New Therapies for MCADD

Triheptanoin/C7/Doljovi

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Phenylbutyrate therapy

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Disclosures

- Research funding
  - NIH
  - Mellon Foundation
- Studies funded by:
  - Ultragenyx (triheptanoin)
  - ACER Therapeutics (phenylbutyrate)

What is Fat?

- Fat is the most efficient energy source in the body
- Fat is made up of chains of carbons and hydrogens
  - Hydrocarbon
- Short chain fats have 4-6 carbons
- Medium chain fats have 6-10 carbons
- Long chain fats have 12-18 carbons
- Fat is oxidized (burned to make energy) in the liver
- Each cycle of fat oxidation takes off 2 carbons that are burned for energy or turned into a ketone and exported out to be burned for energy in another organ

Why do we need treatment for MCADD beyond fasting prevention?

Case Reports > Mol Genet Metab. 2010 Sep;101(1):33-9. doi: 10.1016/j.ymgme.2010.05.007.

Epub 2010 Jun 9.

Sudden death in medium chain acyl-coenzyme a dehydrogenase deficiency (MCADD) despite newborn screening

Roman Yusupov [1], David N Finegold, Edwin W Naylor, Inderneel Sahai, Susan Waisbren, Harvey L Levy

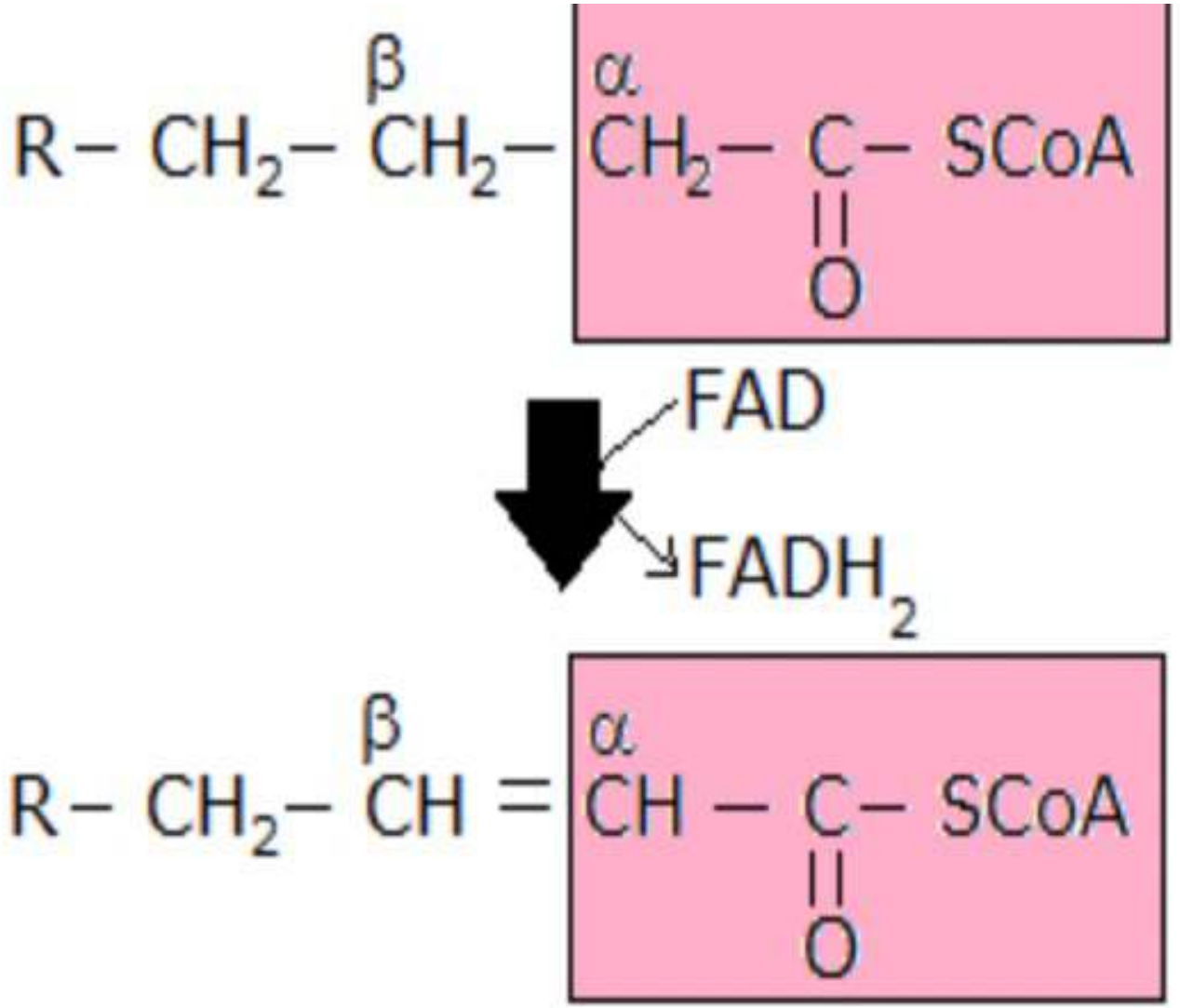
Affiliations + expand

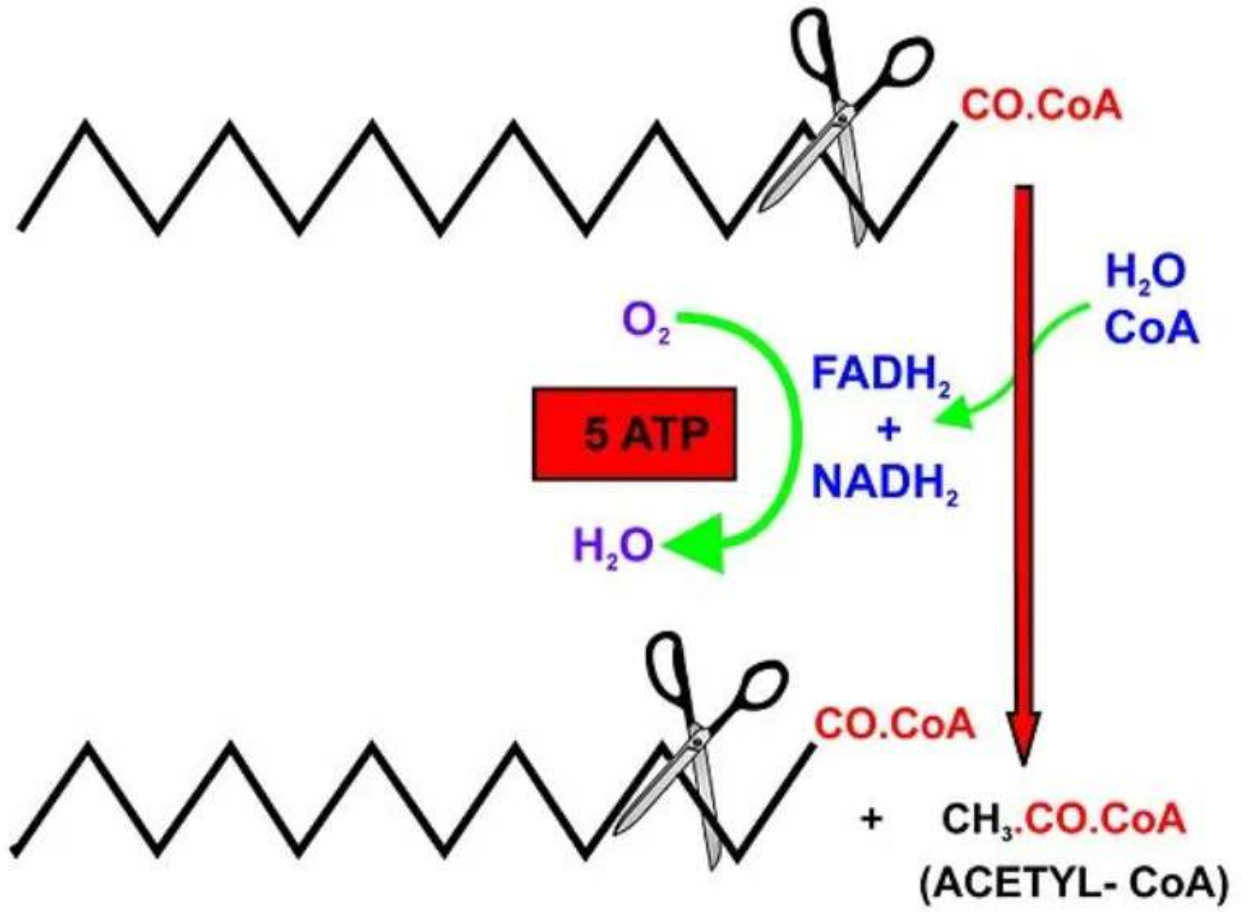
PMID: 20580581 DOI: 10.1016/j.ymgme.2010.05.007

