2018 PROGRAMME

Mitochondrial Patient Engagement Day
Saturday 13th October 2018
Franks & Steel Room, Wellcome Collection, 183 Euston Road, London, NW1 2BE

Organised by Natalie James, Clinical Nurse Specialist on behalf of Professor MG Hanna and the Specialist Mitochondrial Service

1.30 Introduction
Dr Rob Pitceathly, Consultant Neurologist, Mitochondrial service

1.40 Mitochondrial Disease
Dr Rob Pitceathly, Consultant Neurologist, Mitochondrial service

2.00 Research Update and Clinical Trials
Dr Rob Pitceathly, Consultant Neurologist, Mitochondrial service

2.20 Lily Foundation
Alison Maguire

2.30 Action on Hearing Loss
Jean Straus

2.40 Ubiquinone and mitochondrial disease
Dr Iain Hargreaves

3.00 tea/coffee break

3.20 Groups: 30 minutes per group session – 2 sessions in this period.

Mood/psychological involvement – facilitated by Dr Colasanti, Psychiatrist
Ocular problems and mitochondrial disease – facilitated by Dr Jurkute, Ophthalmology fellow, Moorfields
Practical management of mitochondrial disease diabetes – facilitated by Natalie James, Clinical nurse specialist
Exercise and fatigue – facilitated by Sarah Holmes, Neuromuscular physiotherapist and a patient representative

4.30 – 6.00 Social time with food and drink provided by the Lily Foundation – where you can meet the research and clinical teams.
Overview

• Mitochondria and mitochondrial diseases

• Mitochondrial disease genetics: mitochondrial DNA and nuclear DNA

• Current treatment strategies

• Research studies and clinical trials
Mitochondria and mitochondrial diseases
mtDNA and mitochondrial diseases

>250 pathogenic mutations
Maternal Inheritance of mtDNA

Colours reflect inheritance of the same mitochondrial genome.
Nucleus containing Chromosomes (99.9% of genetic Information - hair colour, blood group etc)

mtDNA disease

Mitochondria (batteries)
Nuclear DNA mitochondrial disease

37 genes

>1,500 genes
Genes of mitochondria-localised proteins linked to human disease

Nuclear DNA
mitochondrial disease

Recessive
e.g. some forms of Leigh Disease

Dominant

Each child has 1 in 4 chance of disease

Each child has 1 in 2 chance of disease

A/B
A/A

B/B

A/B

B/B

A/B

B/B

A/B

B/B

A/B

B/B

Unaffected carrier

disease

unaffected

Unaffected carrier
Mitochondrial DNA
mitochondrial disease

Not ‘Yes’ or ‘No’?

But how much?

Nuclear: e.g. Dominant inheritance

Mitochondrial: Maternal inheritance

[Diagram showing genetic inheritance patterns with percentages and symbols for 'well' and 'disease']
So things are complicated...

Nuclear DNA disease

- Dominant
- Recessive
- X-linked

MtDNA disease

- Maternal

Inheritance:
Less mitochondria – less energy

Human Cell (the machine)

Nucleus containing Chromosomes (blueprint)

Mitochondria (batteries)
Genetic variability

mtDNA

polypeptide subunits

nDNA

mtDNA maintenance

mtDNA transcription

mtDNA translation

Complex assembly and remaining 76 subunits

13 polypeptide subunits

Complex I

Complex II

Complex III

Complex IV

Complex V

7/44

0/4

1/11

3/14

2/16
Clinical variability

Respiratory Failure
Cardiomyopathy / Conduction Defects
Liver / Renal Failure
Short stature / Marrow Failure
Diabetes
Optic Atrophy / Retinitis Pigmentosa / Cataracts
CVA / Seizures / Developmental Delay
Deafness
Peripheral Neuropathy
Optic Atrophy / Retinitis Pigmentosa / Cataracts
Cardiomyopathy / Conduction Defects
Liver / Renal Failure
Short stature / Marrow Failure
Diabetes
Optic Atrophy / Retinitis Pigmentosa / Cataracts
CVA / Seizures / Developmental Delay
Deafness
Peripheral Neuropathy
Optic Atrophy / Retinitis Pigmentosa / Cataracts
Cardiomyopathy / Conduction Defects
Liver / Renal Failure
Short stature / Marrow Failure
Diabetes
Optic Atrophy / Retinitis Pigmentosa / Cataracts
CVA / Seizures / Developmental Delay
Deafness
Peripheral Neuropathy
Clinical variability
Age of onset

