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Emerging therapies for FAODs

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Professor of Human Genetics
University of Pittsburgh
Chief of Medical Genetics
Director of the Center for Rare Disease Therapy
Children's Hospital of Pittsburgh

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Mission statement

- The International Network for Fatty Acid Oxidation Research and Management (INFORM) has been formed in order to promulgate information on the research and management of disorders of fatty acid oxidation.
- The Network will provide a collaborative framework for ongoing communication and research between the members.

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Conflicts of interest

- Research funding
  - NIH
  - Ultragenyx
  - Stealth
  - Reata
  - Mitobridge
  - Wellstat
- Consulting
  - American Gene Therapies
  - Mitobridge

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Thanks to Innsbruck

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Welcome to Lyon

INFORM Second Annual Symposium: September 4-5, 2015
Lyon, France

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Mark your calendars!

INFORM Third Annual Symposium: May 9-11, 2016
Boston, MA USA

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Organizing committee

Jerry Vockley, MD, PhD
Co-Chairman
Professor of Human Genetics,
University of Pittsburgh School of Medicine

Ute Spiekerköetter, MD
Co-Chairman
Department of Pediatrics and Adolescent Medicine,
University Children's Hospital, Freiburg, Germany,

Michael Bennett, PhD
Michael J. Palmieri Metabolic Laboratory,
University of Pennsylvania School of Medicine,

Jean Bastin, PhD
INSERM, Hôpital Necker-Enfants Malades

Niels Gregersen, PhD
Professor of Molecular Medicine Research Unit for Molecular medicine,
MMF Aarhus University Hospital, Skejby Brendstrupgaardsvej

Daniela Karall, MD
Department for Child and Adolescent Medicine,
Medical University of Innsbruck

Melanie Gillingham, PhD
Molecular and Medical Genetics Department,
Oregon Health & Science University,

Nicola Longo, M.D., Ph.D
Co-Chair
Professor of Pediatrics
University of Utah School of Medicine

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Sponsors and partners

center for rare disease therapy

Children's Hospital of Pittsburgh | of UPMC

Save Babies Through Screening Foundation, Inc.

ultragenyx

Climb
National Information Centre for Metabolic Diseases

sigma-tau

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Starting line

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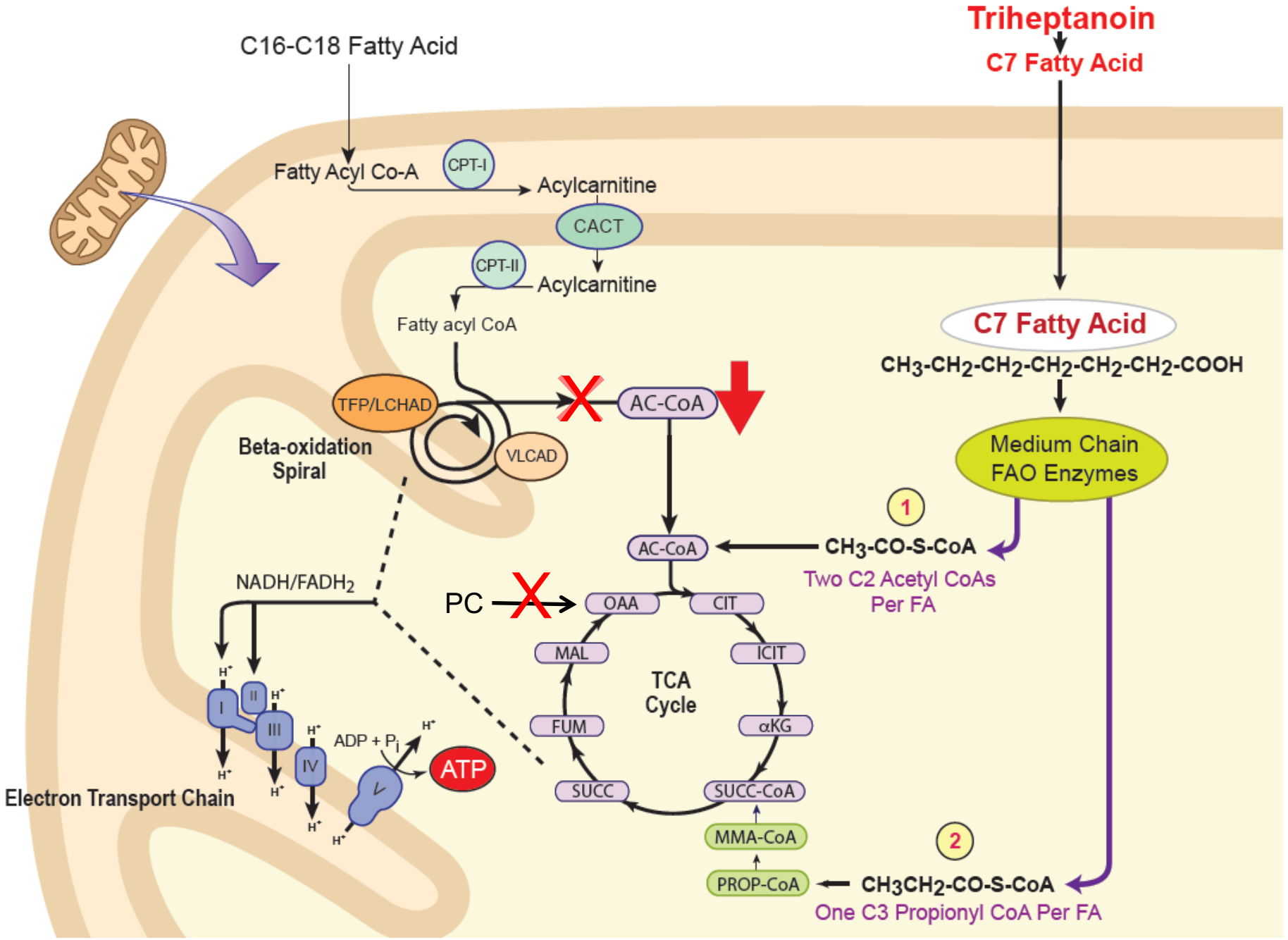
Anaplerotic therpy



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FAODs clinical trials

- Triheptanoin
  - FDA phase 2 complete
  - Publication on compassionate use
  - Phase 3 soon?
- Anti-inflammatories
- Bendavia (Stealth Biotherapeutics)
- RTA408 (Reata Pharm., Inc.)
- Mitobridge
- Uridine
- Ravicti in MCAD (Horizon)

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Triheptanoin Treatment History

Age at Start of Treatment*	Duration of Treatment				
	<1 year	1-2 years	2-5 years	>5 years	Total N (%)
0-1 month (Neonates)	-	-	-	2	2
1 month-2 years (Infants)	1	-	1	3	5
2-12 years (Children)	-	-	-	10	10
12-16 years (Adolescents)	-	-	-	-	-
>16 years (Other)	-	-	1	2	3
Total N (%)	1	-	1	17	20

*Dose levels varied over time and per subject. Target dose levels were initially 2-4 g/kg and later 1-2 g/kg Triheptanoin.

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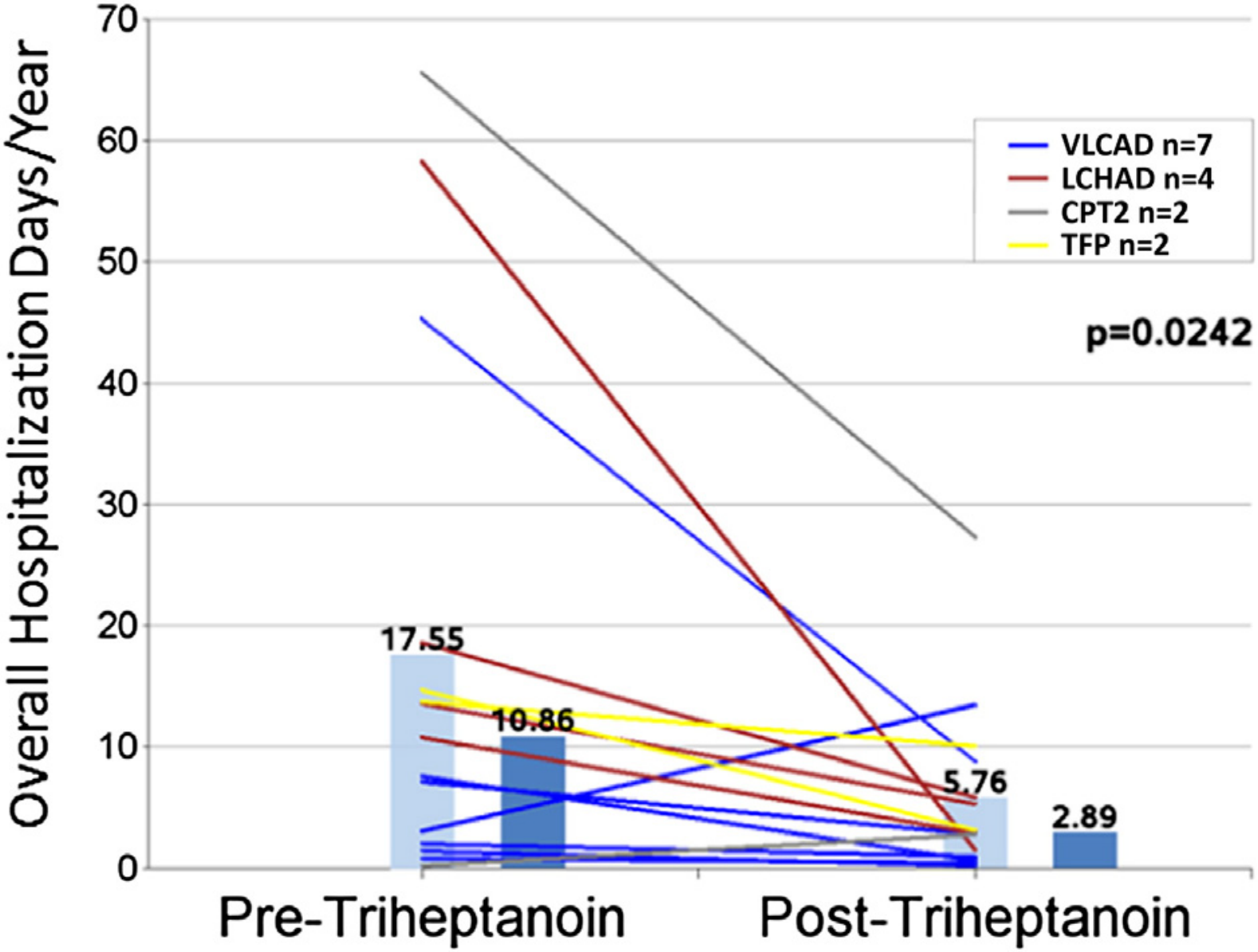
Hospital days/year