What is MCADD

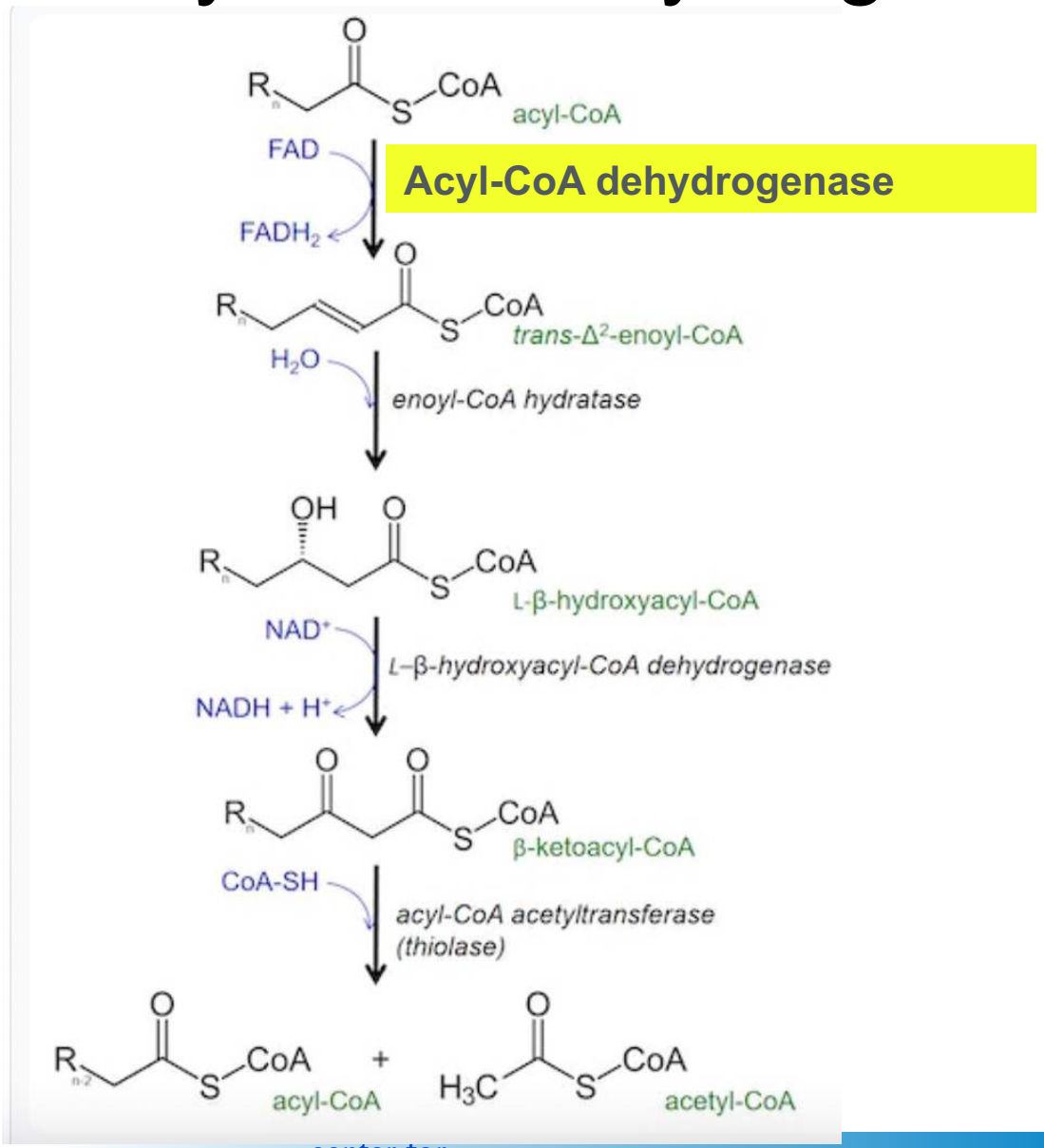
- **M**edium **C**hain (6-10 carbons)
- **A**cyl CoA (the chemical name of the working end of the fat)
- **D**ehydrogenase (takes away hydrogens)
- **D**eficiency

Fatty Acyl CoA




CO.CoA
H_2O
CoA
O_2
$FADH_2$
+
$NADH_2$
5 ATP
H_2O
CO.CoA
+ $CH_3.CO.CoA$
(ACETYL- CoA)

Medium Chain Acyl-CoA Dehydrogenase Deficiency (MCADD)



Supplementation with Medium Chain Fat

- Long Chain FAODD

MCT = 👍

Even better MCT supplement for LCFAOD

- Triheptanoin (Doljovi)
- 7 carbon fat

- FAOD breaks the fat down down (7 carbons, 5 carbons, 3 carbons) until a 3 carbon piece is left
- This 3 carbon piece feeds metabolism by replenishing the Kreb's cycle
- Provides energy from fat metabolism plus replenishes other depleted intermediates
- Might make it easier for the body to make glucose

Supplementation with Medium Chain Fat (MCT Oil)

- Long Chain FAODD

MCT = 👍

- MCADD
- MCT = 🚫

Serendipity

- “We were using the MCAD deficient cell line as what we thought would be a negative control for metabolism of C7 and were surprised to find it used it. When we tested C8 and it was appropriately zero. So I guessed it had to be SCAD metabolizing the C7. Since we had some purified enzyme in the freezer, we pulled it out and indeed found that it metabolized C7”

- Dr. Jerry Vockley

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*

Table 1: SCAD enzyme activity in control and MCADD fibroblast cell lines demonstate clear (albeit reduced) activity to metabolize triheptanoate (C7) in the MCADD. Purified human SCAD enzyme (last row) confirms activity against triheptanoate (C7) but not octanoate (C8).