- Neonate
- Infant
- Child
- Adolescent
- Adult
- Elderly

Congenital Lactic Acidosis
- LS
- PMPS
- HCM
- Alpers

KSS MELAS
- CPEO
- MERRF
- NARP
- Exercise intolerance

Myopathy
Mitochondrial disorders: unravelling the complexity

Any age

Any course

Any organ

Any mode of inheritance

G. Mendel

Maternal Inheritance

Mitochondrial disorders: Any age, Any course, Any organ, Any mode of inheritance. The diagram illustrates various conditions associated with mitochondrial disorders such as heart, skeletal muscle, brain, kidney, liver, and pancreas. G. Mendel is mentioned along with the diagram indicating the concept of maternal inheritance.
From clinical assessment to genetic diagnosis

I

Age, Phenotype, Pedigree

II

BLOOD

A. Nuclear maintenance panel (21 genes)
   - Targeted exome (300 mito genes)
B. Common mtDNA point mutations
   - (3243, 8344, 8993)
   - RFLP >1%
C. Full mtDNA Sequencing
   - NGS >10%
   - (>1% known mutation)

III

MUSCLE

A. Large scale rearrangements
   - LPCR, SB >5%
B. mtDNA copy number
   - RT-PCR
C. Histopathology (COX/SDH, RRF)
D. Biochemistry (RCEA, BN-PAGE)

IV

BLOOD

A. Functional studies
   - Modelling
   - Additional families
B. Novel mutations/genes
C. Exome/Genome (Research)
Current treatment strategies
Exciting times!

- New proteins
- Gene transfer
- Drugs
- Stem cells
- Peptide nucleic acid
- Targeted nucleases
- mtDNA
- tRNA enzymes
What about now!
Pharmacological agents, vitamins and related substances
Vitamins, cofactors and food supplements

CoQ10

Succinate

L-Arginine/Citrulline

Folate/Folinic acid

Vitamin C/E

α-lipoic acid

Carnitine

Idebenone

Riboflavin

Thiamine

Creatine
Pharmacological agents and vitamins

Treatment for mitochondrial disorders (2012)

• >1300 abstracts (1966-2012)
• 12 RCTs:
  – Coenzyme Q10
  – Creatine
  – Creatine/Q10/lipoic acid combo
  – Dichloroacetate
  – Dimethylglycine
  – Cysteine
• No evidence supporting use of any intervention in mitochondrial disorders
Randomised, double-blinded, placebo-controlled clinical trials in mitochondrial disease