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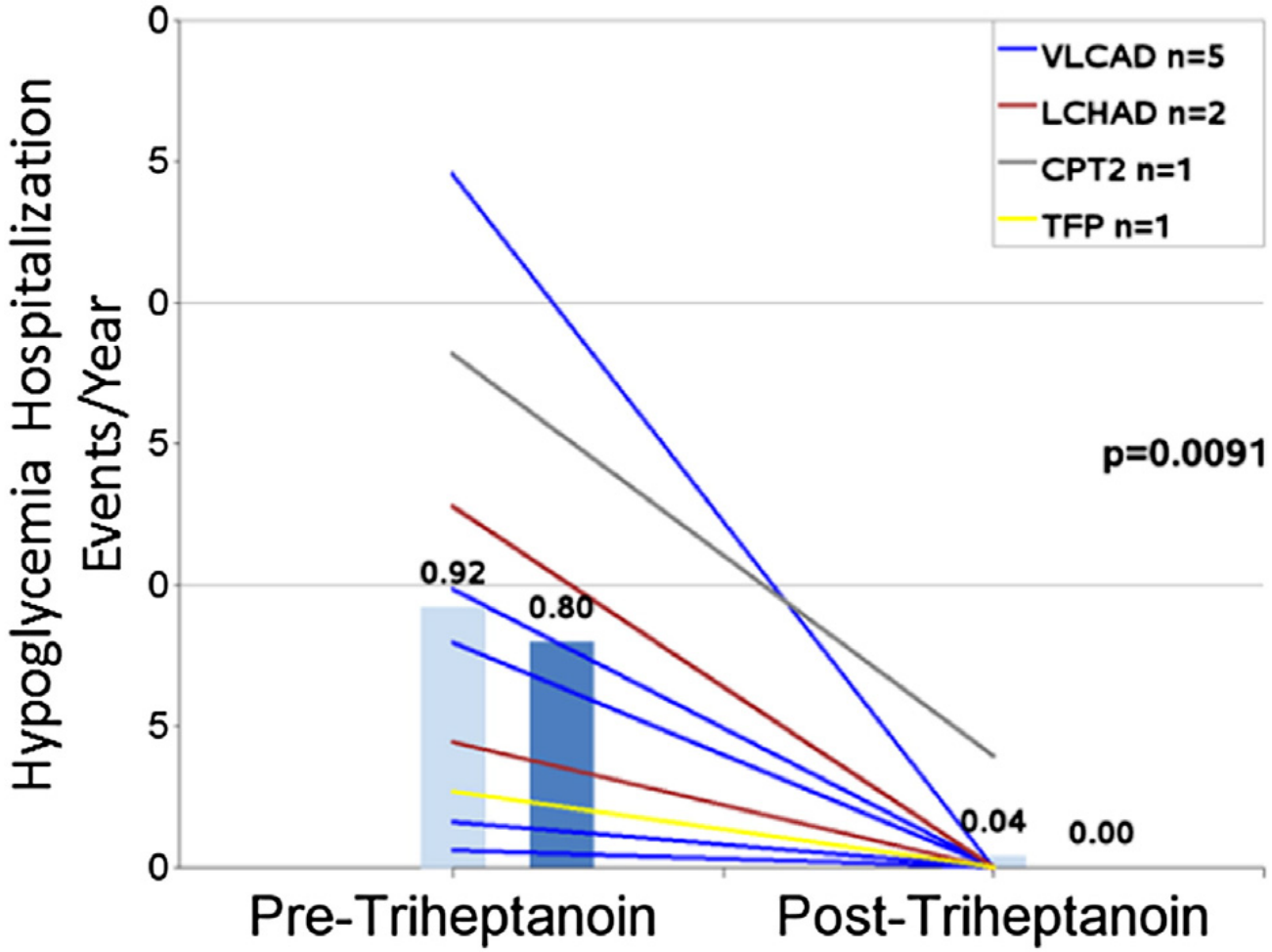
Hypoglycemic events/year



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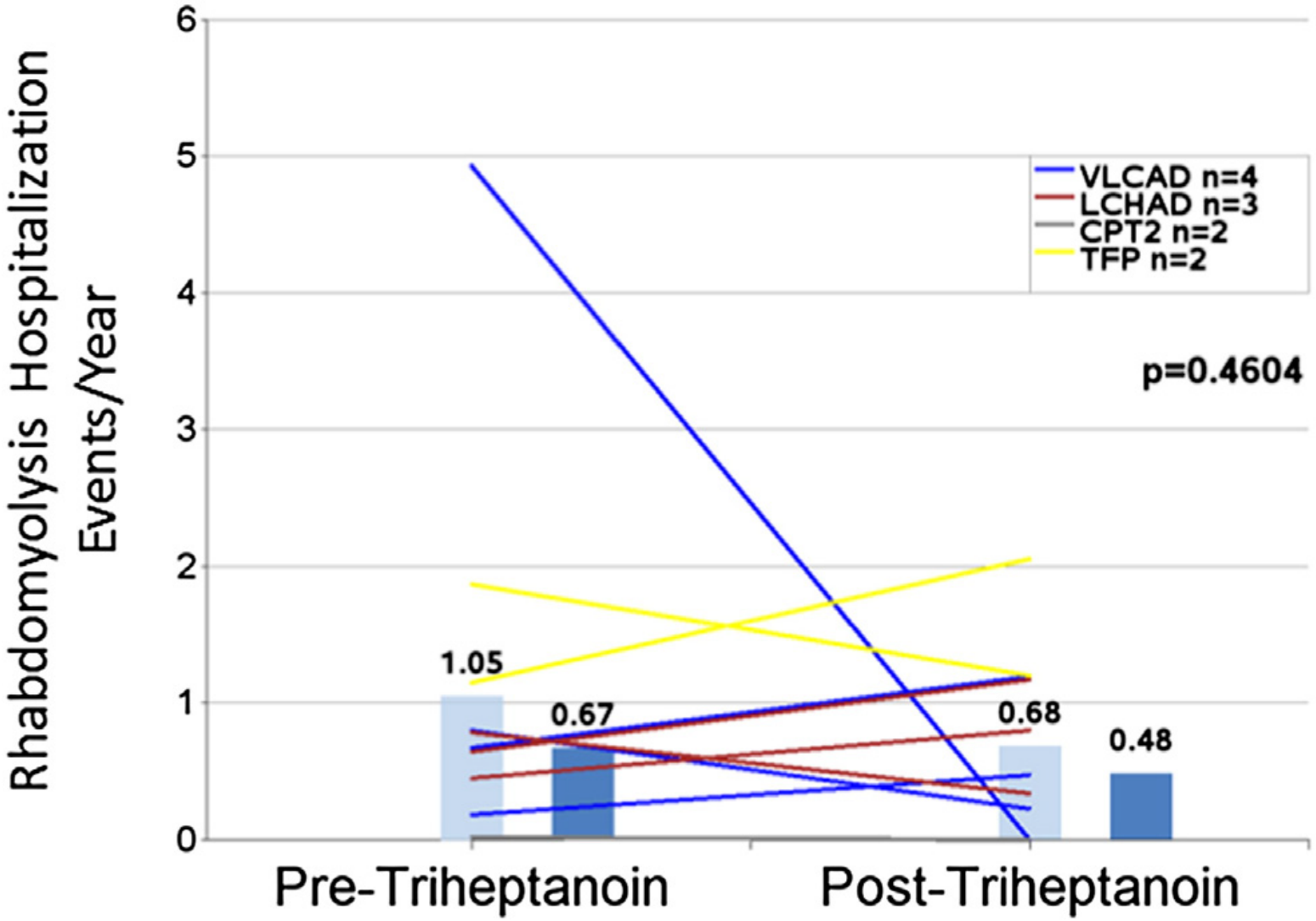
Rhabdo hospitalizations



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Triheptanoin

- LC-FAOD lead to frequent complications/hospitalizations
- Treatment with triheptanoin appears to reduce the hospitalizations and hospital days
- Hypoglycemic hospitalizations were nearly eliminated
- Rhabdomyolysis hospitalization # not changed
- Additional studies planned

	Decrease in Event Rate	Decrease in # of Hospitalization Days
Total Events	30%	67%
Hypoglycemia	96%	98%
Rhabdomyolysis	No Change	60%

