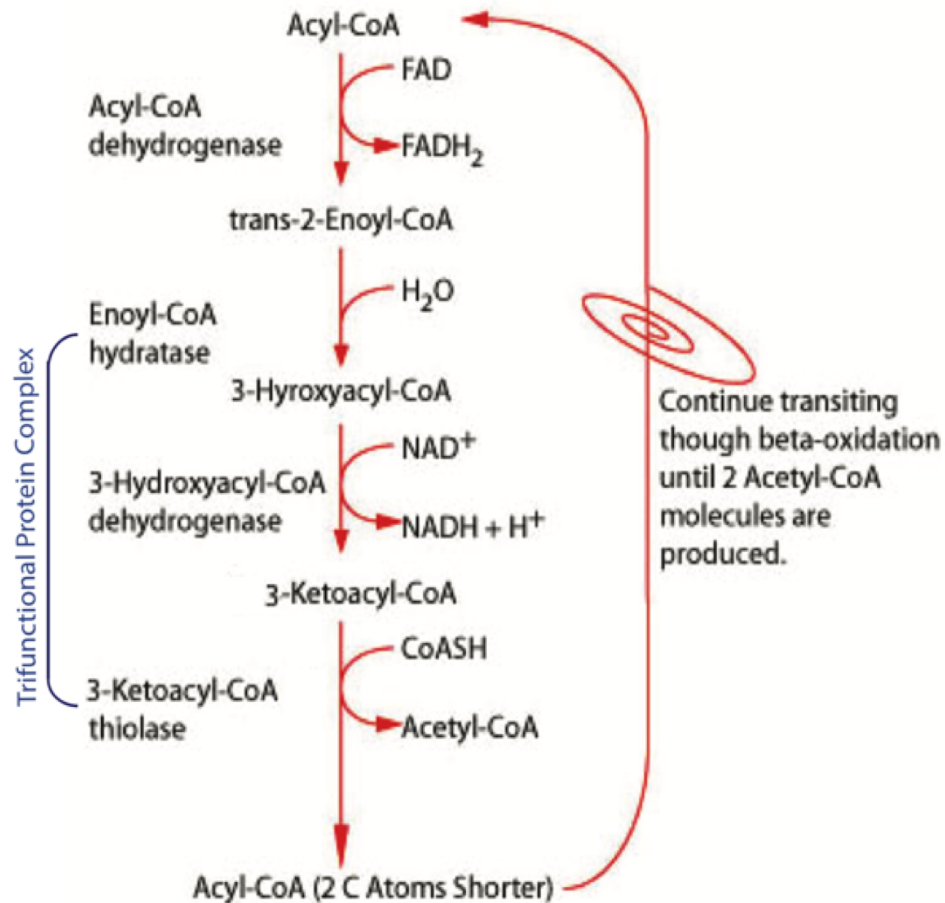
JP4 Rx of LCHADD deficiency



HADHA common mutation 1528G>C mutation