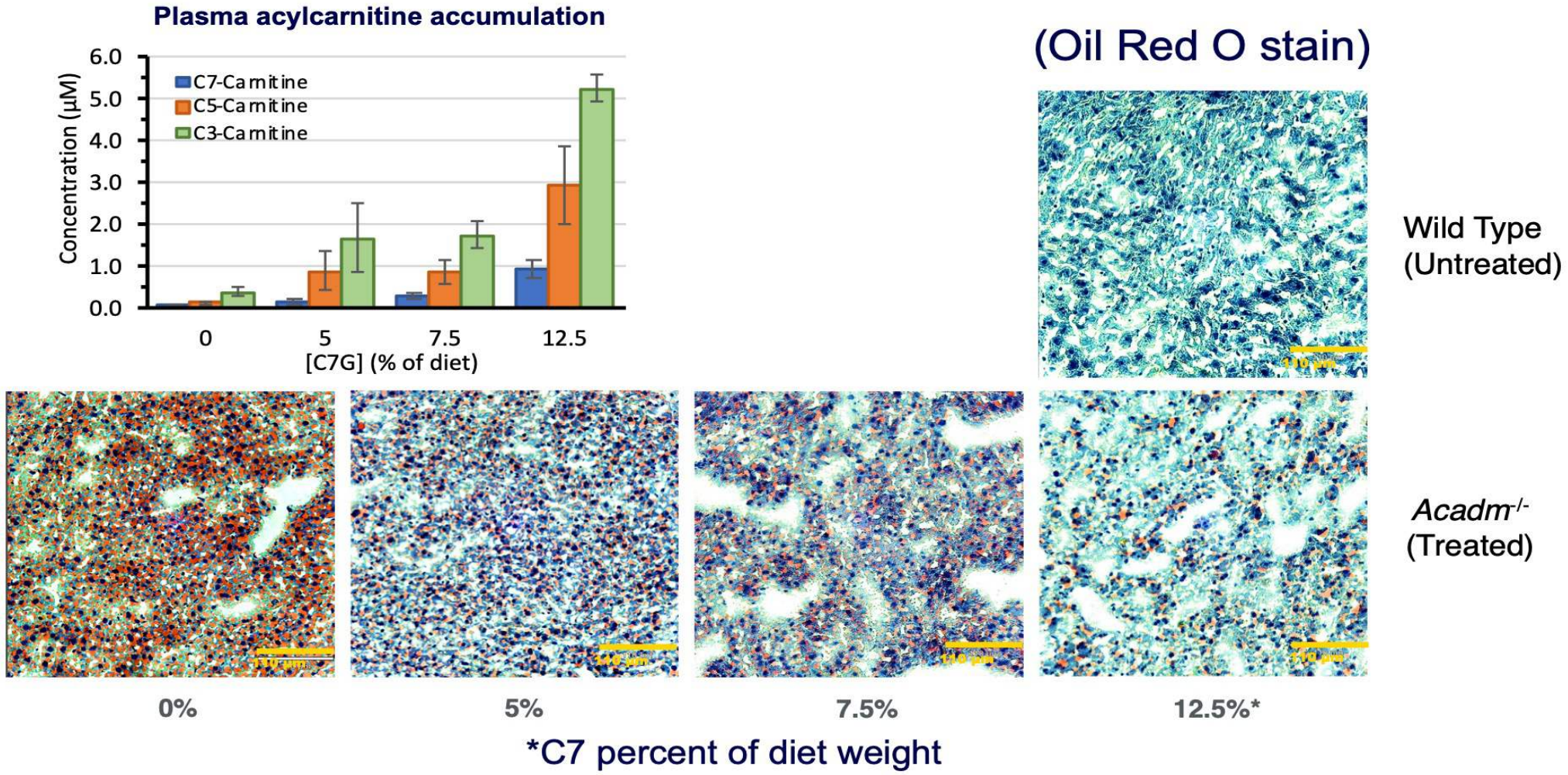


Figure 1. Treatment of MCAD deficient mice with heptanoate followed by cold challenge. Hepatic steatosis resolves and C7 metabolites increase in a dose dependent fashion.