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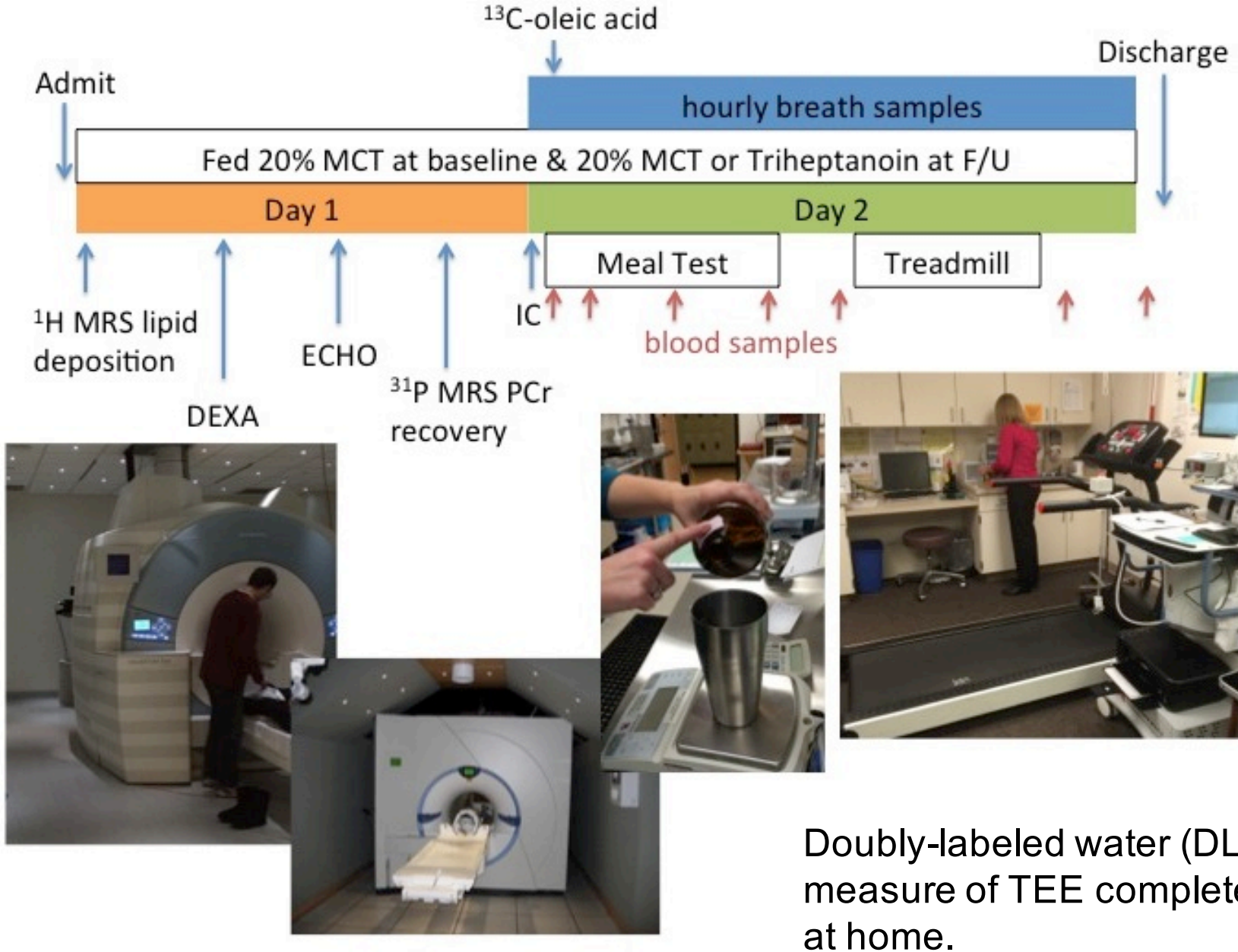
FDA triheptanoin trial



Doubly-labeled water (DLW) measure of TEE completed at home.

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Subjects

Diagnosis	Triheptanoin C7	MCT C8
CPT-2 (n)	**5** Age 21-64; BMI 18-33	**6** Age 8-43; BMI 17-35
VLCAD (n)	**4** Age 7-38; BMI 17-31	**5** Age 23-42; 22-31
LCHAD/TFP (n)	**7** Age 7-29; BMI 14-24	**5** Age 8-17; BMI 15-23
TOTAL:	**16**	**16**
Participant Characteristics	**Triheptanoin C7**	**MCT C8**
Age (years)	7 - 64	8 - 43
BMI (kg/m^2)	14-33	15-35
Males (n)	6	6
Females (n)	10	10

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Adverse events

Expected Adverse Event	C-7		C-8	
	# of events	# of subjects	# of events	# of subjects
Diarrhea/Loose Stools/Steatorrhea	9	5	12	6
Gastrointestinal Upset	24	11	38	12
Emesis/Vomiting	7	6	0	0
Musculoskeletal Pain/Cramping/Elevated CPK	16	11	18	10
Rhabdomyolysis (hospital admission)	7	5	7	4
Fatigue/Lethargy	3	3	2	2
Unexpected Adverse Event	**C-7**		**C-8**	
	# of events	# of subjects	# of events	# of subjects
Headache	17	5	7	3
Viral Illness	22	15	17	11
Localized Pain Not Associated with Rhabdomyolysis	5	4	2	2
Dermatitis	1	1	4	4

- No difference in GI upset or diarrhea between groups
- Emesis occurred in 6 subjects, only in triheptanoin group
- No difference in rhabdomyolysis, fatigue, or unexpected AE's

Triheptanoin is similarly tolerated as MCT

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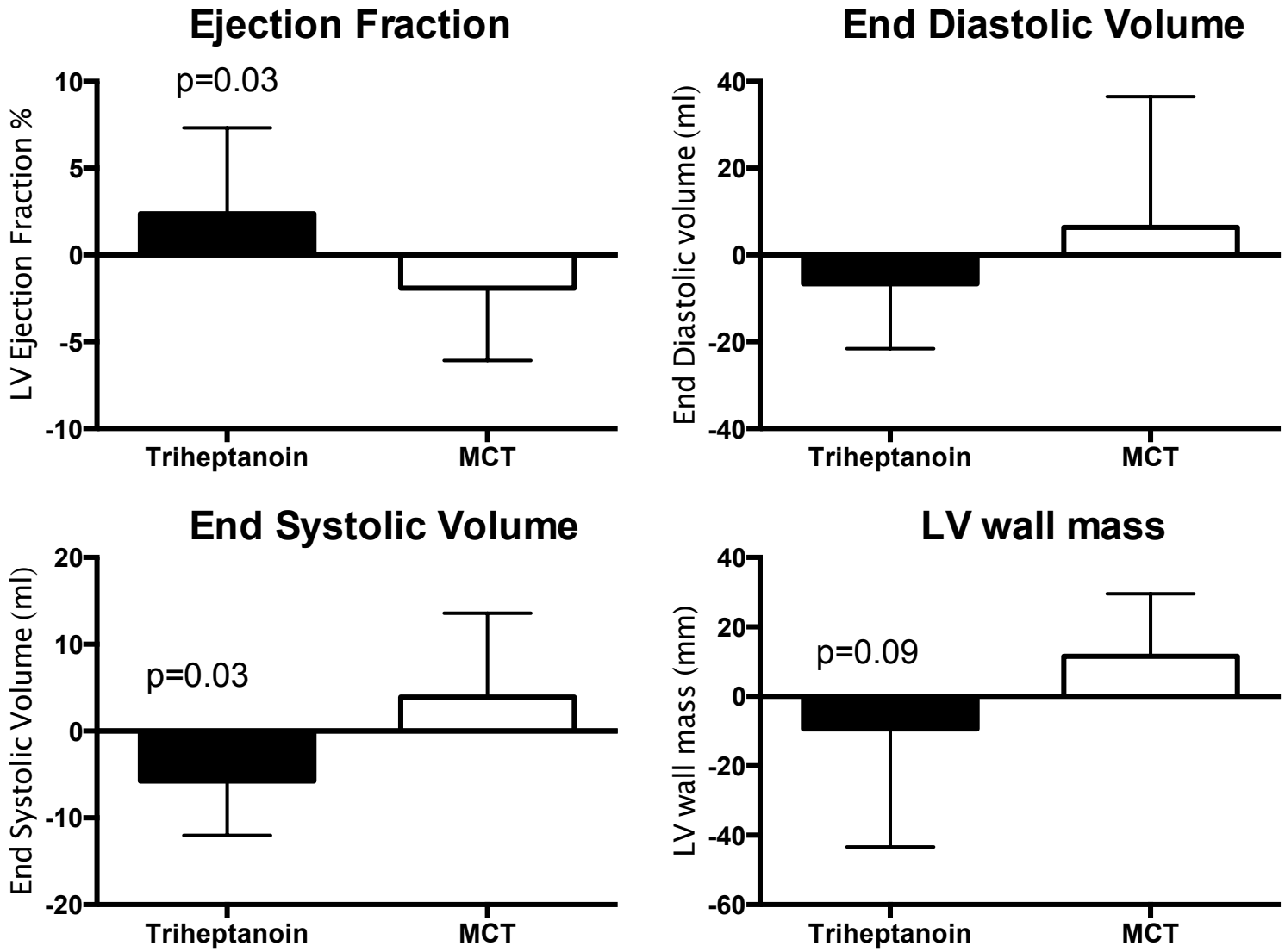
Improved cardiac function



7% increase LV ejection fraction in Triheptanoin group

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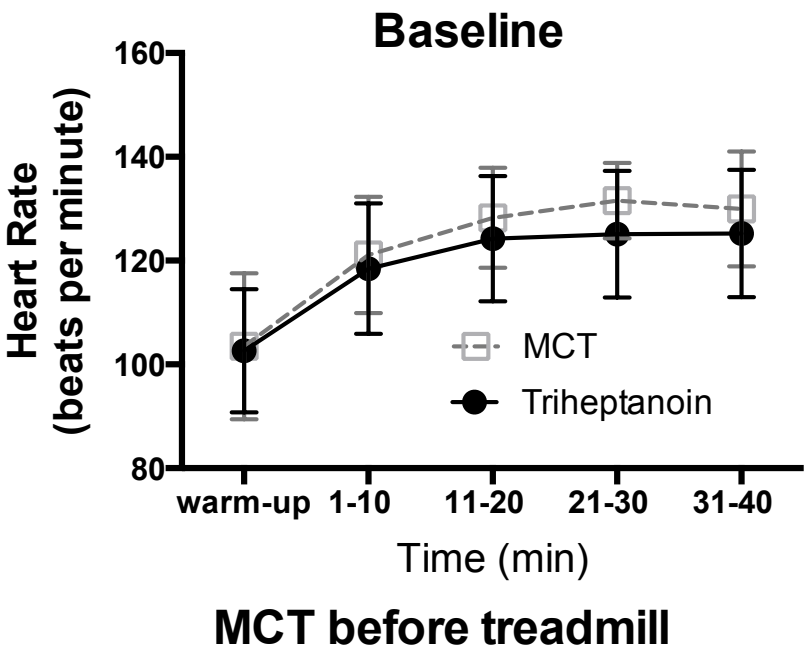
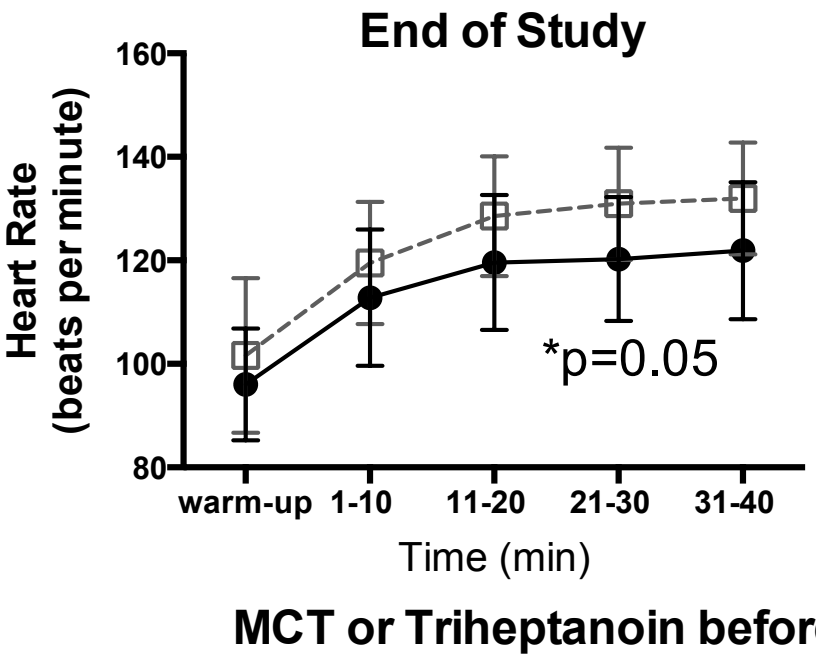
Treadmill response