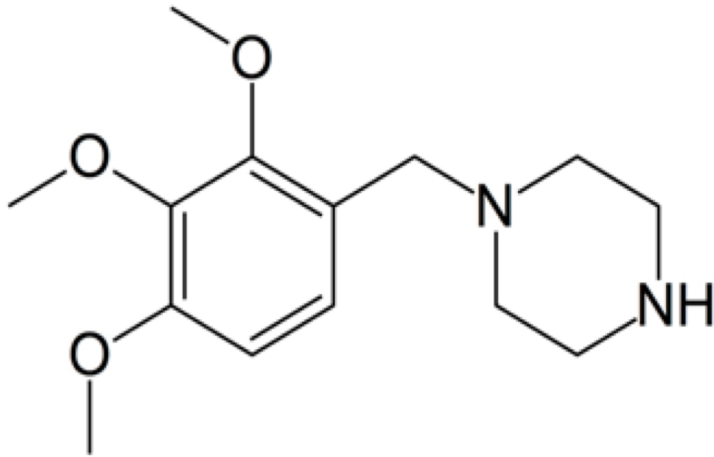


Inhibitor induced chaperonin effect



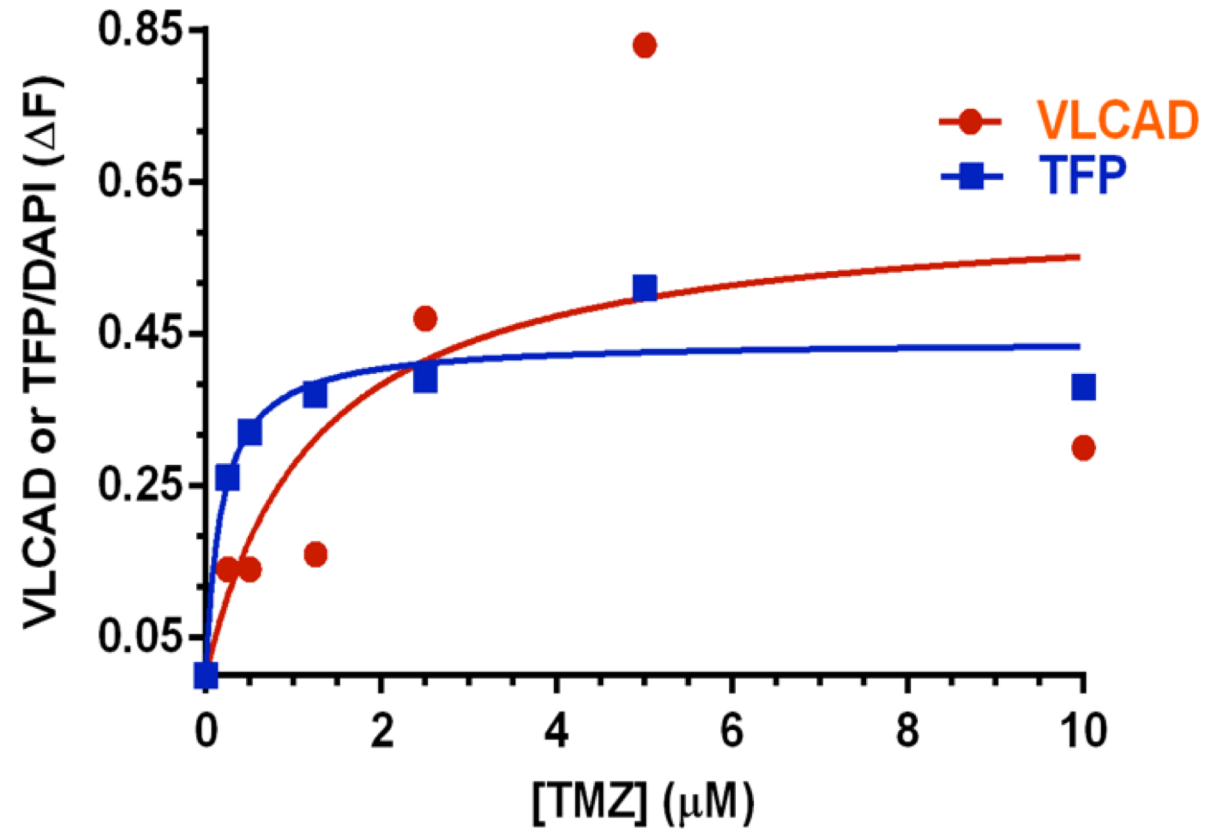


