Therapies for Mitochondrial Diseases
April 7 & 8, 2017

Interventions in Primary Mitochondrial Disorders:
Developing an Evidence Base

Bruce H. Cohen, M.D.
Professor of Pediatrics-Northeast Ohio Medical University Director – NeuroDevelopmental Science Center
<table>
<thead>
<tr>
<th>Company/Institution</th>
<th>Role/Relationship</th>
</tr>
</thead>
<tbody>
<tr>
<td>BioElectron Therapeutics Corporation</td>
<td>Research and Travel</td>
</tr>
<tr>
<td>Stealth Peptides</td>
<td>Research, Travel, Consulting</td>
</tr>
<tr>
<td>Mitokyne</td>
<td>Research</td>
</tr>
<tr>
<td>Horizon Pharma</td>
<td>Research</td>
</tr>
<tr>
<td>USA Department of Justice</td>
<td>Consulting DVIC</td>
</tr>
<tr>
<td>American Academy of Neurology</td>
<td>CPT and Speaker</td>
</tr>
<tr>
<td>Motive Medical Intelligence</td>
<td>Content Editor</td>
</tr>
<tr>
<td>United Mitochondrial Disease Foundation</td>
<td>Speaker</td>
</tr>
</tbody>
</table>
What Are Mitochondria?

- Subcellular organelles
- 1 micron in length
  - cigar shaped (in vitro)
  - complex structure in vivo
- Comprised of ~1100 proteins
  - structural and enzymatic proteins
- ~90 proteins make up the Electron Transport Chain
  - Most of these proteins are encoded by nDNA
- mtDNA has 37 genes & resides in the mitochondria
  - ~16.5kB
  - 37 genes
    - 2rRNA (mito translation system)
    - 22 tRNA (mito translation system)
    - 13 structural proteins of the ETC
      - Therefore 75+ ETC proteins are encoded by nDNA
i a o o c t a n e  o r  2 , 2 , 4 - t r i m e t h y l p e n t a n e

\[
\begin{align*}
&\text{CH}_3 & \text{CH}_3 \\
&\text{CH}_3\text{C}-\text{CH}_2\text{CHCH}_3 & \\
&\text{CH}_3 \\
\end{align*}
\]

\text{octane number = 100}

\[+\]

\text{O}_2

\[+\]

\text{Fuel} + \text{Oxygen} \rightarrow \text{Fire + Exhaust}

\[+\]

\text{Water} + \text{Carbon Dioxide}
Vitamins and Cofactors
CoQ10
Lipoic Acid
B1, B2, B3, B5, Folate
Fe/S Core, Cu Core
Vitamins and Cofactors
CoQ10
Lipoic Acid
B1, B2, B3, B5, Folate
Fe/S Core, Cu Core
What do mitochondria do?

1. generate ATP ★

2. critical component of apoptosis – calcium homeostasis ✔ ➟ ❗

3. generate free radicals $O_2 \Rightarrow O_2\bullet$

4. Roles in most neurodegenerative diseases and some cancers, acquired disorders of oxidative damage (DM, stroke & heart attacks) ❌

5. Basis for toxicity of many antibacterial drugs and cancer chemotherapy drugs
The Electron Transport Chain

OXPHOS

ATP Production

5 Complexes

~90 different proteins

1098 genes supporting the function of the ETC
What Tissues are Targets for Mitochondrial Diseases?

- Those with High energy utilization & Post Mitotic at Birth
- Those biologic systems not able to handle oxidative damage
  - Short term: Brain (stroke), Heart (myocardial infarction)
  - Long term: Brain, Heart, Kidneys, Liver, Pancreas, Retina, Hearing, Peripheral Nervous System
- Muscle was the first organ identified historically
- Nerve cells do not replicate (sort of)
  - But the mitochondria within them replicate constantly
  - No selective advantage to weed out cells with weaker mitochondria --- the defect just stays there
- Remember – 1100 genes (proteins) responsible for mitochondrial function
**Western Medicine**
- Anatomically Based
  - Disease defined by the organ system
    - Cardiology
    - Neurology
    - Rheumatology
    - Pulmonology
    - Gastroenterology
- Life and Death defined by heart beat or brain wave activity
- A dead body looks the same as a live body

