Mitochondrial Medicine
Treating Chronic Fatigue with Mitochondrial Support

Jon D. Kaiser, M.D.
Clinical Faculty, University of California
San Francisco Medical School
Chief Medical Officer
K-PAX Pharmaceuticals
Disclosure Statement

• Jon Kaiser, MD is the Chief Medical Officer of K-PAX Pharmaceuticals, Inc.

• **K-PAX Pharmaceuticals** is an integrative medicine pharmaceutical company developing treatments to strengthen immune function and support energy metabolism.

• This educational activity has been reviewed by the California Naturopathic Doctors Association and contains no commercially biased information.

• Therapeutic use of all prescription medications discussed is off-label.
Diseases Linked to Mitochondrial Dysfunction

Neurodegenerative Diseases
(Dementia, Fatigue, Peripheral neuropathy
ALS, Alzheimer’s, & Parkinson’s Dz.)

Immune Diseases
(Chronic Fatigue Syndrome, Fibromyalgia
Recurrent infections, Chronic inflammation & Cancer)

Hepatic & Metabolic Diseases
(Multiple Chemical Sensitivities, Nonalcoholic Hepatitis,
Type II Diabetes)
Diseases Linked to Mitochondrial Dysfunction

- **Neurodegenerative Diseases**
  - (Dementia, Fatigue, Peripheral neuropathy, ALS, Alzheimer’s, & Parkinson’s Dz.)

- **Immune Diseases**
  - (Chronic Fatigue Syndrome, Fibromyalgia, Recurrent infections, Chronic inflammation & Cancer)

- **Hepatic & Metabolic Diseases**
  - (Multiple Chemical Sensitivities, Nonalcoholic Hepatitis, Type II Diabetes)
Alzheimer’s Disease

Mitochondrial dysfunction is a trigger of Alzheimer's disease pathophysiology.

Reducing mitochondrial decay with mitochondrial nutrients to delay and treat cognitive dysfunction, Alzheimer's disease, and Parkinson's disease.

Deconstructing mitochondrial dysfunction in Alzheimer disease.
Parkinson’s Disease

Mitochondria: A Therapeutic Target for Parkinson’s Disease?

Mitochondrial dysfunction in Parkinson's disease.

Pink1, Parkin, DJ-1 and mitochondrial dysfunction in Parkinson's disease.
Type II Diabetes Mellitus

Mitochondrial dysfunction and type 2 diabetes.

Role of mitochondrial dysfunction in insulin resistance.

Oxidative capacity, lipotoxicity, and mitochondrial damage in type 2 diabetes.

Prevention of mitochondrial oxidative damage as a therapeutic strategy in diabetes.
Fibromyalgia

Oxidative stress and mitochondrial dysfunction in fibromyalgia.

Is inflammation a mitochondrial dysfunction-dependent event in fibromyalgia?

Mitochondrial dysfunction in fibromyalgia and its implication in the pathogenesis of disease.
Chronic Fatigue Syndrome

Mitochondrial dysfunction and oxidative damage may play a critical role in the pathogenesis of CFS [Fulle, et al. *Free Radical Bio Med.* 2000]


Autoimmune Diseases

Mitochondrial dysfunction plays a key role in progressive axonal loss in multiple sclerosis.

Mitochondrial dysfunction contributes to neurodegeneration in multiple sclerosis.

Apoptosis and mitochondrial dysfunction in lymphocytes of patients with systemic lupus erythematosus.
MITOCHONDRIAL DYSFUNCTION

- Alzheimer's Disease
- Parkinson's Disease
- Cancer Fatigue
- Chronic Fatigue Syndrome
- Genetic Mitochondrial Diseases
- Gulf War Illness
- Lyme Disease
- Medication-induced
- Autoimmune Diseases
- Fibromyalgia
Mitochondrial Medicine
Dietary Carbohydrates + Dietary Fats

\[ \text{H}^+ \text{ ions} + \text{H}^+ \text{ ions} + \text{H}^+ \text{ ions} \]