TMZ stabilization of FAO proteins



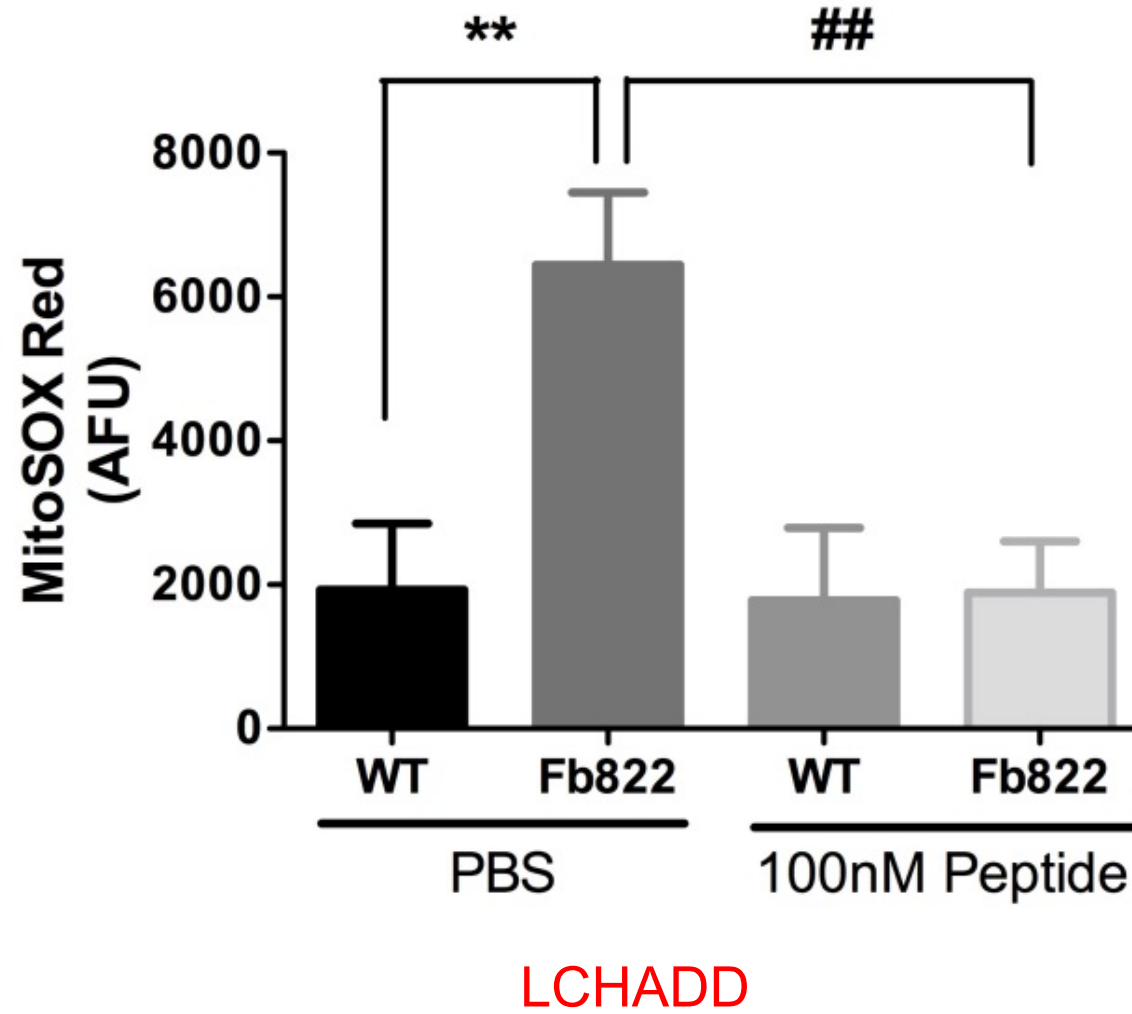
Trimetazidine (TMZ)