<table>
<thead>
<tr>
<th>Treatment</th>
<th>Disease</th>
<th>No. of participants</th>
<th>Type of trial</th>
<th>Outcome</th>
<th>References</th>
</tr>
</thead>
<tbody>
<tr>
<td>CoQ&lt;sub&gt;10&lt;/sub&gt;</td>
<td>MELAS, PEO, complex I deficiency, NARP, LHON</td>
<td>30</td>
<td>Randomized, placebo-controlled, double-blind crossover</td>
<td>Serum CoQ&lt;sub&gt;10&lt;/sub&gt; increased, lactate levels decreased after 1 min of cycle ergometry, but no significant change in other endpoints</td>
<td>Glover et al., 2010</td>
</tr>
<tr>
<td>Creatine</td>
<td>MELAS and MM</td>
<td>7</td>
<td>Randomized, placebo-controlled, double-blind crossover</td>
<td>Increased handgrip strength, NIDT and post-exercise lactate</td>
<td>Tamopolsky et al., 1997</td>
</tr>
<tr>
<td>CPEO and MM</td>
<td></td>
<td>16</td>
<td>Randomized, placebo-controlled, double-blind crossover</td>
<td>No effect</td>
<td>Kioptick et al., 2000</td>
</tr>
<tr>
<td>CPEO and KSS</td>
<td></td>
<td>15</td>
<td>Randomised, placebo-controlled crossover</td>
<td>No effect</td>
<td>Kornblum et al., 2005</td>
</tr>
<tr>
<td>DCA</td>
<td>MM, CPEO, KSS, Leigh syndrome, MELAS</td>
<td>11</td>
<td>Randomized, placebo-controlled, double-blind crossover</td>
<td>Decreased blood lactate, pyruvate and alanine at rest and post-exercise, some improvements in brain MRS</td>
<td>De Stefano et al., 1995</td>
</tr>
<tr>
<td>CPEO, MERRF, MM</td>
<td></td>
<td>8</td>
<td>Randomized, placebo-controlled, double-blind crossover</td>
<td>Decreased resting and exercise lactate and pyruvate</td>
<td>Vising et al., 2001</td>
</tr>
<tr>
<td>Mitochondrial RC disorders</td>
<td></td>
<td>9</td>
<td>Randomized, placebo-controlled, double-blind crossover</td>
<td>Decreased blood lactate levels during exercise</td>
<td>Duncan et al., 2004</td>
</tr>
<tr>
<td>MELAS m.3243A&gt;G</td>
<td></td>
<td>30</td>
<td>Randomized, placebo-controlled crossover</td>
<td>No effect. Study terminated due to side effects (peripheral neuropathy)</td>
<td>Kaufmann et al., 2006</td>
</tr>
<tr>
<td>Congenital lactic acidosis</td>
<td></td>
<td>43</td>
<td>Randomized, double-blinded, placebo-controlled parallel group</td>
<td>Reduced blood lactate levels post high carbohydrate meal</td>
<td>Stacpoole et al., 2006</td>
</tr>
<tr>
<td>Dimethylglycine</td>
<td>SLSJ-COX</td>
<td>5</td>
<td>Randomized, placebo-controlled crossover</td>
<td>No effect</td>
<td>Liet et al., 2003</td>
</tr>
<tr>
<td>Whey-based cysteine</td>
<td>PEO</td>
<td>13</td>
<td>Randomized, placebo-controlled, double-blind crossover</td>
<td>Glutathione levels increased. Advanced oxidation protein products and feric-reducing antioxidant power increased</td>
<td>Mancuso et al., 2010</td>
</tr>
<tr>
<td>Combination therapy (creatine, α-lipoic acid and CoQ&lt;sub&gt;10&lt;/sub&gt;)</td>
<td>CPEO, KSS, MELAS, MNGIE, MM</td>
<td>16</td>
<td>Randomized, placebo-controlled, double-blind crossover</td>
<td>Decreased plasma lactate, slower disease progression (measured by peak angle dorsiflexion strength)</td>
<td>Rodriguez et al., 2007</td>
</tr>
</tbody>
</table>

CPEO, chronic progressive external ophthalmoplegia; MERRF, myoclonic epilepsy, ragged red fibres; NIDT, non-ischaemic, isometric, dorsiflexion torque; SLSJ-COX, Saguenay-Lac-Saint-Jean COX deficiency.
Randomised, double-blinded, placebo-controlled clinical trials in mitochondrial disease