+NAD+ (transport)

\[ \text{OH}^- \text{ radical} + \text{O}^{2-} \text{ radical} + \text{H}_2\text{O}_2 \text{ peroxide} \]

Oxidation

© K-PAX Pharmaceuticals
\[ \text{H}^+ \text{ ions} \quad \text{H}^+ \text{ ions} \quad \text{H}^+ \text{ ions} \]

\[ \text{OH}^- \text{ radical} \quad \text{O}^{2-} \text{ radical} \quad \text{H}_2\text{O}_2 \text{ peroxide} \]

Electron transport chain

ATP

HEAT

CHEMICAL ENERGY

CELLULAR WORK

© K-PAX Pharmaceuticals
**Chemical Energy**

\[ \text{H}^+ \text{ ions} \quad \text{H}^+ \text{ ions} \quad \text{H}^+ \text{ ions} \]

**Smoke and Ash**

\[ \text{OH}^- \quad \text{O}^{-2} \quad \text{H}_2\text{O}_2 \text{ peroxide} \]

**Antioxidant Nutrients and Enzymes**

**Electron Transport Chain**

\[ \text{ATP} \quad \text{ATP} \quad \text{ATP} \]

**CO}_2 \quad \text{H}_2\text{O} \]

**Heat**

**Chemical Energy**

**Cellular Work**
H^+ ions | H^+ ions | H^+ ions
---|---|---
Electron transport chain

OH^- radical | O^-2 radical | H_2O_2 peroxide

Smoke and Ash

ATP | ATP | ATP

CO_2 | H_2O

HEAT

CHEMICAL ENERGY

CELLULAR WORK

Antioxidant Nutrients and Enzymes

CELLULAR DAMAGE
- Lipid peroxidation
- Protein oxidation
- DNA mutations

© K-PAX Pharmaceuticals
H^+ ions + H^+ ions + H^+ ions

Electron transport chain

OH^- radical + O^{-2} radical + H_2O_2 peroxide

Supplement Mitochondrial Nutrients

CELLULAR DAMAGE
- Lipid peroxidation
- Protein oxidation
- DNA mutations

ATP ATP ATP

CO_2 H_2O

HEAT CHEMICAL ENERGY CELLULAR WORK
Mitochondrial Medicine

What stresses the mitochondria?

1) Poor nutrition

2) Chronic stress

3) Sedentary lifestyle

1) Chronic inflammation
Mitochondrial Medicine

What stresses the mitochondria?

5) Prescription drugs
   • Acetaminophen
   • Antidepressants
   • Statins
   • Antivirals
   • Antibiotics
   • Chemotherapy

6) Environmental toxins
   • Pthalates
   • Bisphenol A
   • Organophosphates
   • Plastics, teflon, etc.
Toxic Spill Still Haunts Southwest

Six months after EPA accident at gold mine, snowmelt threatens long-term monitoring. For instance, they say, there is no federal plan to test about 2,000 private wells in New Mexico that border the site.
Mitochondrial Medicine

What occurs when the mitochondria are stressed?

1) Mild to Moderate Dysfunction ➔

2) Mitochondrial Toxicity ➔

3) Mitochondrial Loss ➔

1) Apoptosis (programmed cell death)
When Should You Intervene?

- **Immune System**
  - Frequent infections
  - Chronic inflammation
- **Hepatic System**
  - Increased LFT’s
  - Chemical sensitivities
- **Nervous System**
  - Decreased cognition
  - Brain fog, Fatigue

**Early effects**

**End organ diseases**

Life threatening infections (Pneumonia, MRSA, etc.)

NASH, Hepatitis, Cancer

Alzheimers Dz, MS, ALS

Parkinsons Dz, CFS
When Should You Intervene?