VLCADD fibroblasts



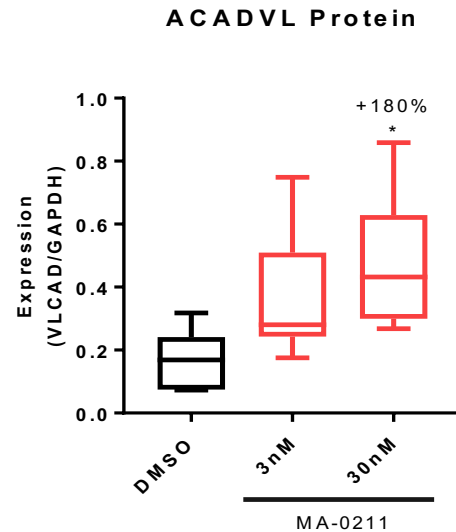
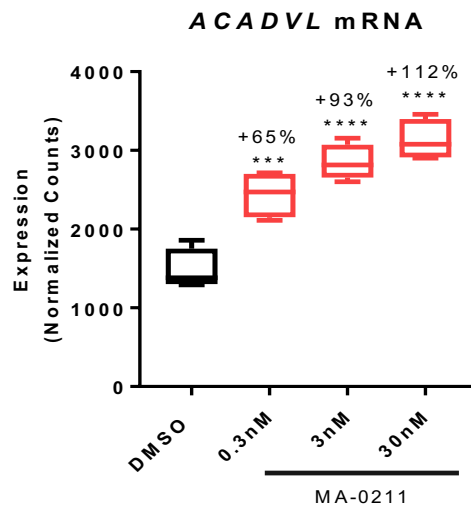


Cardiolipin binding peptide Rx

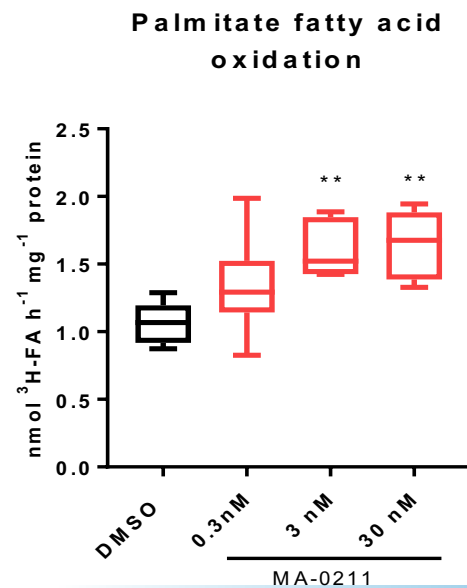
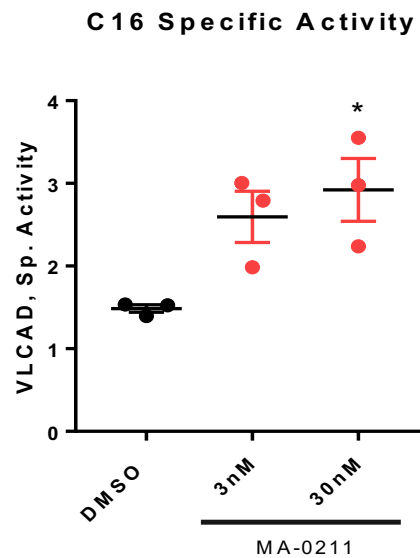