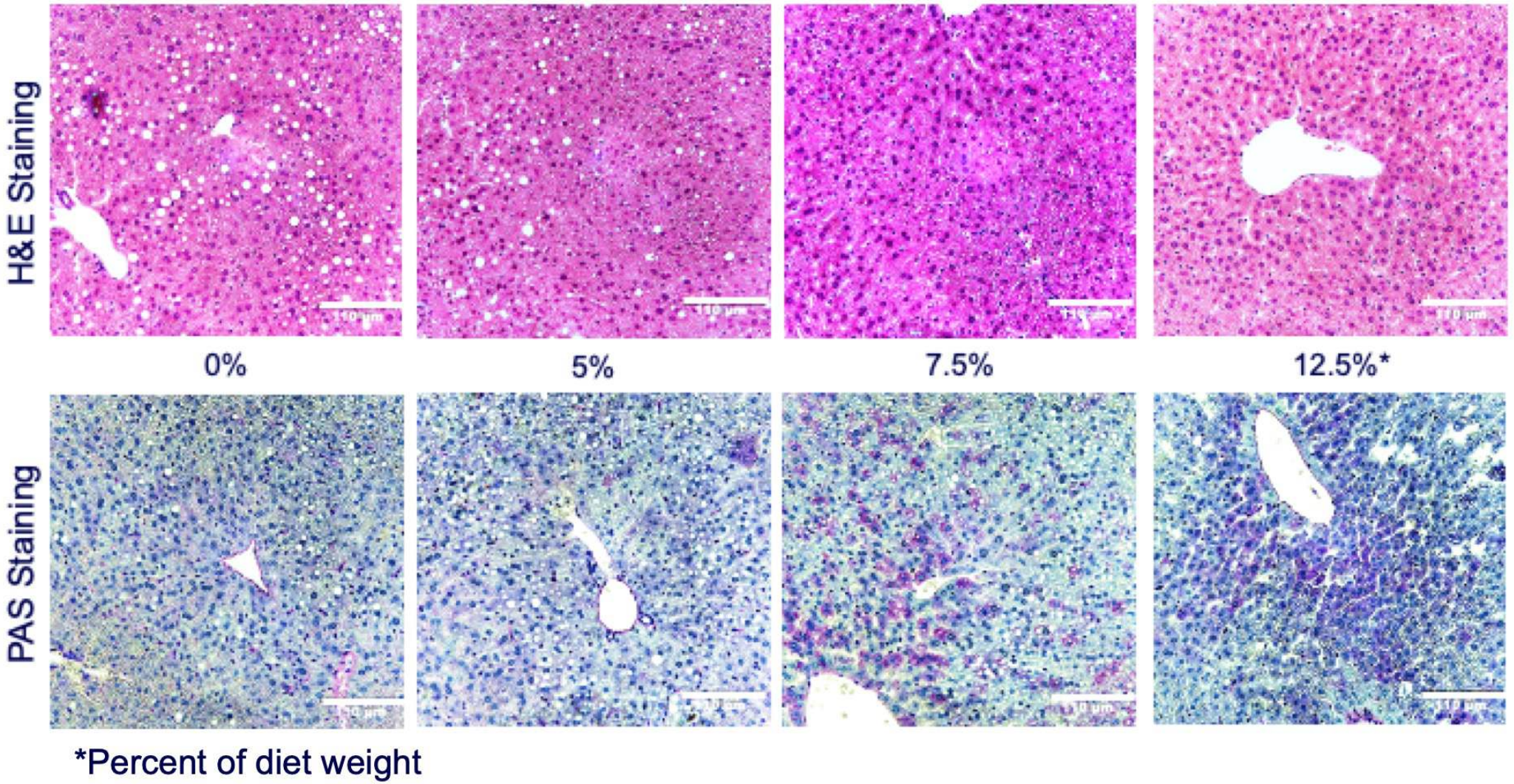


Figure 2. Hepatic glycogen is increased in a dose dependent fashion in MCAD deficient animals treated with triheptanoin.

Phase 2 Clinical Trial of C7 in MCADD

- **Cohort:** The study will include up to 8 patients with MCADD ≥ age 16 years

- **Baseline evaluation:**
  - Assess glucose, acylcarnitines, acylglycines, free fatty acids, beta hydroxybutyrate

- **Fast for up to 24 hours**
  - Assess glucose, acylcarnitines, acylglycines, free fatty acids, beta hydroxybutyrate

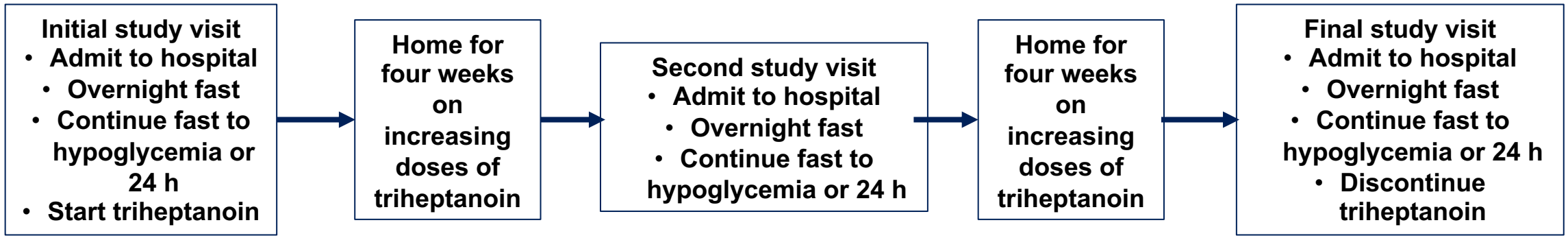
How will we make the fast as safe as possible?

- IV placed for access and blood drawing
- Begin fast after supper
- Check finger stick glucose anytime the patient becomes symptomatic (jittery, sweaty, anxious, feels hypoglycemic)
- Check fingerstick glucose at 6,9,12,15,18, 21,24 hours
- Check blood glucose every hour beginning at 21 hours
- Stop the fast if patient is symptomatic or has blood glucose <60
- Can have water, coffee, tea (no sugar) or sugar free beverages

Dosing with triheptanoin

- **Dose Selection:** Dosing will be with two ascending steps: 0.5 gm/kg of triheptanoin followed by 1 gm/kg. Dose will be increased gradually to avoid gastric upset. Open label (everyone gets drug, no placebo group)
- Dosing Period 1 –
- Days 1-4: 0.2 gm/kg triheptanoin
- Days 5-8: 0.35 gm/kg triheptanoin
- Days 9-28: 0.5 gm/kg triheptanoin
- Repeat 24 hour fast
- Dosing Period 2 –
- Days 29-32: 0.7 gm/kg triheptanoin
- Days 33-36: 0.85 gm/kg triheptanoin
- Days 37-54: 1.0 gm/kg triheptanoin
- Repeat 24 hour fast

Protocol Design



- Study end points
  - Prevention of hypoglycemia or increase in time to hypoglycemia
  - Reduction of fatty acid oxidation intermediates
- Study Cohort
  - ≥16 yrs

Study Goals

- Primary goal – prevention of hypoglycemia
  - Is the patient able to fast longer while on study drug before becoming hypoglycemic
- Secondary – reduced accumulation of toxic metabolites
  - Even if the patient does not develop hypoglycemia, do they have less build-up of toxic metabolites

Next steps

- If this initial study looks promising, a placebo-controlled trial will be planned next (some patients will get triheptanoin and some placebo)
- Details of this future study TBA