MCT before treadmill



MCT or Triheptanoin before treadmill

- Significantly lower Heart Rate for same work performed with Triheptanoin supplementation
- p=0.05 adjusted for baseline
- Mean -7 beats per minute > MCT

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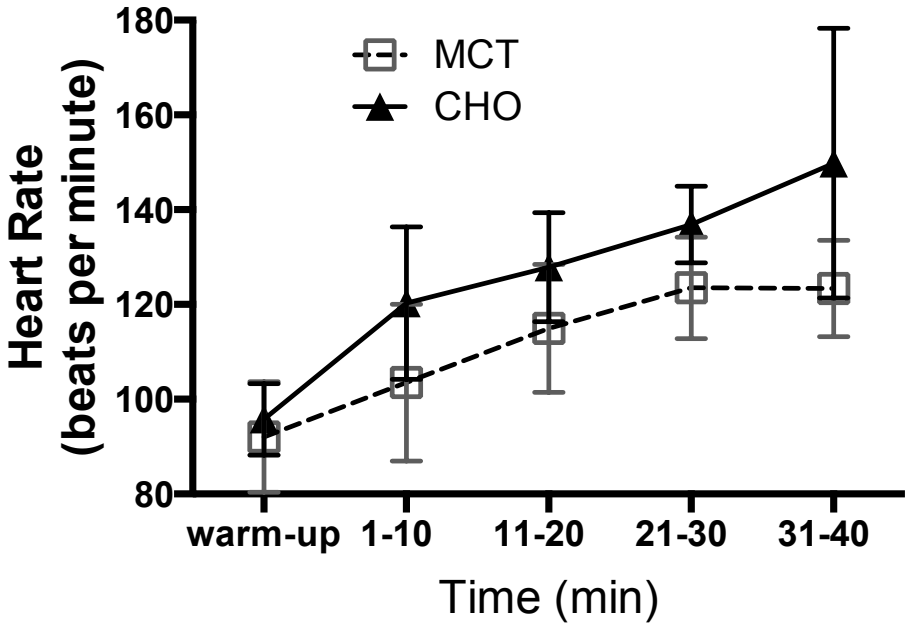
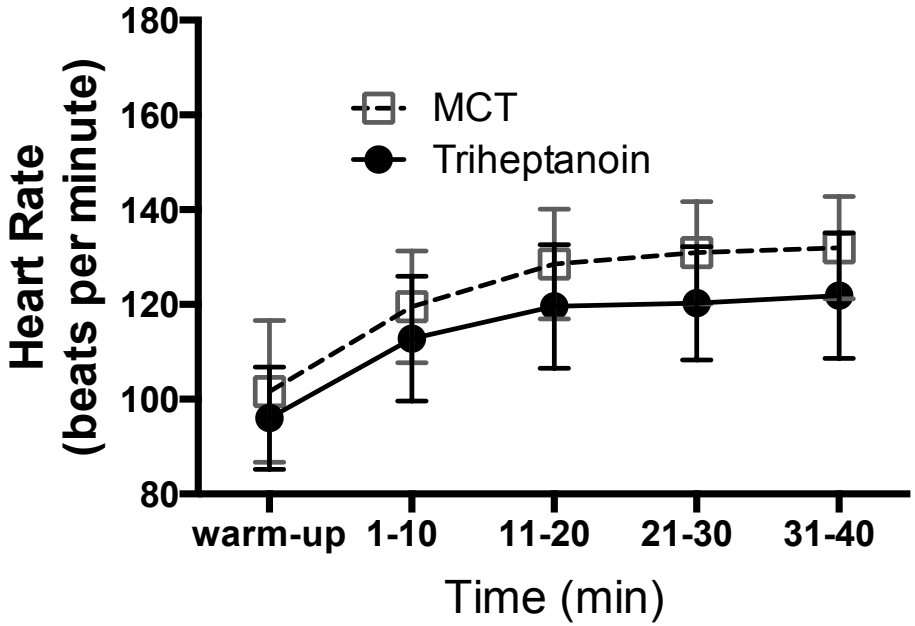
Compared to previous study





Behrend et al. MGM 2012 105: 110-115

- MCT ↓ HR 15 bpm compared to carbohydrate
- Triheptanoin ↓ HR 7 bpm compared with MCT

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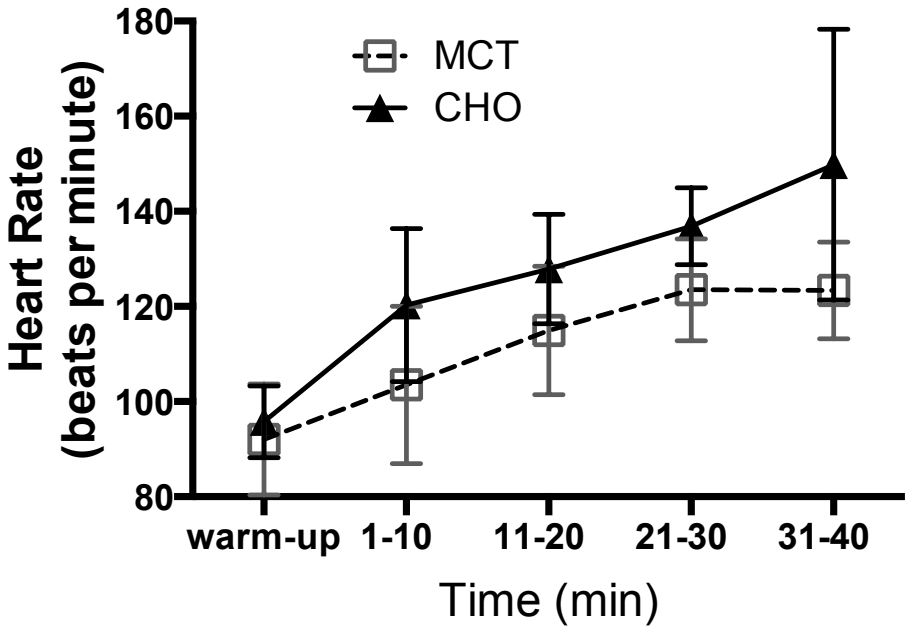
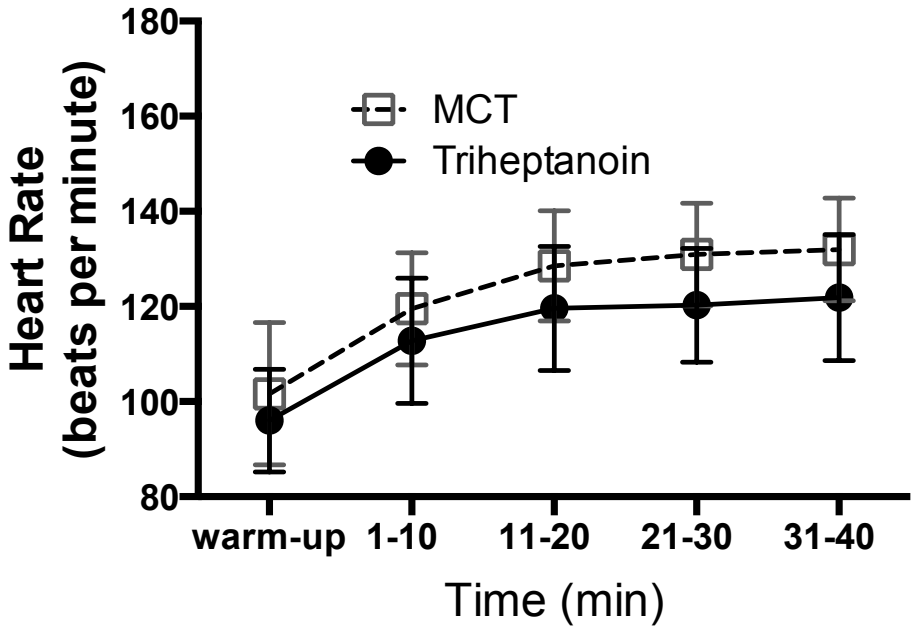
Improvement with C7 > C8





- MCT ↓ HR 15 bpm compared to carbohydrate
- Triheptanoin ↓ HR 7 bpm compared with MCT

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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