- **Immune System**
  - Frequent infections
  - Chronic inflammation

- **Hepatic System**
  - Increased LFT's
  - Chemical sensitivities

- **Nervous System**
  - Decreased cognition
  - Brain fog, Fatigue

*Intervene early* End organ diseases

- Life threatening infections (Pneumonia, MRSA, etc.)
- NASH, Hepatitis, Cancer
- Alzheimers Dz, MS, ALS
- Parkinsons Dz, CFS

**Early effects**

**End organ diseases**
What’s the best way to protect and enhance mitochondrial function?
A Key Triad of Mitochondrial Support Nutrients

- Acetyl-L-Carnitine
- N-Acetyl-Cysteine
- Alpha Lipoic Acid

Cell

Mitochondria

A Key Triad of Mitochondrial Support Nutrients
Broad-Spectrum Mitochondrial Support

**Key Mitochondrial Support Nutrients**

- Acetyl-L-Carnitine 1,000 mg/day
- N-acetyl-cysteine 1,200 mg/day
- Alpha Lipoic Acid 400 mg/day

**Additional Supportive Nutrients**

- Coenzyme Q-10 100 mg/day
- Methyl Folate 400 mcg/day
- Methyl B12 1,000 mcg/day
- Carotenoids 20,000 iu/day
- Vitamin C 2,000 mg/day
- Vitamin D 1,000 iu/day
- Vitamin E 540 iu/day
- Zinc 30 mg/day
Research Data on Mitochondrial Support
Micronutrient Supplementation Increases CD4 Count in HIV-Infected Individuals on Highly Active Antiretroviral Therapy: A Prospective, Double-Blinded, Placebo-Controlled Trial

Jon D. Kaiser, MD,* Adriana M. Campa, PhD,† Joseph P. Ondercin, PA-C,‡ Gifford S. Leoung, MD,§ Richard F. Pless, PhD,/// and Marianna K. Baum, PhD†
“AIDS Drugs Linked To Mitochondrial Toxicity”
Chronic Fatigue Syndrome
________________________
Myalgic Encephalomyelitis
IOM reported these findings in 2015:

- **CFS affects between 836,000 to 2.5 million Americans**
- Up to 90% of people with CFS have not yet been diagnosed, meaning the true prevalence is unknown
- **The average age of onset is 33**, although CFS has been reported in patients < 10 and > 70 years old
- At least 1/4 of CFS patients are homebound at some point during their illness
FDA is highly motivated to identify a treatment
Chronic Fatigue Syndrome Treatment

Mitochondrial Support Nutrients
Low dose Stimulant

Chronic Fatigue Syndrome Treatment

- Rapid improvement in energy level
- Gradual improvement in functional status
- Rapid improvement in alertness and concentration
- Improved safety and long term tolerability

L-phenylalanine

Rt oong Mt spdhmsr
Phase 1

Proof of Concept

Prospective, Open-label Trial in 15 Patients with CFS
Clinically significant improvement in 87% of patients

No other trial has yet shown a >8% improvement in symptoms (graded exercise therapy).
Phase 2

Double-blinded, placebo-controlled
(n=128 patients)

Study Investigators

Jose Montoya, MD (Stanford U.)
Lucinda Bateman, MD (Utah)
Nancy Klimas, MD (Florida)
Susan Levine, MD (NYC)

Completed 2015
CFS Symptoms Score

Baseline

4 weeks

12 weeks

Placebo

-13

(-12%)

KPAX 002

-22

(-20%)

Per Protocol Analysis

(n=87)
Excellent Safety Data

<table>
<thead>
<tr>
<th>Symptom</th>
<th>K-PAX 002 (n=64)</th>
<th>Placebo (n=67)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Feeling Jittery</td>
<td>4 (6)</td>
<td>4 (6)</td>
</tr>
<tr>
<td>Nervousness</td>
<td>0 (0)</td>
<td>0 (0)</td>
</tr>
<tr>
<td>Palpitations</td>
<td>1 (2)</td>
<td>3 (5)</td>
</tr>
<tr>
<td>Restlessness</td>
<td>0 (0)</td>
<td>1 (2)</td>
</tr>
<tr>
<td>Agitation</td>
<td>0 (0)</td>
<td>0 (0)</td>
</tr>
<tr>
<td>Irritability</td>
<td>1 (2)</td>
<td>0 (0)</td>
</tr>
<tr>
<td>Insomnia</td>
<td>2 (3)</td>
<td>1 (2)</td>
</tr>
</tbody>
</table>