Phenylbutyrate therapy for MCAD deficiency – clinical trial

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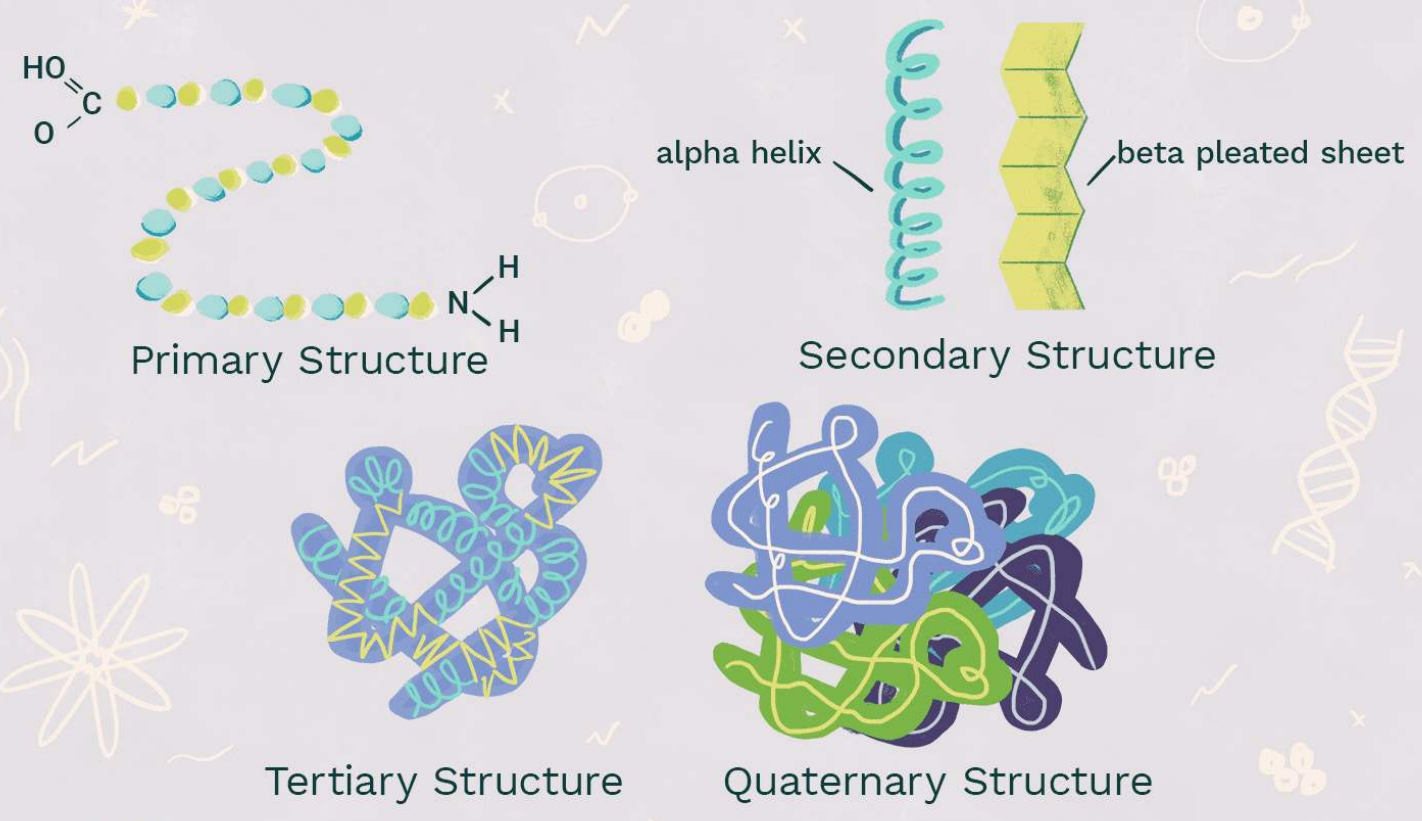
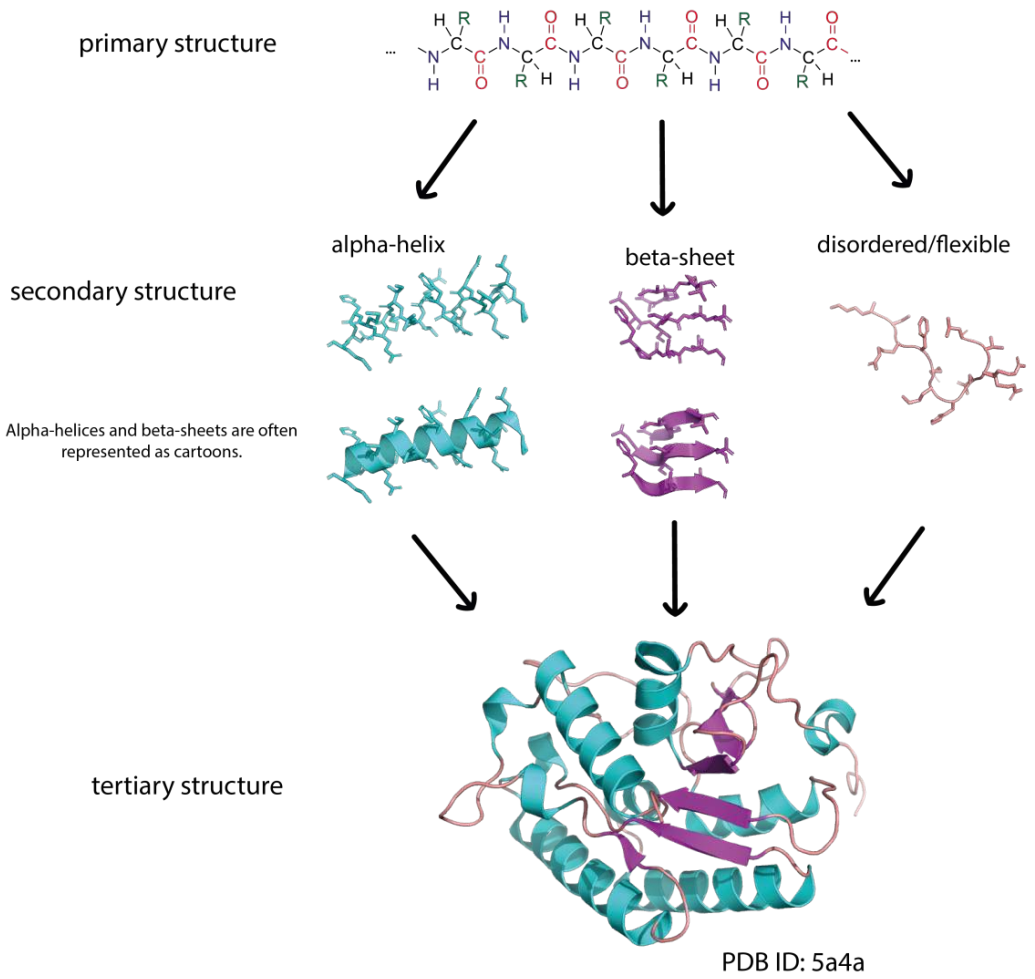
Protein Folding



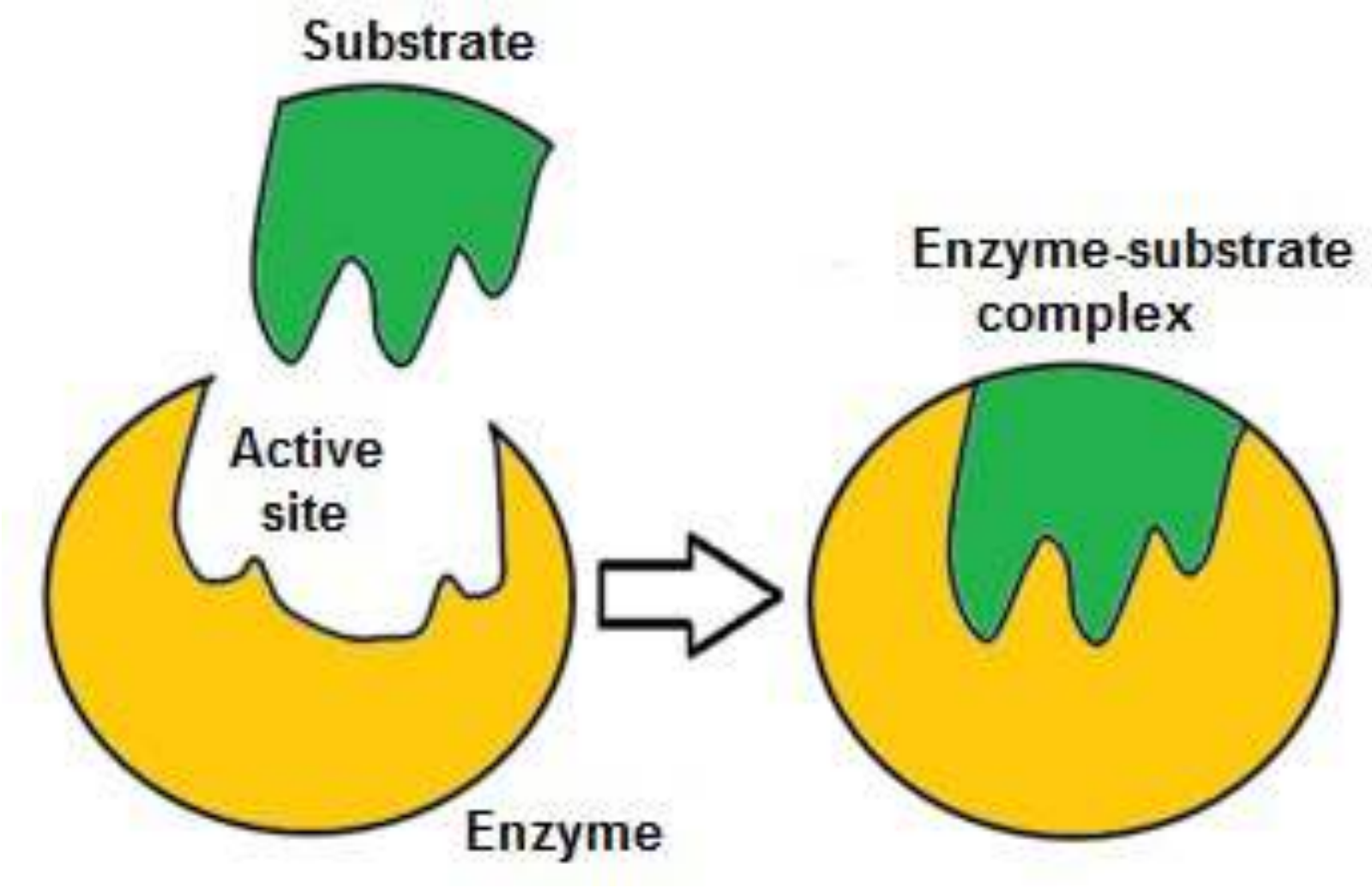
- Proteins are made as a string of amino acids (beads on a string)
- Require a series of folding events to reach final structure
- Folding is facilitated by specialized proteins called chaperonins
- Effect can be mimicked by small molecules (chaperones)