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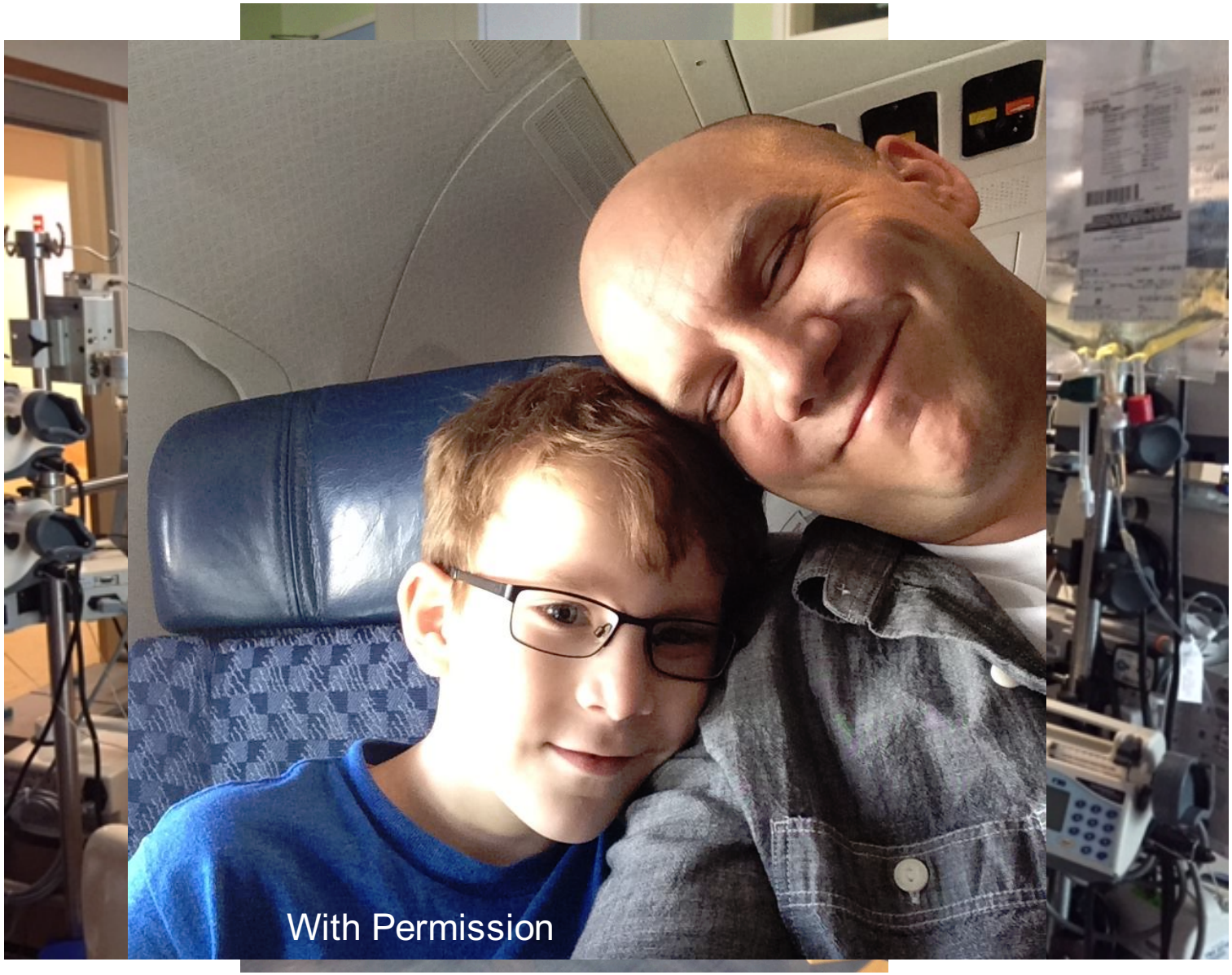
A long summer



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Cardiomyopathy

- Data collection still in progress
- ~12 patients with severe, life-threatening cardiomyopathy while on MCT
- All but one recovered with C7 treatment

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Ultragenyx phase 2 trial

- Open label
- 25 patients treated
- Results reported at 24 weeks
- 8 patients qualified for exercise testing

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Ultragenyx phase 2 results

- Safety
  - Safe and well tolerated
  - No new potential risks identified
  - Most common adverse events GI (similar to MCT)
- Exercise results (8 patients)
  - 60% increase in exercise energy generated compared to baseline
  - 28% increase in 12 minute walk distance compared to baseline
- General outcome
  - Decrease in overall major medical events
  - Event rate to be reported at 78 weeks

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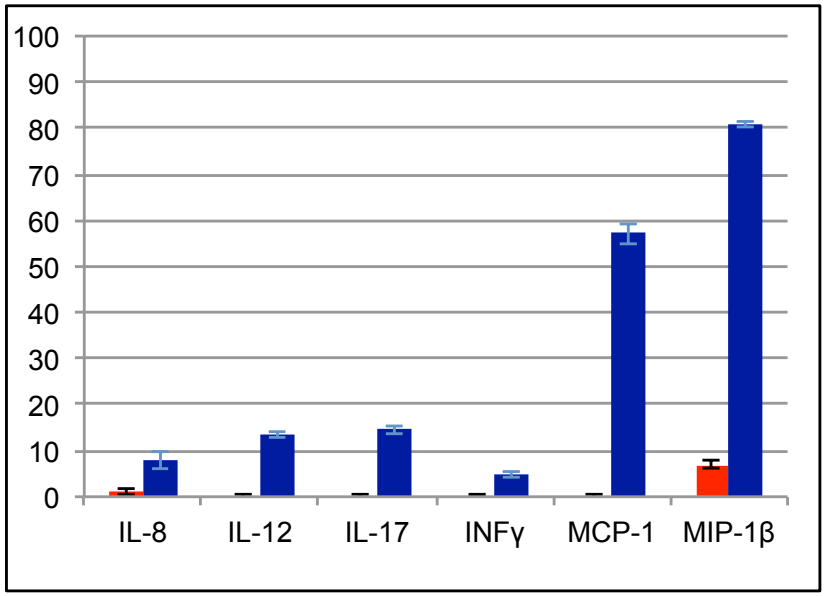
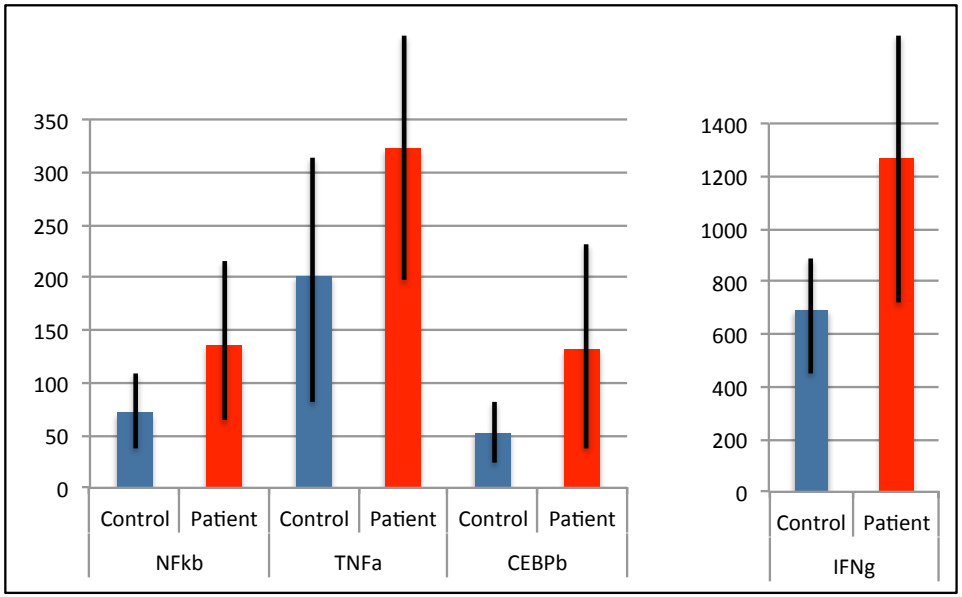
Inflammation in VLCAD patients