**Mitochondrial Medicine**
- Based on chemistry and electricity
  - Disease defined by cellular function
    - ATP production
    - Free radical % production
    - Unbalanced redox
    - Triggering of apoptosis
    - Calcium homeostasis
- Life and Death defined by redox state
- A dead body looks quite different biochemically than a live body
Primary Mitochondrial Disease

Mutation

Mitochondrial Protein Defect
Expression
Function

Primary Cell Effects
\( \Delta \psi \)
ROS
OXPHOS
Substrate accumulation

Secondary Events
↓ ATP
Redox changes
PTP opening
Mitophagy
Apoptosis
Ca\(^{++}\) homeostasis
Signaling
Mito biogenesis
IMM Integrity
Fission & Fusion

Disease
Brain
Muscle
Heart
Skeletal
Smooth
Nerve
Eyes
Ears
Kidney
Liver

Genetic Treatments
Small Molecules
Metabolic Manipulation
Diet & Exercise

Adapted from Koopman et al 2012 NEJM
Scientific Rationale for Vitamin and Cofactor Therapy

- Stimulate poorly functioning enzymes
- Antioxidant activity to reduce oxidative stress and effects
- Alternative energy sources
- Improve muscle bulk
- Scavenge free-fatty acids and poisonous organic acids
- Bypass blocked components of the electron transport chain
- Vascular Effects
- Replace Deficient Vitamins, Cofactors
Clinical Rationale for Vitamin and Cofactor Therapy

- Offers a medical therapy; even if not a proven therapy
- Offers the chance for increased partnership
- Effectiveness of therapy is difficult to prove scientifically, even if there is evidence to the family or clinician of improvement
- Offers hope
Thiamine for PDHC Deficiency
- Stimulate poorly functioning enzymes

CoQ10, N-acetyl cysteine
- Antioxidant activity to reduce oxidative stress and effects

Succinate, MCT Oil
- Alternative energy sources

Creatine Monohydrate
- Improved Muscle Bulk

Levocarnitine
- Scavenge free-fatty acids and poisonous organic acids

Vitamin K +C
- Bypass blocked components of the electron transport chain

L-Arginine, L-Citrulline
- Vascular Effects (?)

CoQ10, Folinic Acid
- Replace Deficient Vitamin/CoFactor
How Do We Judge Effectiveness?

1. Individual benefit; case report demonstrating benefit
2. Series of patients treated under a standard protocol using the medication, published
3. Randomized clinical trial using
   1. A placebo
   2. Neither the doctor or patient knows if they are treated with the active agent
   3. Sometimes there is a crossover
   4. The “improvement” aka “outcome measure” is measured using proven scale – known as a “primary endpoint”. There are “secondary endpoints” as well.
What Makes an Intervention Effective?

the plural of antidote is not data
Who Is The Judge?
Who Is The Judge?

- Get proven therapies to market
- Keep ineffective treatments out of the market
Are Vitamins an Effective Treatment?

● Medications
  - There are no FDA-approved therapies
  - Cochran Review determines RTCs failed to identify clinically effective treatments for populations of patients
  - Literature filled with “n of 1” and cases where the diagnosis of a mitochondrial disease was based on old and not truly diagnostic based on current technology or process
  - 1 clinical study – CoQ10, Creatine, alpha lipoic acid

● Symptomatic and supportive care

● Exercise

● Clinical Trials using new agents
  - manipulating mitochondrial function
My Mitochondrial Therapy
(Not a Trivial “Rx”!!!)

Coenzyme Q₁₀
Levocarnitine
Vitamin B₁
Vitamin B₂
Vitamin B₃
Vitamin B₅
Vitamin B₆
Vitamin B₁₂
Folic Acid
Biotin
Vitamin C
Vitamin E
Beta-carotene
Zinc
Selenium
Magnesium
N-acetyl cysteine
My Mitochondrial Therapy

1989-2007

- Coenzyme Q₁₀
- Levocarnitine
- Vitamin B₁
- Vitamin B₂
- Vitamin B₃
- Vitamin B₅
- Vitamin B₆
- Vitamin B₁₂
- Folic Acid
- Biotin
- Vitamin C
- Vitamin E
- Beta-carotene
- Zinc
- Selenium
- Magnesium
- N-acetyl cysteine

2008-2014

- Alpha Lipoic Acid
- Arginine
- Levocarnitine
- CoQ₁₀
- Riboflavin
- Creatine monohydrate
- Folinic Acid
It should be clear from the series of clinical trials summarized here that anecdotal case reports or common medical practice of specific therapies for mitochondrial disorders are insufficient for evidence-based medicine. When subjected to controlled trials, formerly advocated therapies have not usually been proven to be effective and/or may have unacceptable side effects. This is borne out particularly by experience with DCA, creatine, and CoQ10.
How Did we Get Here?

