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
• 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.
Conflicts of interest

• Research funding
  – NIH
  – Ultragenyx
  – Stealth
  – Reata
  – Mitobridge
  – Wellstat

• Consulting
  – American Gene Therapies
  – Mitobridge
Thanks to Innsbruck

INFORM Inaugural Symposium: September 6, 2014
Innsbruck, Austria
Welcome to Lyon

INFORM Second Annual Symposium: September 4-5, 2015
Lyon, France
Mark your calendars!

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

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

Ute Spiekerkötter, 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
Sponsors and partners

- Center for Rare Disease Therapy
- Children’s Hospital of Pittsburgh of UPMC
- Ultragenyx
- Climb
- Sigma-Tau

(INFORM
INTERNATIONAL NETWORK FOR FATTY ACID OXIDATION RESEARCH AND MANAGEMENT)
Anaplerotic therapy

C16-C18 Fatty Acid

Fatty Acyl Co-A → Acylcarnitine

CPT-I, CPT-II, CACT

Acylcarnitine → Fatty acyl CoA

CPT-I, CPT-II

Triheptanoin
C7 Fatty Acid

CH$_3$-CH$_2$-CH$_2$-CH$_2$-CH$_2$-CH$_2$-COOH

Medium Chain FAO Enzymes

CH$_3$-CO-S-CoA

Two C2 Acetyl CoAs Per FA

C7 Fatty Acid

CH$_3$-CH$_2$-CO-S-CoA

One C3 Propionyl CoA Per FA

Electron Transport Chain

NADH/FADH$_2$

H$^+$ → ATP

TPP/LCHAD

Beta-oxidation Spiral

AC-CoA → OAA → CIT → FUM → αKG → MAL → OAA

TCA Cycle

PC → CH$_3$-CO-S-CoA

ATP

ADP + P$_i$ → H$^+$ → H$^+$ → H$^+$ → H$^+$ → H$^+$ → H$^+$ → H$^+$ → H$^+$ → H$^+$ → H$^+$
• Triheptanoin
  – FDA phase 2 complete
  – Publication on compassionate use
  – Phase 3 soon?
• Anti-inflammatory
• Bendavia (Stealth Biotherapeutics)
• RTA408 (Reata Pharm., Inc.)
• Mitobridge
• Uridine
• Ravicti in MCAD (Horizon)
### Triheptanoin Treatment History

<table>
<thead>
<tr>
<th>Age at Start of Treatment*</th>
<th>Duration of Treatment</th>
<th>Total N (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>&lt;1 year</td>
<td>1-2 years</td>
</tr>
<tr>
<td>0-1 month (Neonates)</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>1 month-2 years (Infants)</td>
<td>1</td>
<td>-</td>
</tr>
<tr>
<td>2-12 years (Children)</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>12-16 years (Adolescents)</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>&gt;16 years (Other)</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Total N (%)</td>
<td>1</td>
<td>-</td>
</tr>
</tbody>
</table>

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

Overall Hospitalization Days/Year

Pre-Triheptanoin

Post-Triheptanoin

VLCAD n=7
LCHAD n=4
CPT2 n=2
TFP n=2

p=0.0242
Hypoglycemic events/year

Hypoglycemia Hospitalization

Events/Year

Pre-Triheptanoin

Post-Triheptanoin

VLCAD n=5
LCHAD n=2
CPT2 n=1
TFP n=1

p=0.0091
Rhabdo hospitalizations
• 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

<table>
<thead>
<tr>
<th></th>
<th>Decrease in Event Rate</th>
<th>Decrease in # of Hospitalization Days</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total Events</td>
<td>30%</td>
<td>67%</td>
</tr>
<tr>
<td>Hypoglycemia</td>
<td>96%</td>
<td>98%</td>
</tr>
<tr>
<td>Rhabdomyolysis</td>
<td>No Change</td>
<td>60%</td>
</tr>
</tbody>
</table>
FDA triheptanoin trial