Assisting Folding



- Chemical chaperones can work at any stage in folding
- Often (but not always) sequence specific
- Personalized metabolic medicine

”Lock and Key” Enzyme Model



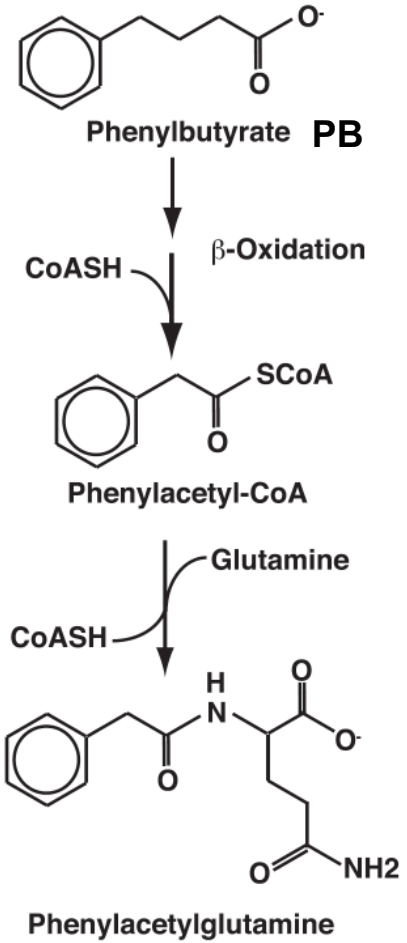
MCAD K329E mutation

- c. 985A>G is the most common MCAD mutation in people of northern European ancestry
  - At DNA base pair 985, adenosine is replaced by guanine
  - This causes amino acid 329 (normally lysine) to be replaced by glutamate (p.K329E) (AKA K304E)

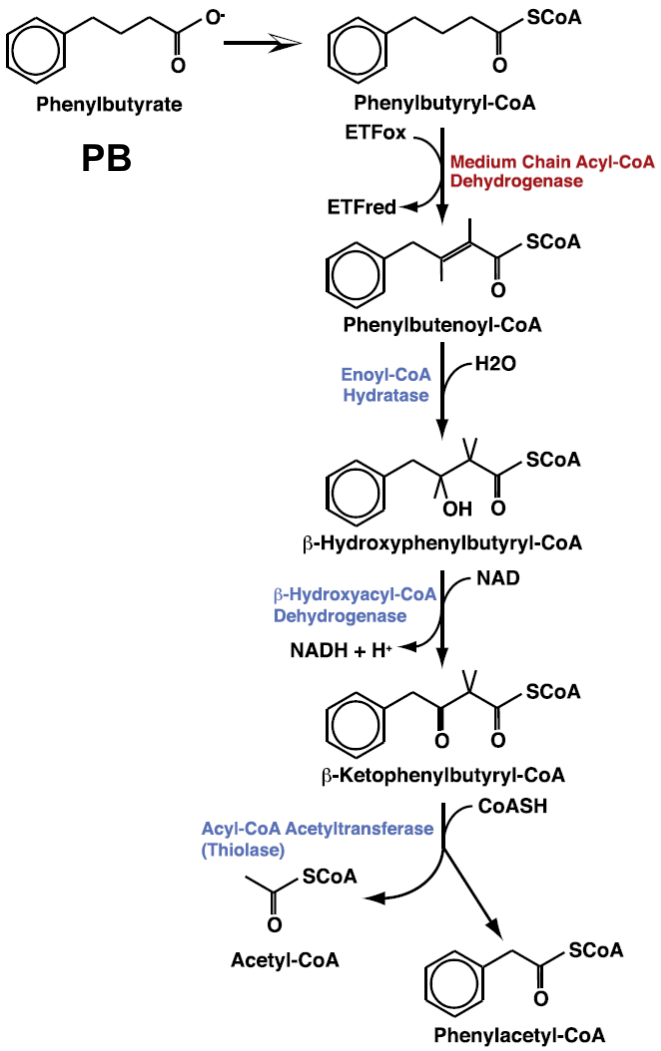
- Most MCADD patients of northern European ancestry have at least one copy of c.985A>G