• The individual vitamins were chosen because it sounded like a good idea.

• Early leaders in the field chose the specific vitamins and dosages.

• Most publications were based on either one patient’s response or the response of a small (<10) group of patients, with unverified diseases and different phenotypes.

• Essentially no clinical trials designed using an accepted phase 3 study approach; those done seldom showed any benefit.
How Do We Measure Success? – Clinically Relevant Endpoints

- Brain
  - Seizure count
  - Age-appropriate neuropsychological testing
  - Headaches Diary
  - Stroke Count
  - Dozens of motor tests

- Muscle
  - Strength Testing (dozens of different tests)
  - OT and PT evaluations
  - Lessen fatigue
  - Cardiac contractility
  - EKGS

- Liver
  - Sequential liver function studies, enzymes
  - Ultrasounds

- Pancreas: Amylase, lipase, stool fat, HbA1c

- Nerve
  - Sequential autonomic function studies
  - Pain diary
  - Sequential NCV

- GI
  - Qualitative testing of motility
  - Symptom diary

- Renal
  - GFR and fractional excretion studies

- Eyes
  - Sequential Va and Vf testing

- Ears
  - Sequential audiology

- Systemic
  - growth charting
  - Cardio-Pulmonary Exercise VO$_2$ max
  - Analyte studies

Not So Easy
BENEFICIAL EFFECTS OF CREATINE, CoQ₁₀, AND LIPOMIC ACID IN MITOCHONDRIAL DISORDERS

M. CHRISTINE RODRIGUEZ, BSc,¹ JAY R. MACDONALD, MD, PhD,² DOUGLAS J. MAHONEY, PhD,² GIANNI PARISE, PhD,¹ M. FLINT BEAL, MD,² and MARK A. TARNOPOLSKY, MD, PhD⁴

17 patients - definitive diagnosis
Double-blind, randomized, placebo-controlled, crossover design
2 months on each treatment, 5 week washout
- 3 grams creatine monohydrate bid
- 300 mg alpha lipoic acid bid
- 120 mg CoQ10 bid

Results:
- lower resting lactate
- prevention of loss of strength at the ankle
- reduction in urine 8-OH dG excretion
- improved fat-free mass
- no change in PFTs, peak handgrip

Today's Cost to Conduct = $100,000 per patient - $1,700,000 study
My Mitochondrial Nutraceutical Therapy

2017

- Alpha Lipoic Acid
- L-Arginine – L- Citrulline
- CoQ10
- Riboflavin
- Creatine monohydrate
- Folinic Acid
What Are The Experts Doing?
Parikh, et al. 2013

<table>
<thead>
<tr>
<th>Supplement</th>
<th>Percentage</th>
</tr>
</thead>
<tbody>
<tr>
<td>L-Arginine</td>
<td>100%</td>
</tr>
<tr>
<td>CoQ10</td>
<td>100%</td>
</tr>
<tr>
<td>L-Carnitine</td>
<td>94%</td>
</tr>
<tr>
<td>Creatine</td>
<td>75%</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th># Vitamins</th>
<th>Percentage</th>
</tr>
</thead>
<tbody>
<tr>
<td>&gt;9</td>
<td>(9%)</td>
</tr>
<tr>
<td>6-9</td>
<td>(19%)</td>
</tr>
<tr>
<td>3-6</td>
<td>(63%)</td>
</tr>
<tr>
<td>&lt;3</td>
<td>(9%)</td>
</tr>
</tbody>
</table>
Shotgun Mitochondrial Therapy
Why it Does Not Make Sense

- 1 approach to 100s of diseases
- No ability to judge efficacy
- Expensive
- Only able to be carried out by overly compulsive parents or patients
- Prescribers viewed as “vitamin pushers”
- Seldom meets therapeutic goals

- Coenzyme Q10
- Levocarnitine
- Vitamin B1, 2, 3, 5, 6, 12
- Folic Acid
- Biotin
- Vitamin C
- Vitamin E
- Beta-carotine
- Zinc
- Selenium
- Magnesium
- Alpha Lipoic Acid
- Arginine
- NADH
- Ribose
- Allopurinol
- Creatine monohydrate
- Folinic Acid
- N-acetyl cysteine
Shotgun Mitochondrial Vitamin Therapy
What is the Big Deal?