Transcriptional activators



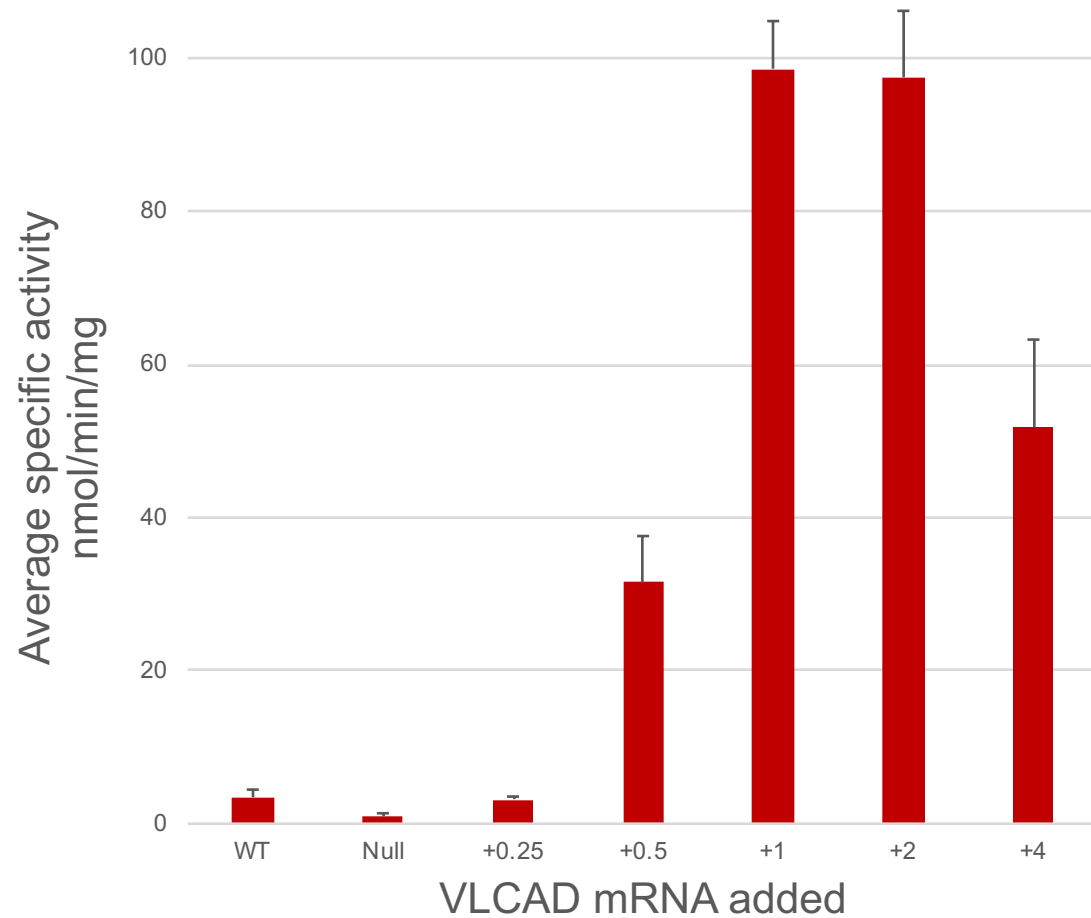
- PPAR δ agonists more potent than bezafibrate
- Increase in expression and function of VLCAD
- Clinical trial starting this year



