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

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  Director of the Center for Rare Disease Therapy
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
- 100s-1000s per cell
- Bacterial origins
- Cytoplasmic
- Subcellular organelles
- Dynamic, pleomorphic, motile
Energy protein complex model

1. Membrane ACADs
2. CPTII
3. TFP
4. ETF
5. ETF
6. ETF
7. ETF
8. ETF
9. ETF
10. ETF
11. ETF

Matrix ACADs

Com I

Com III

Com IV

QH$_2$

H$^+$

NADH

QH$^2$

H$^+$

Energy protein complex model
Clinical implications
A house of cards
Harvesting energy

Complete oxidation to CO₂ and H₂O

<table>
<thead>
<tr>
<th>Source</th>
<th>ATP/molecule</th>
<th>Total ATP</th>
</tr>
</thead>
<tbody>
<tr>
<td>7 FADH₂</td>
<td>2</td>
<td>14</td>
</tr>
<tr>
<td>7 NADH</td>
<td>3</td>
<td>21</td>
</tr>
<tr>
<td>8 Acetyl-CoA</td>
<td>10</td>
<td>80</td>
</tr>
<tr>
<td>Activation</td>
<td>-2</td>
<td>-2</td>
</tr>
<tr>
<td>NET</td>
<td></td>
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</table>
Energy in long chain FAODs

Interrupted oxidation to CO₂ and H₂O

<table>
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<th>ATP/molecule</th>
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<tr>
<td>7 FADH₂</td>
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</table>
Anaplerotic therapy
FDA triheptanoin trial

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

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

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>n (%)</th>
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</thead>
<tbody>
<tr>
<td>Prior treatment with MCT</td>
<td>27 (93)</td>
</tr>
<tr>
<td><strong>Clinical Manifestations</strong></td>
<td></td>
</tr>
<tr>
<td>Skeletal Myopathy</td>
<td>25 (86)</td>
</tr>
<tr>
<td>Hepatic Disease</td>
<td>3 (10)</td>
</tr>
<tr>
<td>Cardiac Disease</td>
<td>2 (7)</td>
</tr>
<tr>
<td><strong>Disease History</strong>&lt;sup&gt;a&lt;/sup&gt;</td>
<td></td>
</tr>
<tr>
<td>Rhabdomyolysis</td>
<td>26 (90)</td>
</tr>
<tr>
<td>Muscle Pain</td>
<td>22 (76)</td>
</tr>
<tr>
<td>Exercise Intolerance</td>
<td>21 (72)</td>
</tr>
<tr>
<td>Hypoglycemia</td>
<td>18 (62)</td>
</tr>
<tr>
<td>Muscle Weakness</td>
<td>16 (55)</td>
</tr>
<tr>
<td>Cardiomyopathy</td>
<td>13 (45)</td>
</tr>
</tbody>
</table>

<sup>a</sup>Occurring in >32% of subjects.
## 78 Week outcomes

<table>
<thead>
<tr>
<th>Major Clinical Event</th>
<th>Mean (SD) Annualized Event/Year</th>
<th>Pre-treatment</th>
<th>Post-treatment</th>
<th>% Change</th>
<th>P Value&lt;sup&gt;b&lt;/sup&gt;</th>
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</thead>
<tbody>
<tr>
<td><strong>Overall MCEs</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Rhabdomyolysis Events</td>
<td>1.69 (1.61)</td>
<td>0.88 (1.14)</td>
<td>-48.1</td>
<td>0.021</td>
<td></td>
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<tr>
<td>Hypoglycemia Events</td>
<td>1.30 (1.50)</td>
<td>0.83 (1.15)</td>
<td>-36.1</td>
<td>0.119</td>
<td></td>
</tr>
<tr>
<td>Cardiac Events</td>
<td>0.32 (0.91)</td>
<td>0.02 (0.12)</td>
<td>-92.8</td>
<td>0.068</td>
<td></td>
</tr>
<tr>
<td>Cardiomyopathy</td>
<td>0.07 (0.27)</td>
<td>0.02 (0.12)</td>
<td>-69.6</td>
<td>0.309</td>
<td></td>
</tr>
<tr>
<td><strong>Hospitalizations&lt;sup&gt;a&lt;/sup&gt;</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Rhabdomyolysis</td>
<td>1.39 (1.35)</td>
<td>0.65 (1.01)</td>
<td>-53.1</td>
<td>0.016</td>
<td></td>
</tr>
<tr>
<td>Hypoglycemia</td>
<td>1.03 (1.90)</td>
<td>0.63 (1.00)</td>
<td>-38.7</td>
<td>0.104</td>
<td></td>
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<td>0.30 (0.83)</td>
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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