- $3000 per year (no folinic acid)
- Add $6000+ for folinic acid
- No evidence this is effective!!!
Vitamins - What Makes Sense (to me)

- CoEnzyme Q10 5 - 20 mg/kg/day ÷ tid
- Riboflavin 100-600 mg/day qHS
- α-Lipoic Acid 10 mg/kg/day ÷ bid
- Creatine Monohydrate 100 mg/kg/day; 5 gms max
- MELAS/Strokes
  - L-arginine 100-300 mg/kg/day
  - L-citrulline 100-300 mg/kg/day
- Folinic Acid 5-50 mg a day
My Typical Treatment

- Maximal exercise ± physical, occupational or speech therapies
  - endurance training
  - resistance training

- Sleep Hygiene - Polysomnograms for Everyone

- Hydration and more hydration; Early IV hydration during viral illnesses

- Basic Supplements: Derived from Evidence, Experience and Costs ($ and other costs)
  - CoEnzyme Q10 - 5-20 mg per kg per day
  - Carnitor only if carnitine deficient
  - B2 100-600 mg per day
  - Creatine monohydrate 0.1 grams per kg per day; max 5 grams a day
  - Alpha-Lipoic Acid 300 mg bid for an adult
  - Folinic Acid for CSF folate-deficient patients: 5-25 mg tid
  - l-arginine 0.15-0.3 gram per kg per day; 4-24 grams a day for an adult
  - l-citrulline 0.1 grams per kg per day
  - ? Antioxidants (Gamma-E 400 IU, C 500 mg bid, Selenium, Zinc)

- Miralax polyethylene glycol for constipation

- Avoid Stress
  - Illness, fever, starvation, sleep
  - treat illness, fever, starvation and sleep disturbance
1) Many Diseases (geneotype-phenotype)
2) Which Outcome Measure(s) to evaluate?
3) Long and unpredictable clinical course
4) Swings in function with prolonged periods of disease inactivity
5) Difficulty in getting patients to meet entry criteria
6) Statistical considerations
7) Cost
8) Travel
Clinical Trials
My Life as a Neuro-Oncologist: What is the Primary Endpoint?

• Time to tumor progression

• Glioblastoma (adults) 18000+ patients per year in the USA with a median time to progression of 9±2 months with surgery alone

• Medulloblastoma (children) 450 children per year in the USA; 90% treated in a network of hospitals

• Infants < 3 years of age with malignant brain tumors; 250 per year; ~ 100% treated in a network of hospitals

• Children’s Oncology Group - a federally funded robust funding network
  – It is a lot easier to raise money for research if you have heard of the disease!
My Life as a Neuro-Oncologist: No Error Bars

A: Biopsy only, n=25
B: Extensive resection, n=28
C: Extensive resection + XRT, n=46
D: ≥95% resection + XRT + Chemo, n=184

Years following surgery
Clinical Trial Design
End Points

Newcastle Pediatric Mitochondrial Disease Scale
Adverse Event Count
RI’s Menu Choice of Scales
  Berry-Albright Dystonia Scale
  Quality of Life Scales
  6-Minute Walk Test
  Gross Motor Function Scale
  Seizure Calendar
  Friedreich Ataxia Rating Scale

keep it simple
Primary End Points

Post-Hoc Gives You Hints at the Next Study
Not FDA Approval
Designing the Perfect Phase 3 Study

- It has to excite the patients and investigators
  - Financially Viable
  - Perception must be Worth the Travel
    - Double-Blind
    - Placebo Controlled
  - Some Type of Crossover
- For studies that do not crossover; treatment and non-treatment arms must be similar (enough)
Ongoing Studies in USA

EPI-743  BioElectron Therapeutics Corporation/Edison
Open Label
Children Leigh Syndrome
Confirmed Mitochondrial Disease RCT in Planning

RP-103  Raptor/Horizon
Children Confirmed Mitochondrial Disease

Bendavia Elamipretide (MTP-131) NCT02367014) Stealth Biotherapeutics
Adults 16-65 Confirmed Mitochondrial Myopathy
Mass General, Akron Children’s, UPMC, UCSD