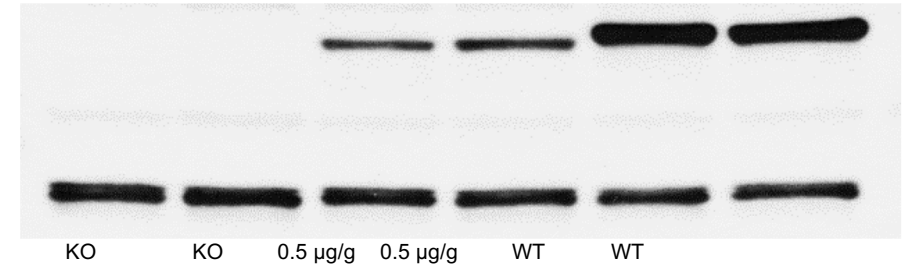
VLCAD patient derived fibroblasts



VLCAD mRNA Treatment

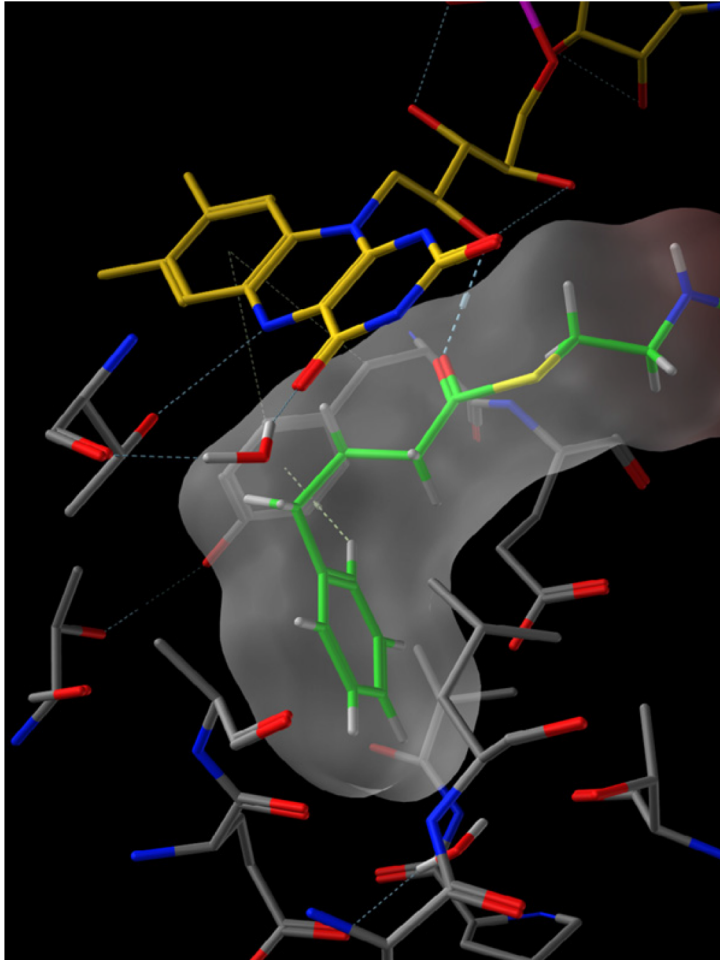


VLCAD
(42 kDa)