Blood cytokine levels



Macropahge surface markers



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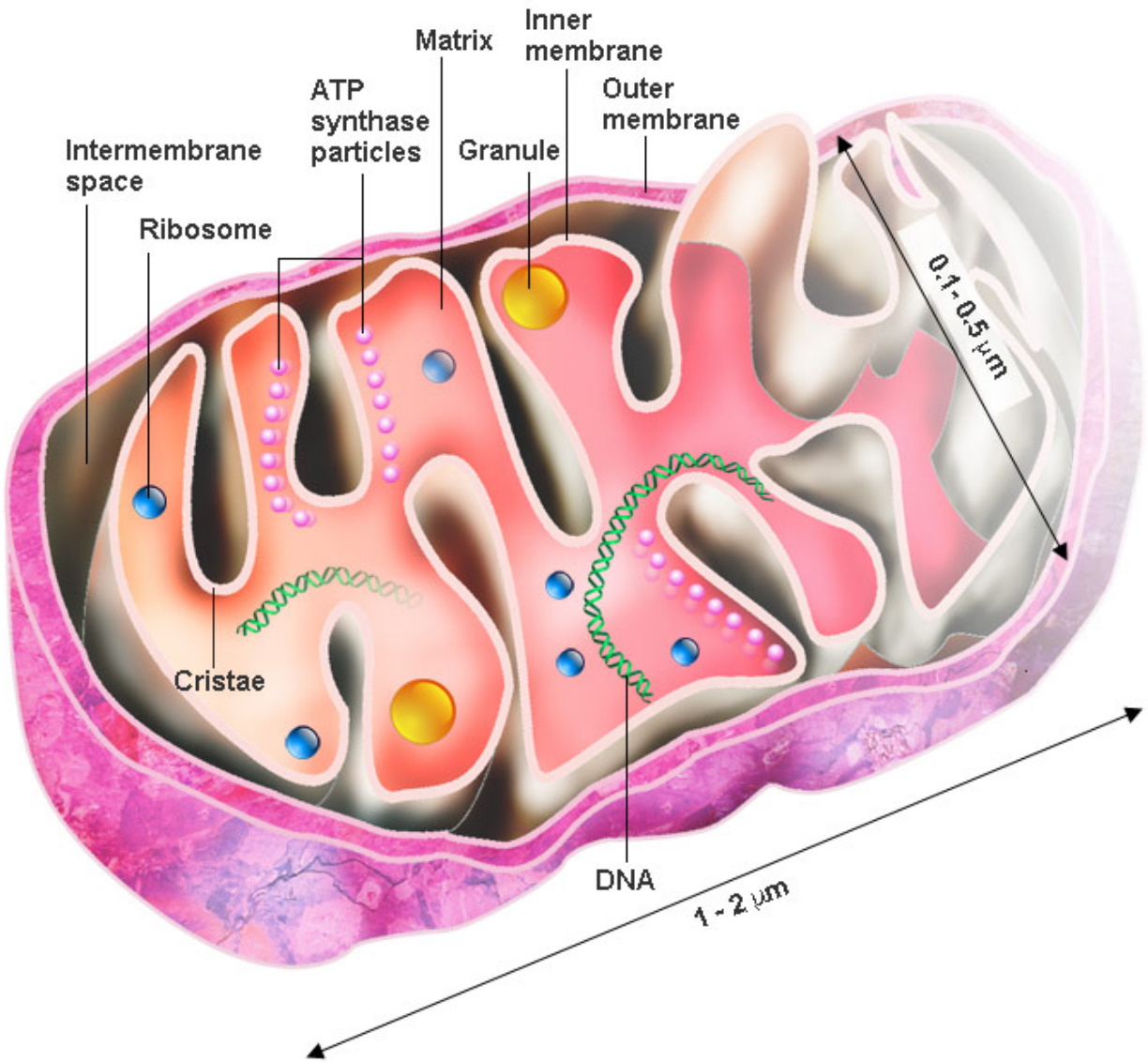
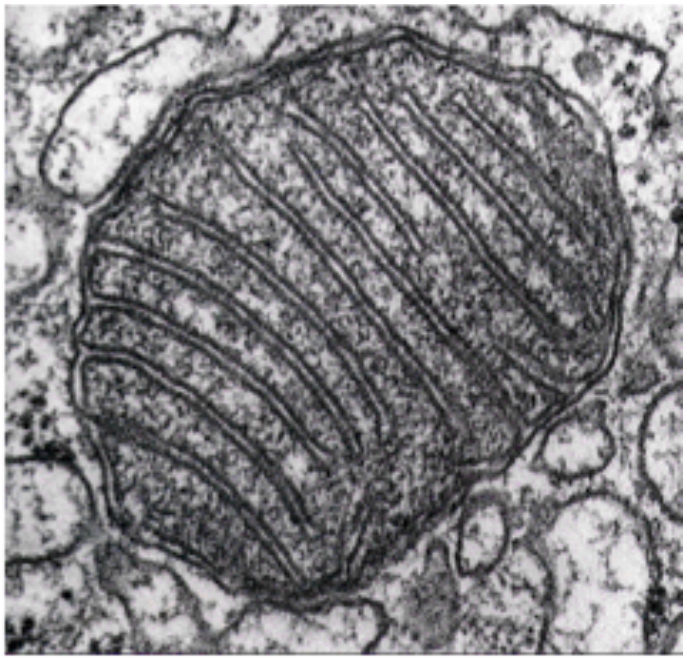
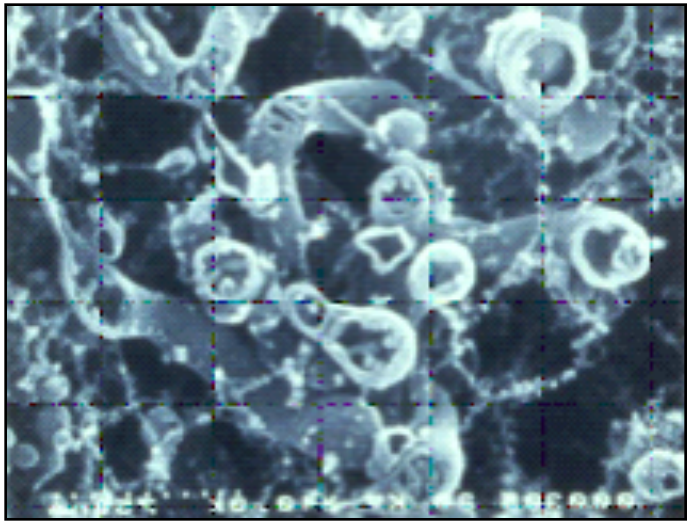
The Mitochondrion







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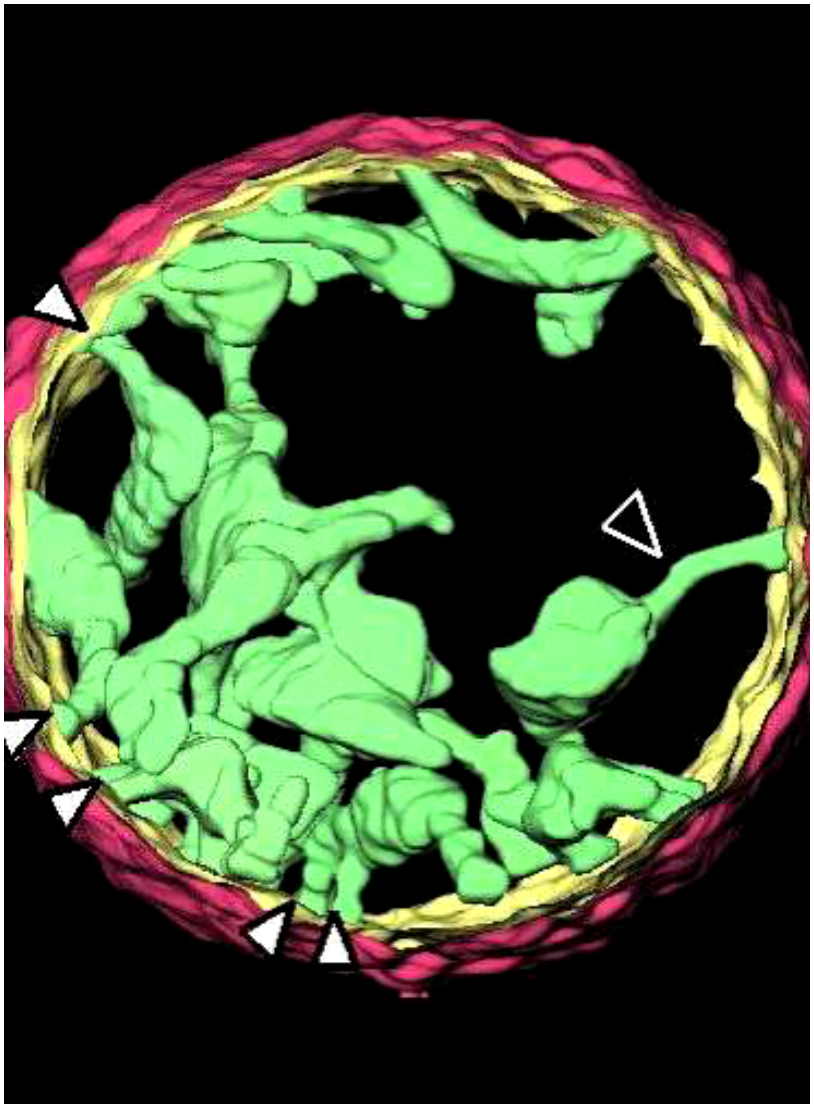
Mitochondria

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



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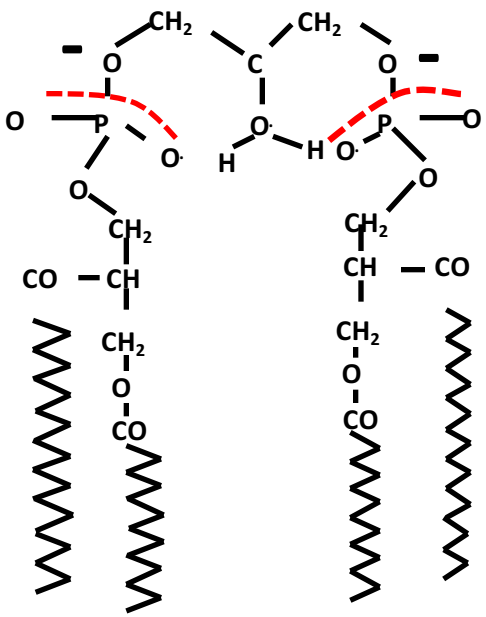
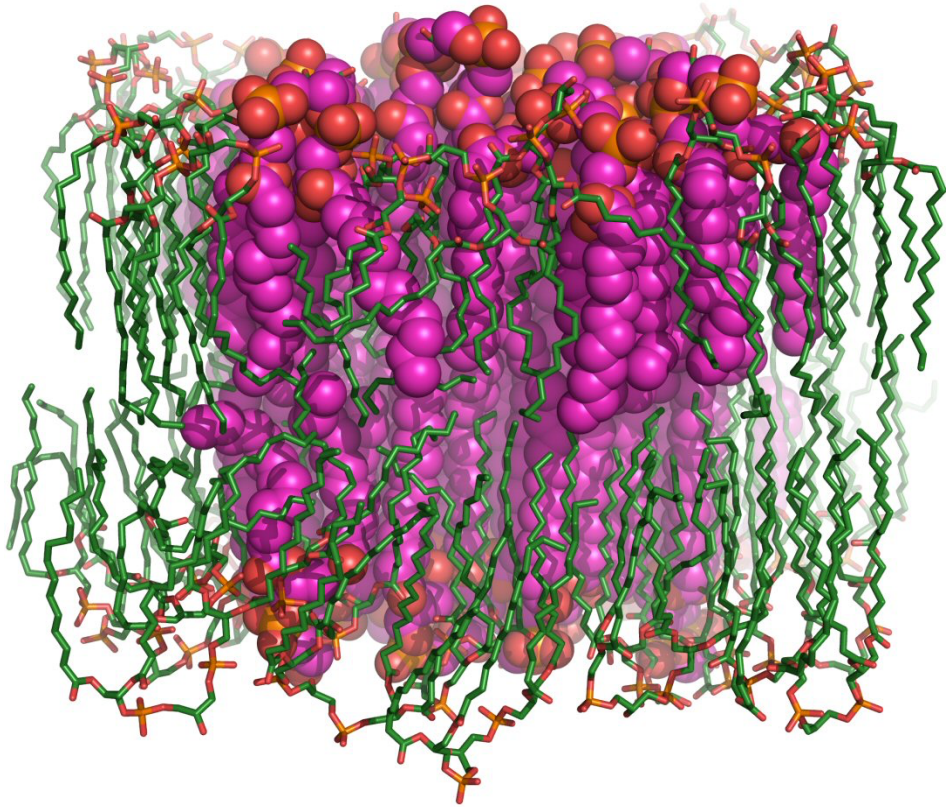
Cardiolipin