Next Phase at IRB

RTA-408  NCT02255422  Reata
Adults 18-75 Confirmed Mitochondrial Myopathy
UCLS, Mass General, Akron Children’s, CHOP, UPMC, Dallas, UT, Baylor, Copenhagen

PN-401  Wellstat
In Planning: Mito Epilepsy, Myopathy and RTA
EPI-743 has unique redox and pharmacologic properties.
EPI-743 enhances cell viability of GSH-depleted cells

Natural history of pediatric Leigh syndrome

"Generally, no causal treatment is available for Leigh syndrome...Despite some therapeutic improvements, the outcome of patients with Leigh syndrome is generally poor. In the vast majority of cases, the disease is fatal, and patients die before age 5 years."

p.232
Ten consecutive children, ages 1-13 years, were enrolled; they possessed seven different genetic defects. All children exhibited reversal of disease progression regardless of genetic determinant or disease severity. The primary endpoints--Newcastle Pediatric Mitochondrial Disease Scale, the Gross Motor Function Measure, and PedsQL Neuromuscular Module--demonstrated statistically significant improvement (p<0.05). In addition, all children had an improvement of one class on the Movement Disorder-Childhood Rating Scale. No significant drug-related adverse events were recorded.
Safety and Efficacy Study of EPI-743 in Children With Leigh Syndrome

This study is ongoing, but not recruiting participants.

Sponsor:
Edison Pharmaceuticals Inc

Collaborators:
Axio Research. LLC
Biosoteria

Information provided by (Responsible Party):
Edison Pharmaceuticals Inc

ClinicalTrials.gov Identifier:
NCT01721733

First received: November 1, 2012
Last updated: October 23, 2013
Last verified: October 2013

<table>
<thead>
<tr>
<th>Condition</th>
<th>Intervention</th>
<th>Phase</th>
</tr>
</thead>
<tbody>
<tr>
<td>Leigh Syndrome</td>
<td>Drug: Placebo</td>
<td>Phase 2</td>
</tr>
<tr>
<td></td>
<td>Drug: EPI-743 15 mg/kg</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Drug: EPI-743 5 mg/kg</td>
<td></td>
</tr>
</tbody>
</table>

Study Type: Interventional
Study Design: Allocation: Randomized
Endpoint Classification: Safety/Efficacy Study
Intervention Model: Crossover Assignment
Masking: Double Blind (Subject, Caregiver, Investigator, Outcomes Assessor)
Primary Purpose: Treatment

Official Title: A Phase 2B Randomized. Placebo Controlled. Double Blind Clinical Trial of EPI-743 in Children With Leigh Syndrome
EPI-743 Leigh syndrome: RCT

• Akron, Baylor, Stanford, Seattle

• 36 patients, randomized to drug at 5mg/kg/day or 15 mg/kg/day vs Placebo (1:1) x 6 months

• All patients on placebo get put on drug at 6 months at 15mg/kg/day, others on drug continue at their dose

• Primary Outcome Measures: Newcastle Pediatric Mitochondrial Disease Scale (NPMDS) Sections 1-3
Outcome Measures

• NPMDS (Scales 1-3)
  — Change from baseline to 6 months will be compared between subjects in active and placebo treatments

• Secondary Outcome
  — Neuromuscular Function
    - Gross Motor Function Measure
    - Barry Albright Dystonia
  — Respiratory Function
    - Need for tracheostomy
  — Disease Morbidity
    - Total # of hospitalizations
  — Glutathione cycle biomarkers
    - Blood levels compared between active and placebo groups
  — # of AEs
  — Mortality
Open-Label, Dose-Escalating Study to Assess Safety, Tolerability, Efficacy, PK and PD of RP103 in Children With Inherited Mitochondrial Disease (RP103-MITO-001)

This study is currently recruiting participants. (see Contacts and Locations)

Verified November 2014 by Raptor Pharmaceuticals Inc.

Sponsor: Raptor Pharmaceuticals Inc.

Information provided by (Responsible Party): Raptor Pharmaceuticals Inc.

ClinicalTrials.gov Identifier: NCT02023866

First received: December 17, 2013
Last updated: November 19, 2014
Last verified: November 2014

History of Changes

Up to 25 patients will be enrolled if there is no toxicity up to the level of 1.3 g/m2/day of RP103. Initial sample size estimate is 25 subjects. Interim analyses will occur after 4 and then 12 subjects complete the study through Week 24. There is a possibility of stopping for efficacy or for futility after either interim analysis. If the study is not stopped early, final analysis will occur after 25 subjects have completed through Week 24.