<table>
<thead>
<tr>
<th>Treatment</th>
<th>Disease</th>
<th>No. of participants</th>
<th>Type of trial</th>
<th>Outcome</th>
<th>References</th>
</tr>
</thead>
<tbody>
<tr>
<td>CoQ&lt;sub&gt;10&lt;/sub&gt;</td>
<td>MELAS, PEO, complex I deficiency, NARP, LHON</td>
<td>30</td>
<td>Randomized, placebo-controlled, double-blind crossover</td>
<td>Serum CoQ&lt;sub&gt;10&lt;/sub&gt; increased, lactate levels decreased after 1 min of cycle ergometry, but no significant change in other endpoints</td>
<td>Glover et al., 2010</td>
</tr>
<tr>
<td>Creatine</td>
<td>MELAS and MM</td>
<td>7</td>
<td>Randomized, placebo-controlled, double-blind crossover</td>
<td>Increased handgrip strength, NIDT and post-exercise lactate</td>
<td>Tamopolsky et al., 1997</td>
</tr>
<tr>
<td>CPEO and MM</td>
<td></td>
<td>16</td>
<td>Randomized, placebo-controlled, double-blind crossover</td>
<td>No effect</td>
<td>Klopstock et al., 2000</td>
</tr>
<tr>
<td>CPEO and KSS</td>
<td></td>
<td>15</td>
<td>Randomised, placebo-controlled crossover</td>
<td>No effect</td>
<td>Kornblum et al., 2005</td>
</tr>
<tr>
<td>DCA</td>
<td>MM, CPEO, KSS, Leigh syndrome, MELAS</td>
<td>11</td>
<td>Randomized, placebo-controlled, double-blind crossover</td>
<td>Decreased blood lactate, pyruvate and alanine at rest and post-exercise, some improvements in brain MRS</td>
<td>De Stefano et al., 1995</td>
</tr>
<tr>
<td>CPEO, MERRF, MM</td>
<td></td>
<td>8</td>
<td>Randomized, placebo-controlled, double-blind crossover</td>
<td>Decreased resting and exercise lactate and pyruvate</td>
<td>Vissing et al., 2001</td>
</tr>
<tr>
<td>Mitochondrial RC disorders</td>
<td></td>
<td>9</td>
<td>Randomized, placebo-controlled, double-blind crossover</td>
<td>Decreased blood lactate levels during exercise</td>
<td>Duncan et al., 2004</td>
</tr>
<tr>
<td>MELAS m.3243A&gt;G</td>
<td></td>
<td>30</td>
<td>Randomized, placebo-controlled crossover</td>
<td>No effect. Study terminated due to side effects (peripheral neuropathy)</td>
<td>Kaufmann et al., 2006</td>
</tr>
<tr>
<td>Congenital lactic acidosis</td>
<td></td>
<td>43</td>
<td>Randomized, double-blinded, placebo-controlled parallel group</td>
<td>Reduced blood lactate levels post high carbohydrate meal</td>
<td>Stacpoole et al., 2006</td>
</tr>
<tr>
<td>Dimethylglycine</td>
<td>SLSJ-COX</td>
<td>5</td>
<td>Randomized, placebo-controlled crossover</td>
<td>No effect</td>
<td>Liet et al., 2003</td>
</tr>
<tr>
<td>Whey-based cysteine</td>
<td>PEO</td>
<td>13</td>
<td>Randomized, placebo-controlled, double-blind crossover</td>
<td>Glutathione levels increased. Advanced oxidation protein products and ferric-reducing antioxidant power increased</td>
<td>Mancuso et al., 2010</td>
</tr>
<tr>
<td>Combination therapy</td>
<td>CPEO, KSS, MELAS, MNGIE, MM</td>
<td>16</td>
<td>Randomized, placebo-controlled, double-blind crossover</td>
<td>Decreased plasma lactate, slower disease progression (measured by peak angle dorsiflexion strength)</td>
<td>Rodriguez et al., 2007</td>
</tr>
</tbody>
</table>

CPEO, chronic progressive external ophthalmoplegia; MERRF, myoclonic epilepsy, ragged red fibres; NIDT, non-ischaemic, isometric, dorsiflexion torque; SLSJ-COX, Saguenay-Lac-Saint-Jean COX deficiency.
Randomised, placebo-controlled, double-blind, clinical trials in mitochondrial disease