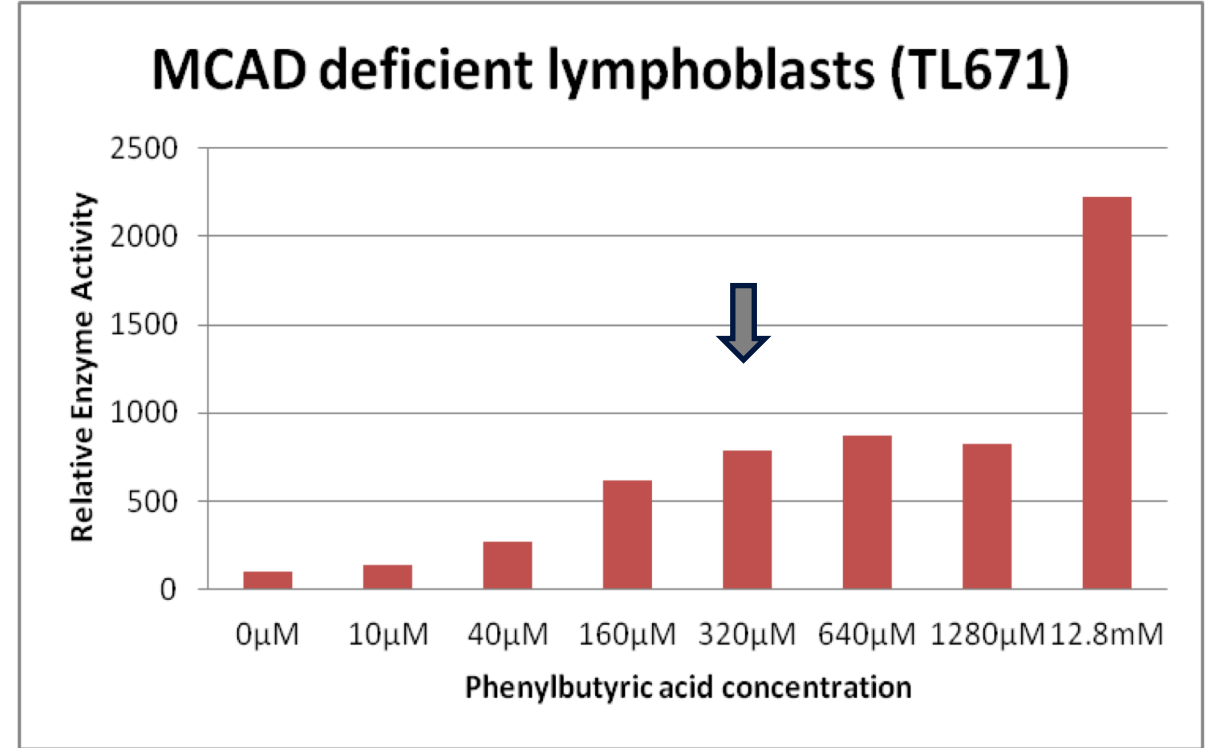
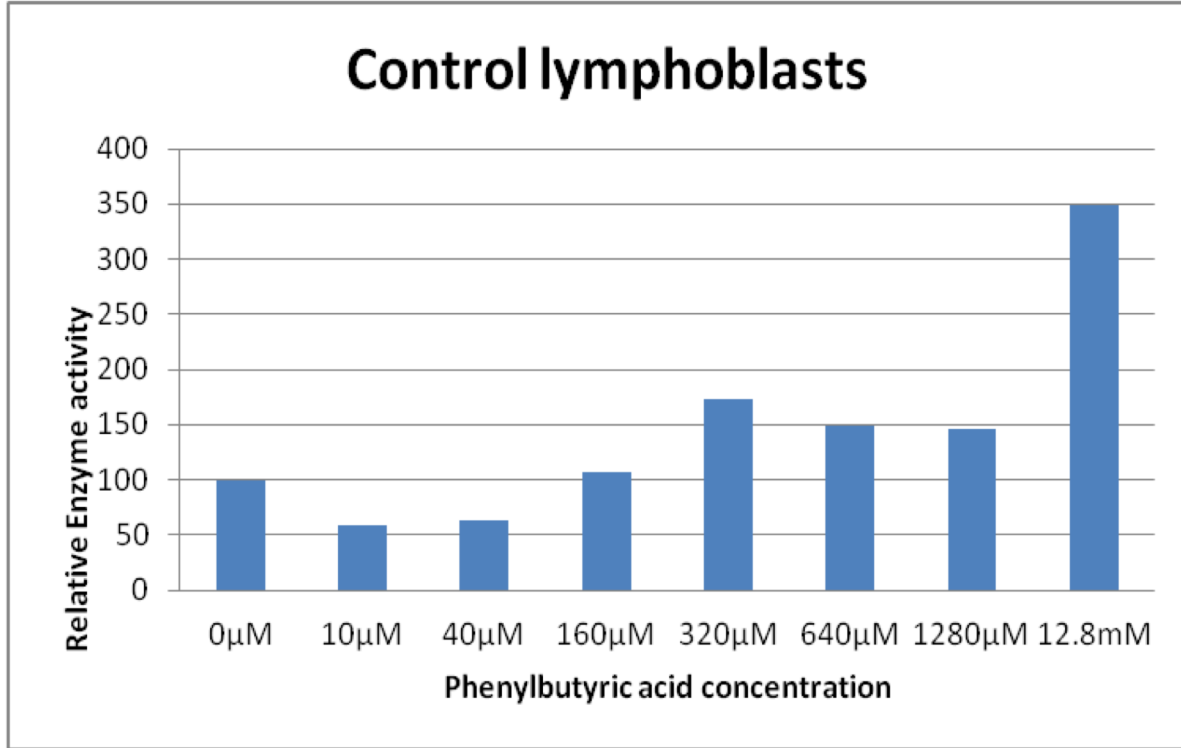
MCAD deficiency