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

<table>
<thead>
<tr>
<th>Diagnosis</th>
<th>Triheptanoin C7</th>
<th>MCT C8</th>
</tr>
</thead>
<tbody>
<tr>
<td>CPT-2 (n)</td>
<td>5</td>
<td>6</td>
</tr>
<tr>
<td></td>
<td>Age 21-64; BMI 18-33</td>
<td>Age 8-43; BMI 17-35</td>
</tr>
<tr>
<td>VLCAD (n)</td>
<td>4</td>
<td>5</td>
</tr>
<tr>
<td></td>
<td>Age 7-38; BMI 17-31</td>
<td>Age 23-42; 22-31</td>
</tr>
<tr>
<td>LCHAD/TFP (n)</td>
<td>7</td>
<td>5</td>
</tr>
<tr>
<td></td>
<td>Age 7-29; BMI 14-24</td>
<td>Age 8-17; BMI 15-23</td>
</tr>
<tr>
<td><strong>TOTAL:</strong></td>
<td><strong>16</strong></td>
<td><strong>16</strong></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Participant Characteristics</th>
<th>Triheptanoin C7</th>
<th>MCT C8</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (years)</td>
<td>7 - 64</td>
<td>8 - 43</td>
</tr>
<tr>
<td>BMI (kg/m²)</td>
<td>14-33</td>
<td>15-35</td>
</tr>
<tr>
<td>Males (n)</td>
<td>6</td>
<td>6</td>
</tr>
<tr>
<td>Females (n)</td>
<td>10</td>
<td>10</td>
</tr>
</tbody>
</table>
### Expected Adverse Event

<table>
<thead>
<tr>
<th>Event</th>
<th>C-7 # of events</th>
<th>C-7 # of subjects</th>
<th>C-8 # of events</th>
<th>C-8 # of subjects</th>
</tr>
</thead>
<tbody>
<tr>
<td>Diarrhea/Loose Stools/Steatorrhea</td>
<td>9</td>
<td>5</td>
<td>12</td>
<td>6</td>
</tr>
<tr>
<td>Gastrointestinal Upset</td>
<td>24</td>
<td>11</td>
<td>38</td>
<td>12</td>
</tr>
<tr>
<td>Emesis/Vomiting</td>
<td>7</td>
<td>6</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Musculoskeletal Pain/Cramping/Elevated CPK</td>
<td>16</td>
<td>11</td>
<td>18</td>
<td>10</td>
</tr>
<tr>
<td>Rhabdomyolysis (hospital admission)</td>
<td>7</td>
<td>5</td>
<td>7</td>
<td>4</td>
</tr>
<tr>
<td>Fatigue/Lethargy</td>
<td>3</td>
<td>3</td>
<td>2</td>
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### Unexpected Adverse Event

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<tbody>
<tr>
<td>Headache</td>
<td>17</td>
<td>5</td>
<td>7</td>
<td>3</td>
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<tr>
<td>Viral Illness</td>
<td>22</td>
<td>15</td>
<td>17</td>
<td>11</td>
</tr>
<tr>
<td>Localized Pain Not Associated with Rhabdomyolysis</td>
<td>5</td>
<td>4</td>
<td>2</td>
<td>2</td>
</tr>
<tr>
<td>Dermatitis</td>
<td>1</td>
<td>1</td>
<td>4</td>
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- 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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**Triheptanoin is similarly tolerated as MCT**
Improved cardiac function

7% increase LV ejection fraction in Triheptanoin group
Treadmill response

- Significantly lower Heart Rate for same work performed with Triheptanoin supplementation
- \( p=0.05 \) adjusted for baseline
- Mean -7 beats per minute > MCT
Compared to previous study

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

Behrend et al. MGM 2012 105: 110-115
• MCT ↓ HR 15 bpm compared to carbohydrate
• Triheptanoin ↓ HR 7 bpm compared with MCT
• 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
A long summer
• Data collection still in progress
• ~12 patients with severe, life-threatening cardiomyopathy while on MCT
• All but one recovered with C7 treatment
Ultragenyx phase 2 trial

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

Blood cytokine levels

Macrophage surface markers
The Mitochondrion

Diagram of a mitochondrion showing various parts:
- Intermembrane space
- ATP synthase particles
- Matrix
- Inner membrane
- Outer membrane
- Granule
- Cristae
- Ribosome
- DNA

Measurements:
- 0.1-0.5 μm
- 1-2 μm

The Mitochondrion

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

Monolysocardiolipin
• Cardiolipin binding tetrapeptide (D-Arg-dimethyl-Tyr-Lys-Phe-NH₂)
• Up-regulates expression of nuclear encoded mito genes
• Reduces cardiomyocyte apoptosis post-ischemia
• Decreases amyloid β induced mito abnormalities
• Improves skeletal muscle function
Gene regulation

Fatty acid oxidation genes

↑ Fatty acid oxidation

corepressor

coactivator

PPRE

Ligand
- 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

RTA408

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

**Control lymphoblasts**

**MCAD deficient lymphoblasts (TL671)**
The sky is the limit
Thank You!