<table>
<thead>
<tr>
<th>Treatment</th>
<th>Disease</th>
<th>No. of participants</th>
<th>Type of trial</th>
<th>Outcome</th>
<th>References</th>
</tr>
</thead>
<tbody>
<tr>
<td>CoQ₁₀</td>
<td>MELAS, PEO, complex I deficiency, NARP, LHON</td>
<td>30</td>
<td>Randomized, placebo-controlled, double-blind crossover</td>
<td>Serum CoQ₁₀ increased, lactate levels decreased after 1 min of cycle ergometry, but no significant change in other endpoints</td>
<td>Glover et al., 2010</td>
</tr>
<tr>
<td>Creatine</td>
<td>MELAS and MM</td>
<td>7</td>
<td>Randomized, placebo-controlled, double-blind crossover</td>
<td>Increased handgrip strength, NIDT and post-exercise lactate</td>
<td>Tamopolsky et al., 1997</td>
</tr>
<tr>
<td>CPEO and MM</td>
<td></td>
<td>16</td>
<td>Randomized, placebo-controlled, double-blind crossover</td>
<td>No effect</td>
<td>Kiolpstock et al., 2000</td>
</tr>
<tr>
<td>CPEO and KSS</td>
<td></td>
<td>15</td>
<td>Randomized, placebo-controlled crossover</td>
<td>No effect</td>
<td>Kornblum et al., 2005</td>
</tr>
<tr>
<td>DCA</td>
<td>MM, CPEO, KSS, Leigh syndrome, MELAS</td>
<td>11</td>
<td>Randomized, placebo-controlled, double-blind crossover</td>
<td>Decreased blood lactate, pyruvate and alanine at rest and post-exercise, some improvements in brain MRS</td>
<td>De Stefano et al., 1995</td>
</tr>
<tr>
<td>CPEO, MERRF, MM</td>
<td></td>
<td>8</td>
<td>Randomized, placebo-controlled, double-blind crossover</td>
<td>Decreased resting and exercise lactate and pyruvate</td>
<td>Vissing et al., 2001</td>
</tr>
<tr>
<td>Mitochondrial RC disorders</td>
<td></td>
<td>9</td>
<td>Randomized, placebo-controlled, double-blind crossover</td>
<td>Decreased blood lactate levels during exercise</td>
<td>Duncan et al., 2004</td>
</tr>
<tr>
<td>MELAS m.3243A&gt;G</td>
<td></td>
<td>30</td>
<td>Randomized, placebo-controlled crossover</td>
<td>No effect. Study terminated due to side effects (peripheral neuropathy)</td>
<td>Kaufmann et al., 2006</td>
</tr>
<tr>
<td>Congenital lactic acidosis</td>
<td></td>
<td>43</td>
<td>Randomized, double-blinded, placebo-controlled parallel group</td>
<td>Reduced blood lactate levels post high carbohydrate meal</td>
<td>Stacpoole et al., 2006</td>
</tr>
<tr>
<td>Dimethylglycine</td>
<td>SLSJ-COX</td>
<td>5</td>
<td>Randomized, placebo-controlled crossover</td>
<td>No effect</td>
<td>Liet et al., 2003</td>
</tr>
<tr>
<td>Whey-based cysteine</td>
<td>PEO</td>
<td>13</td>
<td>Randomized, placebo-controlled, double-blind crossover</td>
<td>Glutathione levels increased. Advanced oxidation protein products and fercin-reducing antioxidant power increased</td>
<td>Mancuso et al., 2010</td>
</tr>
<tr>
<td>Combination therapy (creatine, α-lipoic acid and CoQ₁₀)</td>
<td>CPEO, KSS, MELAS, MNGIE, MM</td>
<td>16</td>
<td>Randomized, placebo-controlled, double-blind crossover</td>
<td>Decreased plasma lactate, slower disease progression (measured by peak angle dorsiflexion strength).</td>
<td>Rodriguez et al., 2007</td>
</tr>
</tbody>
</table>

CPEO, chronic progressive external ophthalmoplegia; MERRF, myoclonic epilepsy, ragged red fibres; NIDT, non-ischaemic, isometric, dorsiflexion torque; SLSJ-COX, Saguesay-Lac-Saint-Jean COX deficiency.
Reactive oxygen species and their detoxification
Modified Fatigue Severity Scale

Please read each statement and circle a number from 1 to 7, depending on how appropriate you feel the statement applies to you over the last week. A low value indicates that the statement is not very appropriate whereas a high value indicates agreement.

<table>
<thead>
<tr>
<th>During the past week, I have found that…</th>
<th>Never</th>
<th>Hardly anytime</th>
<th>Some of the time</th>
<th>About half of the time</th>
<th>A lot of the time</th>
<th>Nearly all of the time</th>
<th>All of the time</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. My motivation is lower when I am fatigued</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
<td>5</td>
<td>6</td>
<td>7</td>
</tr>
<tr>
<td>2. Exercise brings on my fatigue</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
<td>5</td>
<td>6</td>
<td>7</td>
</tr>
<tr>
<td>3. I am easily fatigued</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
<td>5</td>
<td>6</td>
<td>7</td>
</tr>
<tr>
<td>4. Fatigue interferes with my physical functioning</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
<td>5</td>
<td>6</td>
<td>7</td>
</tr>
<tr>
<td>5. Fatigue causes frequent problems for me</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
<td>5</td>
<td>6</td>
<td>7</td>
</tr>
<tr>
<td>6. My fatigue prevents sustained physical functioning</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
<td>5</td>
<td>6</td>
<td>7</td>
</tr>
<tr>
<td>7. Fatigue interferes with carrying out certain duties and responsibilities</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
<td>5</td>
<td>6</td>
<td>7</td>
</tr>
<tr>
<td>8. Fatigue is among my three most disabling symptoms</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
<td>5</td>
<td>6</td>
<td>7</td>
</tr>
<tr>
<td>9. Fatigue interferes with my work, family or social life</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
<td>5</td>
<td>6</td>
<td>7</td>
</tr>
</tbody>
</table>
Mitochondrial diseases with specific treatment options