The rationale for choosing patients with inherited mitochondrial disease who are age 2 and older is based on available clinical data collected in previous and current RP103 studies in other indications, in subjects aged 2 years and older.
Cysteamine bitartrate
Theory: Cysteamine reduces the Oxidized Glutathione

\[
\text{Cysteamine: } \text{NH}_2 - (\text{CH}_2)_2 - \text{SH}
\]

\[
\text{Cystamine: } \text{NH}_2 - (\text{CH}_2)_2 - \text{S}
\]

\[
\text{Reduced Protein: } \text{S-H}
\]

\[
\text{Oxidized Protein: } \text{S-OH}
\]
Outcome Measures

• NPMDS (Scales 1-3)
  — Change from baseline

• Secondary Outcome
  — Glutathione
  — Acetoacetate, betahydroxybuterate
  — Lactate
  — 2 of 6 Scales
    - Barry Albright Dystonia
    - GMFS + Grip Jama Dyanometer
    - Modified Lansky Play Performance
    - GMFS
    - Friedreich Ataxia Rating Scale
    - Seizure Calendar
A Study Investigating the Safety, Tolerability, and Efficacy of MTP-131 for the Treatment of Mitochondrial Myopathy (MMPOWER)

This study is currently recruiting participants. (see Contacts and Locations)

Verified December 2015 by Stealth BioTherapeutics Inc.

Sponsor:
Stealth BioTherapeutics Inc.

Information provided by (Responsible Party):
Stealth BioTherapeutics Inc.
SS Peptides
Hazel H. Sezto and Peter W. Schiler

Small Cell Permeable Peptides < 10 AA

Designed to Target the IMM

Scavenge ROS
Reduce mitochondrial ROS production
Inhibit mitochondrial permeability transition
Inhibit Apoptosis and necrosis
d-Arg-2', 6'-dimethyltyrosine-Lys-Phe-NH2
Cardiolipin

1',3'-Bis-[1,2-di-(9Z-octadecenoyl)-sn-glycero-3-phospho]-sn-glycerol
What is Wrong with this Picture?

Hint: It is not about the supercomplex structure
Phospholipid Content

- Phosphatidylethanolamine 37%
- Phosphatidylcholine 26%
- Cardiolipin 37%
- Phosphatidylinositol 5%
SS-31 Stabilizes Cardiolipin

A
A  

Bink et al  
JASN 24: 1250-61, 2013  
Ischemia Model
Reperfusion Injury after Renal Revascularization

Eirin A et al. Hypertension. 2012;60:1242-1249
Ocuvia in Diabetic Retinopathy
Restores Visual Function

Ocuvia has no effect:
- On normal animals
- On blood glucose or body weight
NCT02367014: MMPower - SPIMM-201

- Phase II
- Multicenter trial
- Randomized, double blind, placebo controlled
- Multiple ascending-dose study
- Genetically confirmed mitochondrial disease
- Myopathy + exercise intolerance
- 3 cohorts, 12 patients each, 9 randomized to receive elamipretide and 3 to receive placebo
- Daily 2 hour IV infusions x 5 days (0.01, 0.10, 0.25 mg/kg/hr)
NCT02367014: MMPower - SPIMM-201

• Safety and Tolerability
  – AE
  – Changes in VS
  – ECGs
  – Clinical laboratory evaluations

• Efficacy
  – 6MWT (primary)
  – Cardiopulmonary exercise testing (CPET)
  – Patient-reported symptoms
    - NMDAS
    - Daily symptom questionnaire
      – Abdominal pain, limitation of activities, muscle pain, physical fatigue, mental fatigue
  – Biomarkers (glutathione, urine 8-isoprostane and 8-OH-2-deoxyguanosine)
Table 1: Demographics and Baseline Clinical Characteristics