- K329E (K304E) is a folding defect

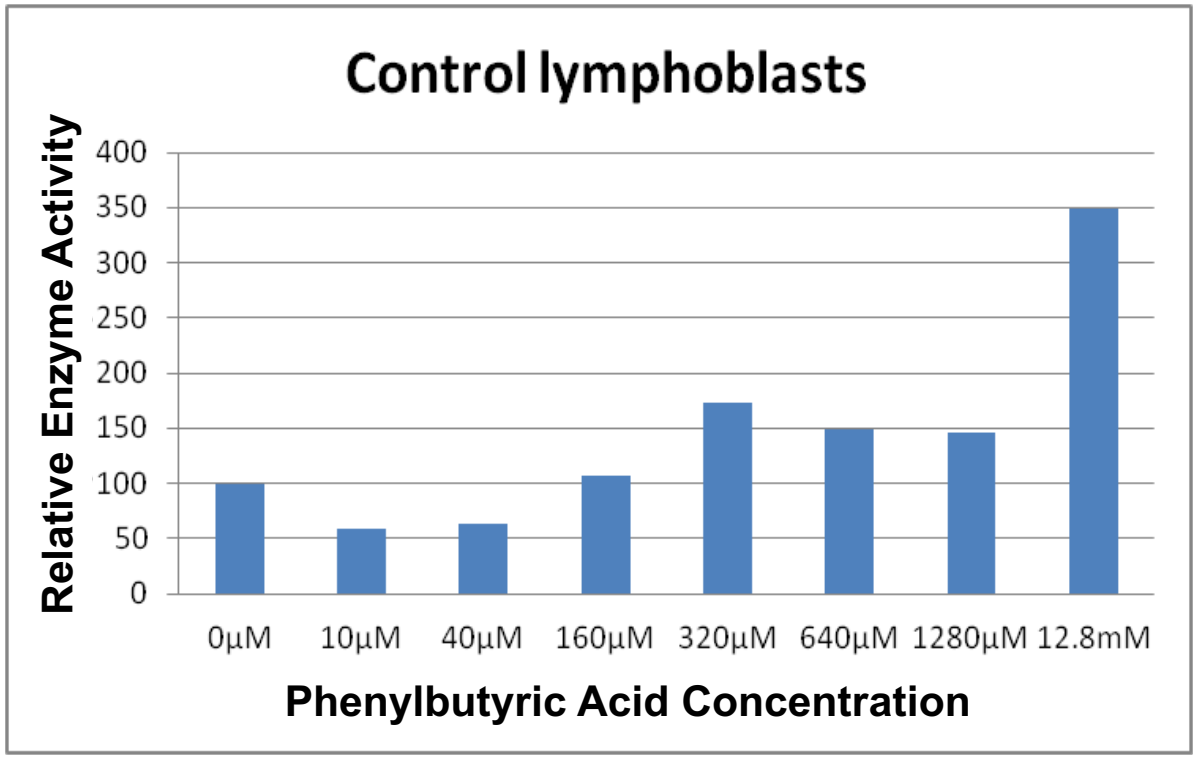
Phenyl butyrate (PB) used as a nitrogen scavenger in Urea Cycle Disorders