<table>
<thead>
<tr>
<th>Affected pathway</th>
<th>Clinical syndrome</th>
<th>Affected gene(s)</th>
<th>Clinical phenotype</th>
<th>Therapeutic substance</th>
<th>Treatment response</th>
</tr>
</thead>
<tbody>
<tr>
<td>Primary disorders of mitochondrial vitamin cofactor metabolism</td>
<td>Brown-Vialette-Van Laere syndrome / Fazio-Londe disease</td>
<td>SLC52A2, SLC52A3, SLC52A1</td>
<td>Sensorineural hearing loss, cranial nerve palsies</td>
<td>Riboflavin (oral: 10–50 mg/kg/day)^a</td>
<td>Generally good</td>
</tr>
<tr>
<td></td>
<td>Biotin-thiamine-responsive basal ganglia disease</td>
<td>SLC19A3</td>
<td>Episodic encephalopathy, dystonia, seizures</td>
<td>Thiamine (oral: 10–20 mg/kg/day), biotin (oral: 10–15 mg/kg/day)^c</td>
<td>Generally good</td>
</tr>
<tr>
<td></td>
<td>Biotinidase deficiency</td>
<td>BTD</td>
<td>Dermatitis, muscular hypotonia, developmental regression</td>
<td>Bioin (oral: 5–10 mg/kg/day)^d</td>
<td>Generally good</td>
</tr>
<tr>
<td></td>
<td>Holocarboxylase synthetase deficiency</td>
<td>HCCS</td>
<td>Skin lesions, metabolic acidosis, seizures, developmental delay</td>
<td>Bioin (oral: 10–15 mg/kg/day)^c</td>
<td>Generally good</td>
</tr>
<tr>
<td></td>
<td>Thiamine pyrophosphatase deficiency</td>
<td>TPK1</td>
<td>Episodic encephalopathy, dystonia, spasticity</td>
<td>Thiamine (oral: ~20 mg/kg/day)^b</td>
<td>Variable but generally good</td>
</tr>
<tr>
<td></td>
<td>ACAD9 deficiency</td>
<td>ACAD9</td>
<td>Encephalopathy, myopathy, hypertrophic cardiomyopathy</td>
<td>Riboflavin (oral: 10–20 mg/kg/day)^a</td>
<td>Variable</td>
</tr>
<tr>
<td>Disorders with indirect response to mitochondrial vitamin cofactor supplementation</td>
<td>Multiple acyl-CoA dehydrogenase deficiency</td>
<td>ETFB, ETFB, ETRDH, SLC25A32, FLAD1</td>
<td>Early childhood multisystem disease or late-onset form with muscle weakness, hepatopathy, etc.</td>
<td>Riboflavin (oral: ~10 mg/kg/day)^a</td>
<td>Generally good</td>
</tr>
<tr>
<td></td>
<td>Thiamine-responsive pyruvate dehydrogenase deficiency</td>
<td>PDHAI</td>
<td>Neonatal lactic acidosis, seizures, developmental regression, spasticity</td>
<td>Thiamine (oral: 30–40 mg/kg/day)^a</td>
<td>Variable</td>
</tr>
<tr>
<td>Disorders of mitochondrial non-vitamin cofactor metabolism</td>
<td>Coenzyme Q10 deficiency</td>
<td>PDSS1, PDSS2, COQ2, COQ4, COQ6, COQ7, ADCK3, ADCK4, COQ9</td>
<td>Variable phenotypes, ranging from adult-onset myopathy to fatal neonatal presentations</td>
<td>Coenzyme Q10 (oral: 10–30 mg/kg/day)</td>
<td>Highly variable depending on the underlying defect</td>
</tr>
<tr>
<td>Disorders of mitochondrial inorganic cofactor metabolism</td>
<td>Cytochrome c oxidase deficiency</td>
<td>SCO2, COA6</td>
<td>Infantile encephalomyopathy</td>
<td>Copper-histidine (dose unclear; subcutaneous injections of up to 500 μg daily were suggested)^4</td>
<td>Unclear, only one SCC2 patient treated; only in vitro evidence for COA6</td>
</tr>
<tr>
<td>'Inhibitors' of mitochondrial metabolism</td>
<td>Molybdenum cofactor deficiency</td>
<td>MOCS1, MOCS2, GPHN</td>
<td>Infantile-onset epileptic encephalopathy, progressive brain damage</td>
<td>Cyclic pyruvate monophosphate (intravenous: 80–320 μg/kg/day)^4</td>
<td>Generally good in MoCD type A patients</td>
</tr>
<tr>
<td></td>
<td>3-Hydroxyisobutyryl-CoA hydrolase deficiency</td>
<td>HIBCH</td>
<td>Infantile Leigh-like phenotype</td>
<td>Valine-restricted diet^5</td>
<td>Unclear, only few patients treated</td>
</tr>
<tr>
<td></td>
<td>Enoyl-CoA hydratase deficiency</td>
<td>ECHS1</td>
<td>Infantile Leigh-like phenotype</td>
<td>Valine-restricted diet^5</td>
<td>Unclear, only few patients treated so far</td>
</tr>
<tr>
<td></td>
<td>Thioredoxin 2 deficiency</td>
<td>TXN2</td>
<td>Cerebellar atrophy, dystonia, seizures, peripheral neuropathy</td>
<td>Antioxidant treatment (e.g. Idebenone up to 20 mg/kg/day)^a</td>
<td>Apparently good (only one patient reported)</td>
</tr>
<tr>
<td></td>
<td>Ethylmalonic encephalopathy</td>
<td>ETHE1</td>
<td>Severe, multisystem infantile disorder</td>
<td>Merondiazole, N-acetyl cysteine as glutathione precursor, liver transplantation^a</td>
<td>Variable</td>
</tr>
</tbody>
</table>