<table>
<thead>
<tr>
<th>Most Frequent TEAEs</th>
<th>%</th>
</tr>
</thead>
<tbody>
<tr>
<td>Diarrhea</td>
<td>55</td>
</tr>
<tr>
<td>Rhabdomyolysis</td>
<td>48</td>
</tr>
<tr>
<td>Vomiting</td>
<td>48</td>
</tr>
<tr>
<td>Upper respiratory tract infection</td>
<td>41</td>
</tr>
<tr>
<td>Viral gastroenteritis</td>
<td>34</td>
</tr>
<tr>
<td>Headache</td>
<td>31</td>
</tr>
<tr>
<td>Pyrexia</td>
<td>31</td>
</tr>
<tr>
<td>Abdominal pain</td>
<td>28</td>
</tr>
<tr>
<td>Gastroenteritis</td>
<td>21</td>
</tr>
</tbody>
</table>
Energy protein complex model

![Energy protein complex model diagram](image-url)
VLCADD oxygen consumption is impaired

A

+ Glucose

OCR (pmol/min)

Time (minutes)

Oligomycin

FCCP

Rotenone / Antimycin A

WT

FB671

FB773

FB833

FB777

B

+ Glucose

- Glucose

pmol/min/cells

WT

FB671

FB773

FB833

C

+ Glucose

- Glucose

pmol/min/cells

WT

FB671

FB773

FB833

Basal respiration

Reserve capacity
Superoxide production is increased in LC-FAODs

VLCADD

LCHADD

+ Glucose

+ Glucose

− Glucose
Cytokines in VLCAD patients

(n=16) VLCAD Patient Luminex Cytokine Profiles

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
Antioxidant treatment of VLCADD

JP4-039

AFU

D 40 D 40

WT FB671

*** ##
JP4 Rx of LCHADD deficiency

MitoSOX Red (AFU)

**

WT LCHAD WT LCHAD
with glucose without glucose

HADHA common mutation 1528G>C mutation
Inhibitor induced chaperonin effect
TMZ stabilization of FAO proteins

Trimetazidine (TMZ)

VLCADD fibroblasts

![Diagram showing the effect of TMZ on VLCADD fibroblasts]
Cardiolipin (CL)

- Dimeric phospholipid
- Conical shape maintains membrane curvature, optimizes electron transfer
- Anionic CL serves as a proton trap on the outer leaflet of the IMM channeling protons to ATP synthase
- Monolysocardiolipin acetyltransferase contained on C-terminus of αTFP (HADHA)
Cardiolipin binding peptide Rx

**LCHADD**
**Transcriptional activators**

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

VLCAD patient derived fibroblasts
VLCAD mRNA Treatment

Average specific activity
nmol/min/mg

VLCAD mRNA added

WT Null +0.25 +0.5 +1 +2 +4

VLCAD (42 kDa)

KO KO 0.5 µg/g 0.5 µg/g WT WT
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

Control lymphoblasts

MCAD deficient lymphoblasts (TL671)
**Clinical trial urine acylglycines**

**Urine Acylglycines**

- **Subject 1**: 3-Phenypropionylglycine
  - 0 G: 16.69 mg/g Creatinine
  - 2 G/M2/DAY: 12.15
  - 4 G/M2/DAY: 12.69
  - 6 G/M2/DAY: 14.55

- **Subject 2**: Phenylbutyrate
  - 0 G: 7.31
  - 2 G/M2/DAY: 6.6
  - 4 G/M2/DAY: 6.87
  - 6 G/M2/DAY: 5.18

- **Subject 3**: 3-Phenypropionylglycine
  - 0 G: 12.15
  - 2 G/M2/DAY: 1.71
  - 4 G/M2/DAY: 3.19
  - 6 G/M2/DAY: 2.11

- **Subject 4**: n-Hexanoylglycine
  - 0 G: 12.69
  - 2 G/M2/DAY: 6.6
  - 4 G/M2/DAY: 6.87
  - 6 G/M2/DAY: 4.21
Collaborators

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