<table>
<thead>
<tr>
<th></th>
<th>Cohort 1 0.01mg/kg/hr</th>
<th>Cohort 2 0.10mg/kg/hr</th>
<th>Cohort 3 0.25mg/kg/hr</th>
<th>Placebo 0mg/kg/hr</th>
<th>All N=36</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>N=9</td>
<td>N=9</td>
<td>N=9</td>
<td>N=9</td>
<td>N=36</td>
</tr>
<tr>
<td>Age (Years)</td>
<td>41 ± 11</td>
<td>45 ± 14</td>
<td>42 ± 17</td>
<td>42 ± 16</td>
<td>43 ± 14</td>
</tr>
<tr>
<td>Gender</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Female</td>
<td>7</td>
<td>8</td>
<td>6</td>
<td>9</td>
<td>30</td>
</tr>
<tr>
<td>Male</td>
<td>2</td>
<td>1</td>
<td>3</td>
<td>0</td>
<td>6</td>
</tr>
<tr>
<td>Weight (kg)</td>
<td>71 ± 21</td>
<td>64 ± 8</td>
<td>59 ± 8</td>
<td>56 ± 6</td>
<td>62 ± 13</td>
</tr>
<tr>
<td>BMI (kg/m2)</td>
<td>26 ± 7</td>
<td>24 ± 3</td>
<td>22 ± 5</td>
<td>21 ± 2</td>
<td>23 ± 5</td>
</tr>
<tr>
<td>Symptom</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Fatigue</td>
<td>9</td>
<td>9</td>
<td>9</td>
<td>8</td>
<td></td>
</tr>
<tr>
<td>Exercise Intolerance</td>
<td>9</td>
<td>7</td>
<td>9</td>
<td>9</td>
<td></td>
</tr>
<tr>
<td>Muscle weakness</td>
<td>8</td>
<td>8</td>
<td>8</td>
<td>7</td>
<td></td>
</tr>
<tr>
<td>Muscle cramps</td>
<td>2</td>
<td>3</td>
<td>3</td>
<td>4</td>
<td></td>
</tr>
<tr>
<td>Muscle atrophy</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>3</td>
<td></td>
</tr>
<tr>
<td>Fasiculations</td>
<td>2</td>
<td>1</td>
<td>0</td>
<td>1</td>
<td></td>
</tr>
<tr>
<td>Genetic Findings</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mitochondrial DNA</td>
<td>2</td>
<td>3</td>
<td>5</td>
<td>3</td>
<td>13</td>
</tr>
<tr>
<td>deletions</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mitochondrial DNA</td>
<td>2</td>
<td>5</td>
<td>3</td>
<td>5</td>
<td>15</td>
</tr>
<tr>
<td>missense mutations</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Nuclear DNA mutations</td>
<td>5</td>
<td>1</td>
<td>1</td>
<td>1</td>
<td>8</td>
</tr>
<tr>
<td>NMDAS Score*</td>
<td>12 ± 6</td>
<td>16 ± 6</td>
<td>16 ± 6</td>
<td>16 ± 7</td>
<td></td>
</tr>
</tbody>
</table>

* Score based on the Newcastle Mitochondrial Disease Scale.
Table 2  Summary of Change From Baseline in Distance Walked (meters) in the 6MWT after 5 days or treatment and two days following treatment (ITT Population)

<table>
<thead>
<tr>
<th></th>
<th>Elamipretide</th>
<th></th>
<th></th>
<th>Placebo</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>0.01 mg/kg/hr</td>
<td>0.10 mg/kg/hr</td>
<td>0.25 mg/kg/hr</td>
<td></td>
</tr>
<tr>
<td>(N = 9)</td>
<td>(N = 9)</td>
<td>(N = 9)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Baseline Mean (SD)</td>
<td>363.9 (143.15)</td>
<td>421.9 (66.85)</td>
<td>360.2 (100.99)</td>
<td>369.8 (96.82)</td>
</tr>
<tr>
<td>Change on Day 5</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mean (SD)</td>
<td>14.2 (49.4)</td>
<td>34.3 (43.5)</td>
<td>65.4 (45.7)</td>
<td>20.9 (45.2)</td>
</tr>
<tr>
<td>LS Mean p-value</td>
<td>0.75</td>
<td>0.47</td>
<td>0.053</td>
<td></td>
</tr>
<tr>
<td>Change at 2 days following treatment</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mean (SD)</td>
<td>31.8 (41.1)</td>
<td>35.1 (56.6)</td>
<td>63.6 (63.3)</td>
<td>39.4 (60.7)</td>
</tr>
<tr>
<td>LS Mean p-value</td>
<td>0.76</td>
<td>0.97</td>
<td>0.39</td>
<td></td>
</tr>
</tbody>
</table>

Abbreviations: SD = Standard deviation ; LS = Least squares; LSM Diff = Least Squares Mean Difference;.