\(^a\)Values shown as number (%) of patients.
Direct Mitochondrial Function Assay

Nothings promotes the advancement of knowledge so much as a new instrument

<table>
<thead>
<tr>
<th>Humphry Davy</th>
<th>Electric Battery</th>
<th>Sodium</th>
<th>Calcium</th>
<th>Potassium</th>
<th>Magnesium</th>
</tr>
</thead>
<tbody>
<tr>
<td>Marie Curie</td>
<td>Radiation Detector</td>
<td>Radium</td>
<td>Polonium</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Diagram:

- Humphry Davy: Electric Battery → Sodium, Calcium, Potassium, Magnesium
- Marie Curie: Radiation Detector → Radium, Polonium
Seahorse XF Mitochondrial Analyzer
Seahorse XF Mitochondrial Analyzer

...bioenergetic status of a cell
The Bioenergetic Health Index: a new concept in mitochondrial translational research

Balu K. CHACKO*,†, Philip A. KRAMER*†, Saranya RAVI*†, Gloria A. BENAVIDES*†, Tanecia MITCHELL*†, Brian P DRANKA‡, David FERRICK‡, Ashwani K. SINGAL§, Scott W. BALLINGER*†, Shannon M. BAILEY‡, Robert W. HARDY*†, Jianhua ZHANG*‡||, Degui ZHI¶ and Victor M. DARLEY-USMAR*†1

*Creates a Single Numerical Score
That Directly Measures Mitochondrial Health

\[ \text{BHI} = \log \left( \frac{\text{reserve capacity}^a \times \text{(ATP-linked)}^b}{\text{(non-mitochondrial)}^c \times \text{(proton leak)}^d} \right) \]

Victor Darley-Usmar, PhD.
University of Alabama, Birmingham
The Emerging Paradigm of Mitochondrial Medicine
The Emerging Paradigm of Mitochondrial Medicine

Healthy Function

Degenerative Diseases

- ALS
- CFS
- Diabetes
- Parkinson’s
- Alzheimer’s
- Multiple Sclerosis
The Emerging Paradigm of Mitochondrial Medicine

Healthy Function

Degenerative Diseases

• ALS
• CFS
• Diabetes
• Parkinson’s
• Alzheimer’s
• Multiple Sclerosis

AGE
The Emerging Paradigm of Mitochondrial Medicine

Healthy Function

Degenerative Diseases

- ALS
- CFS
- Diabetes
- Parkinson’s
- Alzheimer’s
- Multiple Sclerosis
The Emerging Paradigm of Mitochondrial Medicine

Healthy Function

Acquired Mitochondrial Disease (AMD)

Degenerative Diseases

- ALS
- CFS
- Diabetes
- Parkinson’s
- Alzheimer’s
- Multiple Sclerosis
The Emerging Paradigm of Mitochondrial Medicine

Healthy Function

Positive Intervention

Acquired Mitochondrial Disease (AMD)

Degenerative Diseases

• ALS
• CFS
• Diabetes
• Parkinson’s
• Alzheimer’s
• Multiple Sclerosis
The Emerging Paradigm of Mitochondrial Medicine

Healthy Function

Positive Intervention

Acquired Mitochondrial Disease (AMD)

- ALS
- CFS
- Diabetes
- Parkinson’s
- Alzheimer’s
- Multiple Sclerosis

AGE
The Emerging Paradigm of Mitochondrial Medicine

Healthy Function

Positive Intervention

Acquired Mitochondrial Disease (AMD)
Mitochondrial Medicine
Treating Chronic Fatigue with Mitochondrial Support

Jon D. Kaiser, M.D.
Clinical Faculty, University of California
San Francisco Medical School
Chief Medical Officer
K-PAX Pharmaceuticals