TAZ



Monolysocardiolipin



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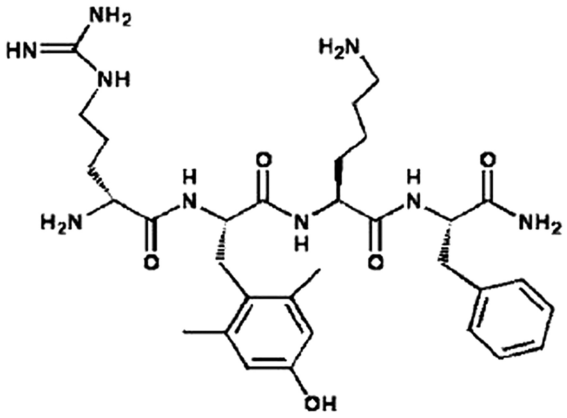
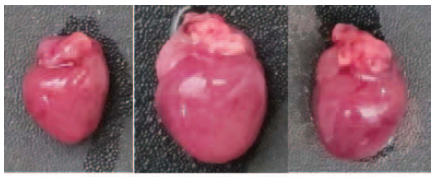
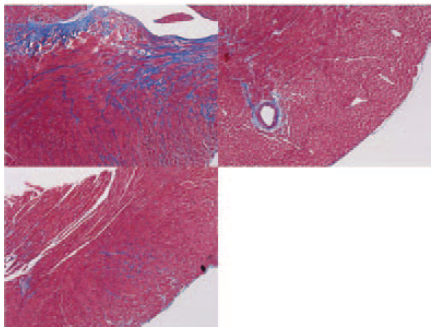
Bendavia

- Cardiolipin binding tetrapeptide (D-Arg-dimethyl-Tyr-Lys-Phe-NH_2
- Up-regulates expression of nuclear encoded mito genes
- Reduces cardiomyocyte apoptosis post-ischemia
- Decreases amyloid β induced mito abnormalities
- Improves skeletal muscle funciton







Stealth BIOTHERAPEUTICS | Leading Mitochondrial Medicine

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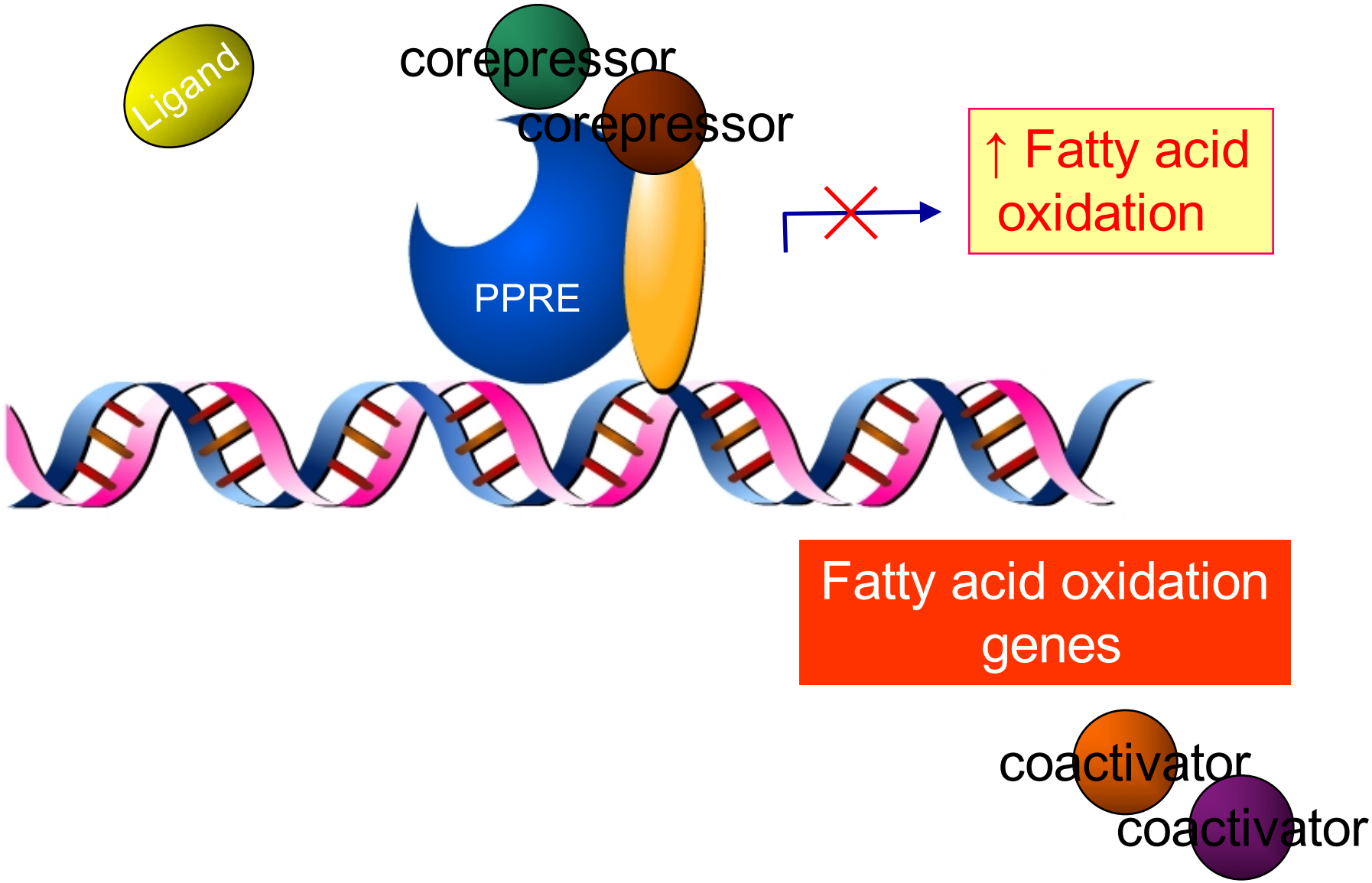
Gene regulation



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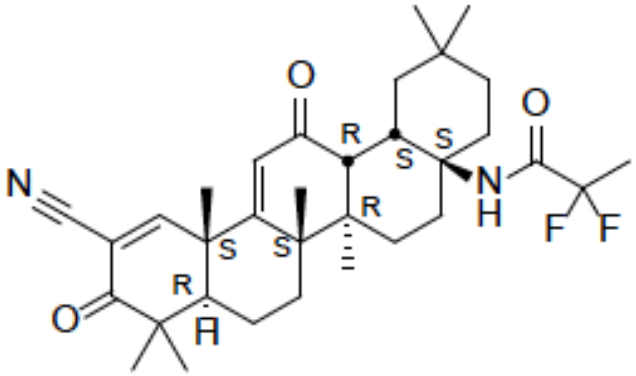
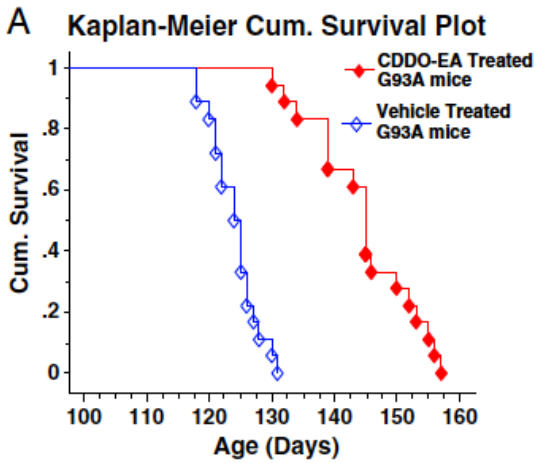
RTA408

- Semi-synthetic triterpenoid
- Nrf2 promoter activator (induces PGC1a)
- Improves antioxidant gene response to oxidative stress in Friedrich's ataxia cells
- Related compound improves survival in ALS mouse model
- ETC deficiency study in progress
- Mitobridge with similar compounds



N-(2-cyano-3,12-dioxo-28-noroleana-1,9(11)-dien-17-yl)-2,2-difluoro-propanamide



REATA PHARMACEUTICALS

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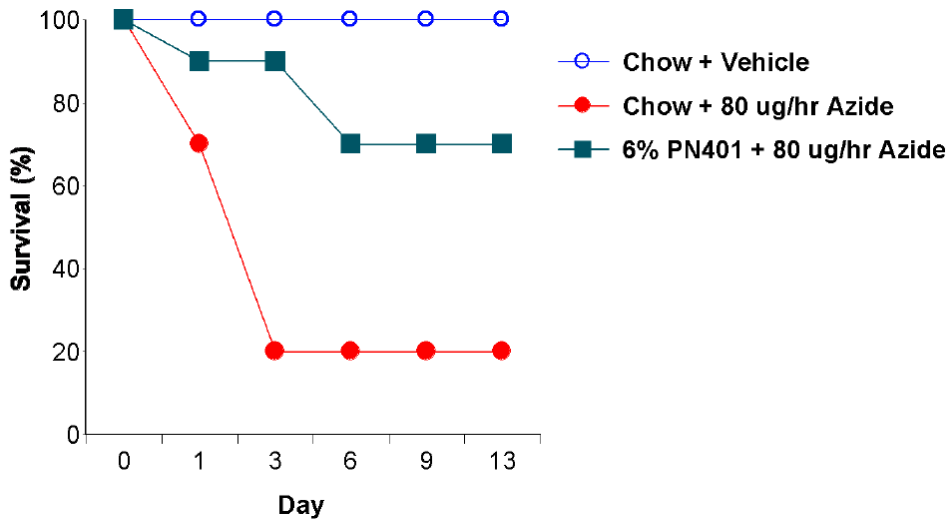
Uridine triacetate

- Regulates mito ATP-sensitive potassium channel
  - Prevents ATP depletion, Ca^{++} overload, and ROS production
  - Regulates mito volume and pH
- Activation of mito-KATP increases ATP synthesis rate in hypoxic tissues
- Decreases inflammatory signalling?