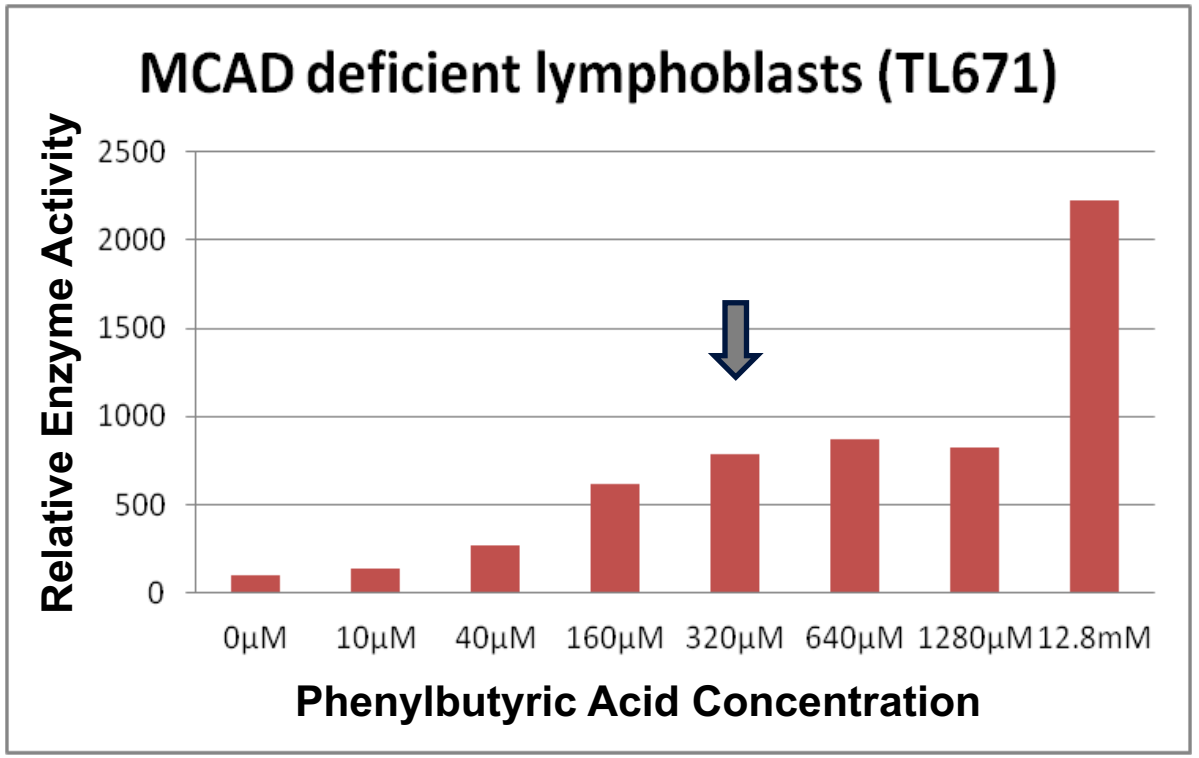


MCAD metabolizes phenylbutyryl-CoA (PB-CoA) as substrate



MCAD and PB

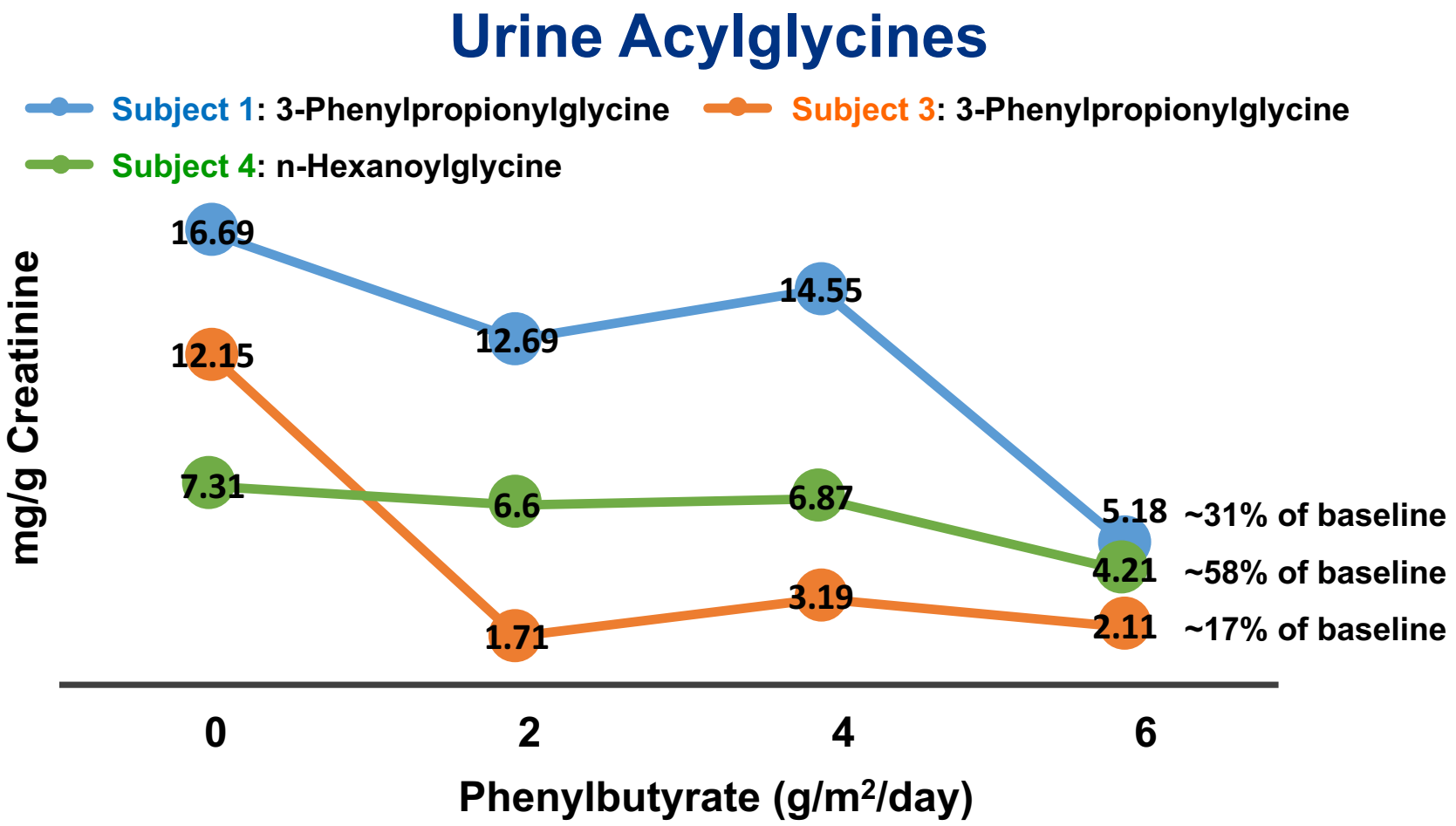

Control lymphoblasts
Relative Enzyme Activity
400
350
300
250
200
150
100
50
0
0μM
10μM
40μM
160μM
320μM
640μM
1280μM
12.8mM
Phenylbutyric Acid Concentration


MCAD deficient lymphoblasts (TL671)
Relative Enzyme Activity
2500
2000
1500
1000
500
0
0μM
10μM
40μM
160μM
320μM
640μM
1280μM
12.8mM
Phenylbutyric Acid Concentration

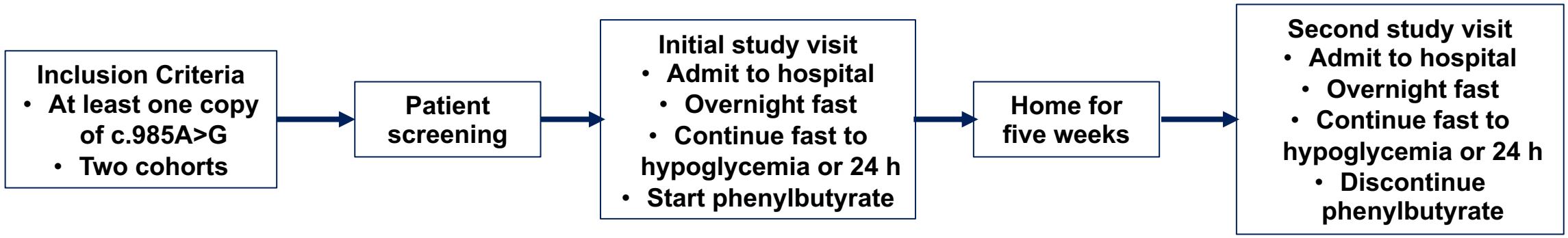
BASELINE CHARACTERISTIC of PHASE I STUDY SUBJECTS				
Subject #	Age (y)	Gender	Mutations	MCAD-related symptoms
1	42	F	**c.985A>G & c.985A>G**	fatigue with endurance exercises
2	31	F	**c.985A>G & c.985A>G**	
3	20	F	**c.985A>G** & c.244insT	nausea and vomiting with intercurrent illness, requiring infrequent hospitalization
4	22	F	**c.985A>G** & c.600-18G>A	hypoglycemia as a child; occasional nausea and vomiting with intercurrent illness

c.985A>G p.K329E (mature MCAD Lys304Glu; 25 AA mitochondrial targeting peptide)
c.985A>G carrier frequency in White ~1 in 65 (95% CI: 1 in 74, 1 in 61)
Homozygous c.985A>G MCADD birth prevalence ~7 in 100,000 (95% CI: 5.2–8.8) in White
Khalid et al. (**2008**) *J. Medical Screening*

Clinical Trial – Urine Acylglycines



Protocol Design



- Study end points
  - Prevention of hypoglycemia or increase in time to hypoglycemia
  - Reduction of fatty acid oxidation intermediates
  - Improvement in patient wellbeing (PEDs SQL)
- Study Cohorts
  - ≥16 yrs
  - ≥10-15 yrs

Study Cohorts

- Two cohorts with up to 12 subjects per cohort
- Subjects randomized to one of three dose regimens within each cohort.
- Cohort 1: ≥16 years of age (12 subjects)
  - 3.0 g/m^2/day qd (4 subjects)
  - 3.0 g/m^2/day divided q12h (4 subjects)
  - 4.0 g/m^2/day divided q12h (4 subjects)
- Cohort 2: ≥10-15 years of age (12 subjects)
  - 3.0 g/m^2/day divided qd (4 subjects)
  - 3.0 g/m^2/day divided q12h (4 subjects)
  - 4.0 g/m^2/day divided q12h (4 subjects).

Inclusion Criteria – All Patients

- Documented MCADD
- Able to perform and comply with overnight admission to CHP PCTRC, placement of an IV catheter, and all blood draws
- Negative pregnancy test for all females of childbearing age
- Signed informed consent by the subject or parent/guardian of minors
- All females of childbearing age and all sexually active males must agree to use an acceptable method of contraception throughout the study. Abstinence is an acceptable form of birth control, though appropriate contraception must be used if the subject becomes sexually active.

Inclusion Criteria

- Triheptanoin Study –
  - ≥ 16 years of age

- Phenylbutyrate Study –
  - ≥10-15 years of age or ≥ 16 years of age
  - At least one copy of the 985A>G variant

Exclusion Criteria

- Investigational drug use within 30 days of Day 1
- Active infection or any other intercurrent condition at screening
- Elevations in liver enzymes, i.e, 5–20x ULN
- Any clinical or laboratory abnormality or medical condition that, at the discretion of the investigator, may put the subject at increased risk by participating in this study, including renal insufficiency, including taking valproate or depekote (for phenybutyrate study).
- Subjects with renal insufficiency will be excluded. Cutoff eGFR <60 mL/min/1.73m^2
- Breastfeeding or lactating females.

Other Studies

- FDA requests results of 24 hour glucose monitoring for people with MCADD
  - Involves wearing a continuous glucose monitor
  - Details TBA

- Patients can do more than one study
  - Need at least a 30 day “washout” between studies

To Participate

- Contact:
- elizabeth.mccracken@chp.edu or
- lindenbergerjn2@upmc.edu

- Clinicaltrials.gov

Questions?

Thank you!