LSM Difference is MTP-131 dose (0.01, 0.10, or 0.25 mg/kg/hr) minus Placebo.
P-value and 90% CI of the difference are based on the ANCOVA model which included treatment as a factor and baseline measure as a covariate.
Change in Distance walked following 5 days of treatment adjusting for gender with an interaction between baseline distance walked and treatment. The test for trend for change in distance walked and dose was significant at p=0.01.
RTA 408 Capsules in Patients With Mitochondrial Myopathy - MOTOR

This study is currently recruiting participants. (see Contacts and Locations)

Verified November 2015 by Reata Pharmaceuticals, Inc.

Sponsor:
Reata Pharmaceuticals, Inc.

Collaborator:
AbbVie

Information provided by (Responsible Party):
Reata Pharmaceuticals, Inc.

ClinicalTrials.gov Identifier:
NCT02255422

First received: September 30, 2014
Last updated: November 4, 2015
Last verified: November 2015
History of Changes
• RTA 402 (Bard) and RTA 408 (AIMs) bind to Keap-1 activating transcription factor Nrf2 and inhibiting transcription factor NF-kB (nuclear factor kappa-light-chain-enhancer of activated B cells) - controls transcription of DNA, cytokine production and cell survival

**Pharmacology of AIMs**

**Antioxidative Enzymes**
- ROS/RNS Detox: NQO1, SOD1, catalase, HO-1
- GSH Homeostasis: GCLC, GCLM, GSR
- NADPH Production: G6PD, PGD
- Iron Detoxification: FTH1, FPN

**Bioenergetics (ATP Synthesis)**
- ↑ Glucose Uptake
- ↑ Fatty Acid Oxidation: ACOX, CPT1
- ↑ FADH2 and NADH
- ↑ Biogenesis: PGC1α

**Pro-Inflammatory mediators**
- Cytokines: IL1b, IL-6, TNF
- Chemokines: MCP-1, MIP-2
- Cell Adhesion: ICAM-1, VCAM-1
- ROS, RNS, iNOS

**Proliferative/Anti-Apoptotics**
- Bcl-2, VEGF, Cyclin D1
RTA 408 Improves Mitochondrial Function

- RTA 408 tested in Parkinson’s Disease, ALS, and FA patient fibroblasts
  - RTA 408 restores mitochondrial function, as assessed by transmembrane potential and ATP levels
  - RTA 408 increases the glutathione and the NADH pool (reducing equivalents for electron transport chain)
- Work is ongoing in models of epilepsy, dementia, and others
Overview of Design and Timing of NDA-Enabling FA and MM Studies

- Capturing clinical, quality of life, physiological, and biochemical data
- Phase 2 portion starting in 4Q 2014 followed by Phase 3 portion in 2Q 2015

<table>
<thead>
<tr>
<th>Design</th>
<th>Randomized, placebo-controlled, double-blind, dose-ranging study</th>
</tr>
</thead>
<tbody>
<tr>
<td>Size</td>
<td>40 to 52 patients</td>
</tr>
<tr>
<td>Patients</td>
<td>Genetically confirmed MM or FA</td>
</tr>
<tr>
<td>Treatment</td>
<td>2-Part study with 12 week treatment duration for all patients</td>
</tr>
</tbody>
</table>
| Part 1 | • Cohort 1: Patients randomized 3:1 to 2.5 mg RTA 408 or placebo. After the Week 2 visit, patient receiving RTA 408 2.5 mg will dose escalate to RTA 408 5 mg, unless a dose-limiting toxicity is reported.  
  • Cohort 2: Patients will be randomized 3:1 to 10 mg RTA 408 or placebo. |
| Part 2 | • Patients randomized 1:1:1 to receive RTA 408 (2.5 mg or 10 mg) or placebo. |
| Key Endpoints | Primary: Change in peak work during maximal exercise testing  
  Secondary: MM – 6MWD; FA - Modified Friedreich’s Ataxia Rating Scale Score (FARS) |
Triacetyl Uridine

5FU Overdose
Hereditary Orotic Aciduria

Xuriden™
(urdine triacetate)

Full Prescribing Information

Instructions for Use
Clinical Trial Work