- 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

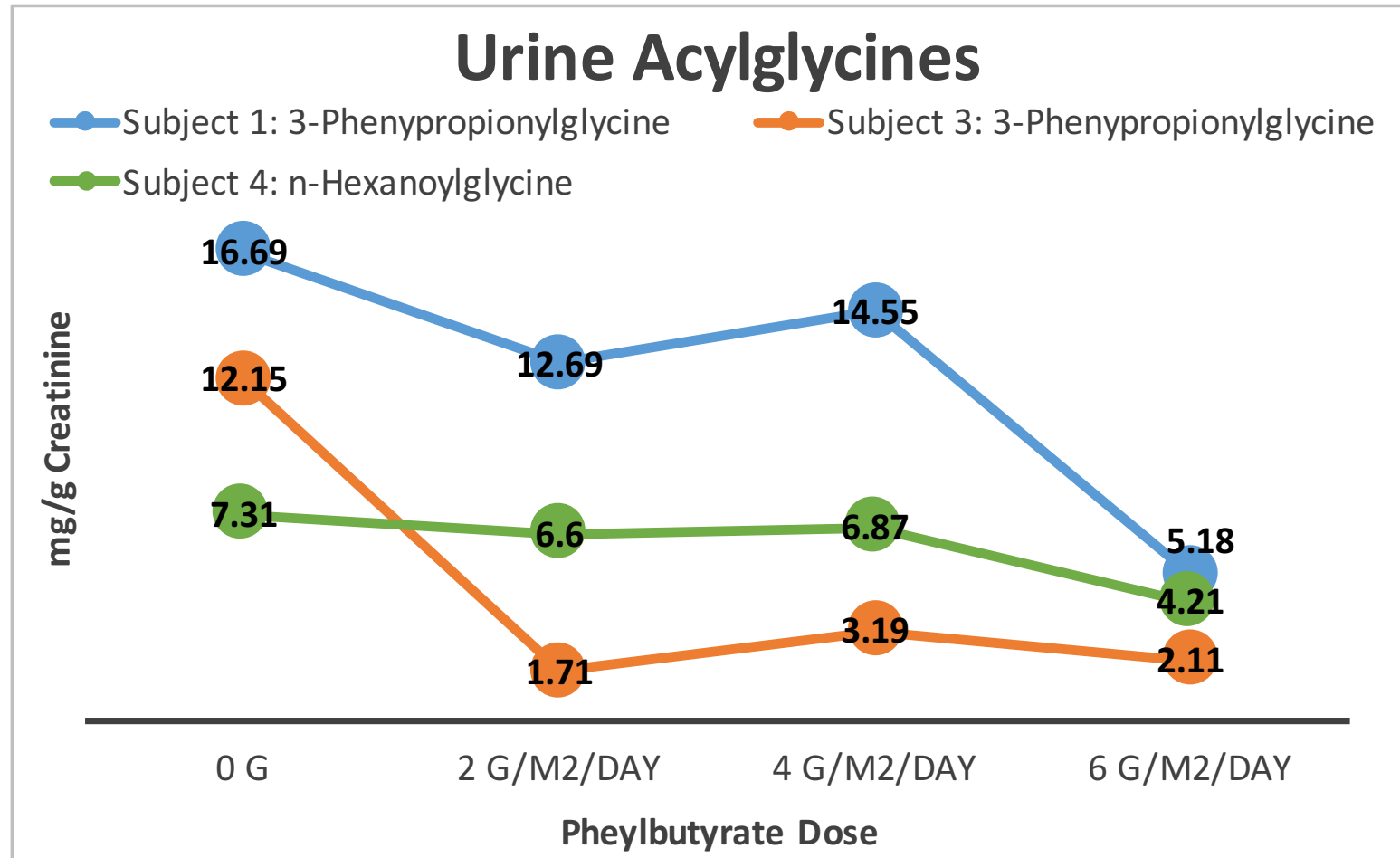


MCAD and phenylbutyrate





Clinical trial urine acylglycines





Collaborators

- Ben Van Houten
- Peter Wipf
- Abbe de Vallejo
- Melanie Gillingham
- James Conway
- Simon Watkins



Thank you!