Wellstat Therapeutics™
CORPORATION



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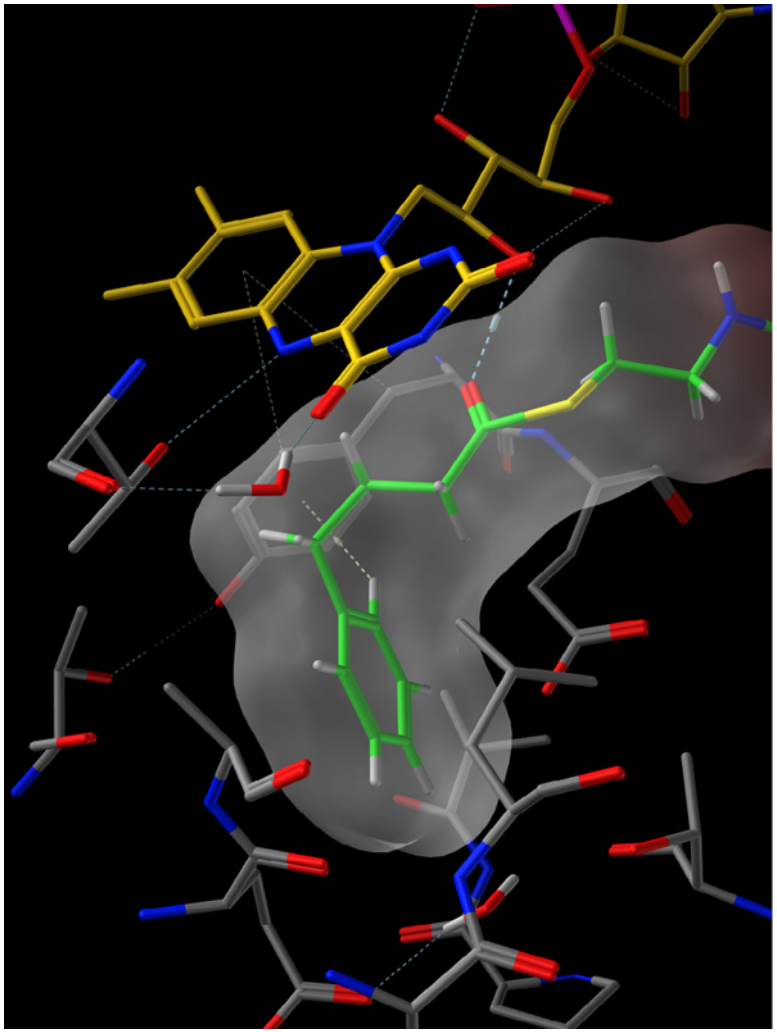
MCAD deficiency

- Common 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



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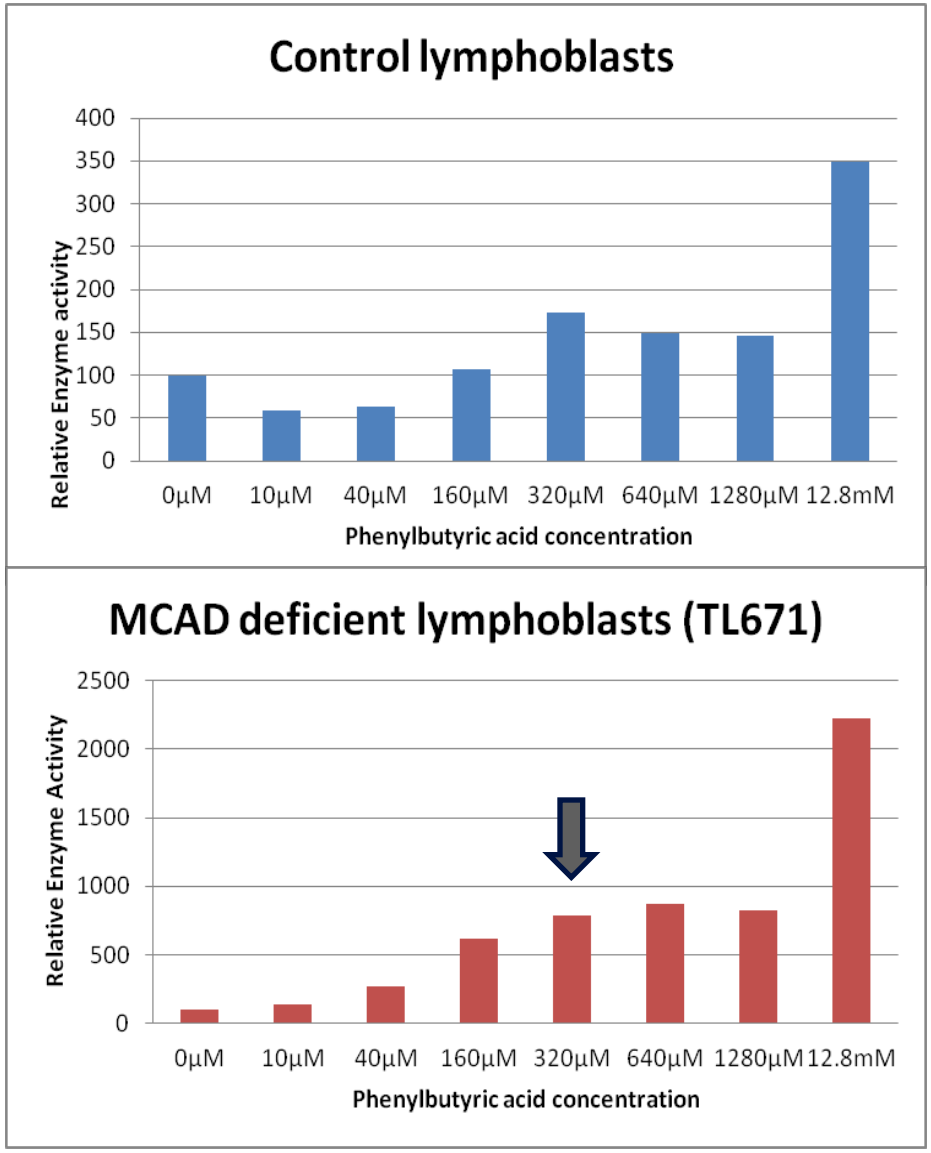
MCAD and phenylbutyrate

HORIZON PHARMA



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The sky is the limit

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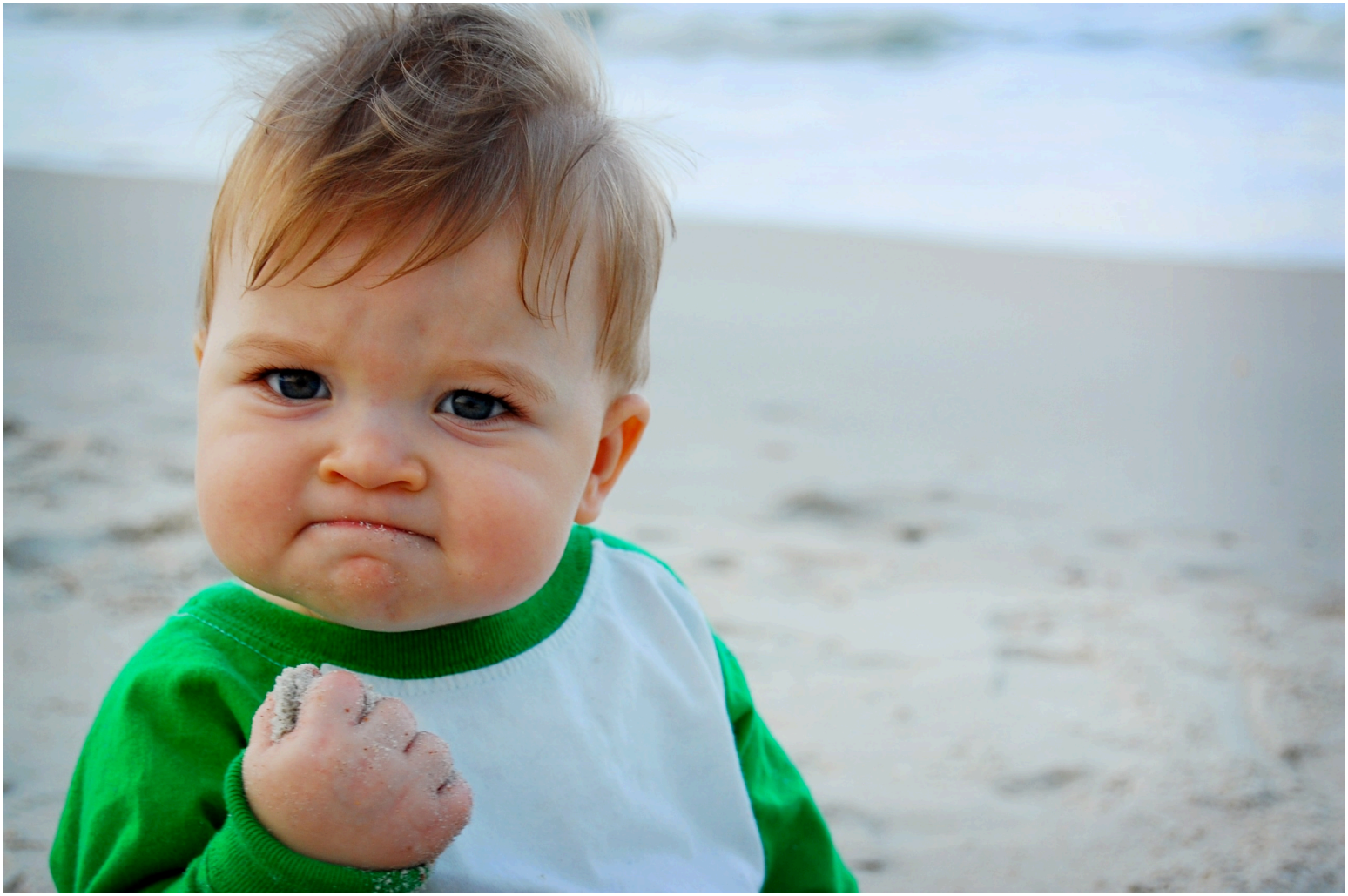
Just do it!



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Thank You!

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INTERNATIONAL NETWORK FOR FATTY ACID OXIDATION RESEARCH AND MANAGEMENT

Questions?