Mitochondrial diseases with specific treatment options

<table>
<thead>
<tr>
<th>Affected pathway</th>
<th>Clinical syndrome</th>
<th>Affected gene(s)</th>
<th>Clinical phenotype</th>
<th>Therapeutic substance</th>
<th>Treatment response</th>
</tr>
</thead>
<tbody>
<tr>
<td>Primary disorders of mitochondrial vitamin cofactor metabolism</td>
<td>Brown-Vialetto-Van Laere syndrome / Fazio-Londe disease</td>
<td>SLC52A2, SLC52A3, (SLC52A1)</td>
<td>Sensorineural hearing loss, cranial nerve palsies</td>
<td>Riboflavin (oral: 10–50 mg/kg/day)</td>
<td>Generally good</td>
</tr>
<tr>
<td></td>
<td>Biotin-thiamine-responsive basal ganglia disease</td>
<td>SLC19A3</td>
<td>Episodic encephalopathy, dystonia, seizures</td>
<td>Thiamine (oral: 10–20 mg/kg/day), biotin (oral: 10–15 mg/kg/day)</td>
<td>Generally good</td>
</tr>
<tr>
<td></td>
<td>Biotinidase deficiency</td>
<td></td>
<td>Dermatitis, muscular hypotonia, developmental regression</td>
<td>Bioin (oral: 5–10 mg/kg/day)</td>
<td>Generally good</td>
</tr>
<tr>
<td></td>
<td>Holocarboxylase deficiency</td>
<td></td>
<td>Skin lesions, metabolic acidosis, seizures, developmental delay</td>
<td></td>
<td>Variable but generally good</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Episodic encephalopathy, spasticity</td>
<td>Bioin (oral: 10 mg/kg/day)</td>
<td>Variable</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Dermatitis, muscular hypotonia, developmental regression</td>
<td>Thiamine (oral: ~20 mg/kg/day)</td>
<td>Variable</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Early childhood multisystem disease or late-onset form with weakness, hepatopathy,</td>
<td>Riboflavin (oral: 10–20 mg/kg/day)</td>
<td>Generally good</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>dermatitis, edema, seizures, peripheral neuropathy</td>
<td></td>
<td>Variable</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Thiamine (oral: 30–40 mg/kg/day)</td>
<td>Variable</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Riboflavin (oral: ~10 mg/kg/day)</td>
<td>Highly variable depending on the underlying defect</td>
</tr>
<tr>
<td>Disorders with increased response to cofactor supplementation</td>
<td>Thiamine-responsive pyruvate dehydrogenase deficiency</td>
<td></td>
<td></td>
<td>Enzyme Q10 (oral: 10–30 mg/kg/day)</td>
<td>Unclear; only one SC02 patient treated; in vitro evidence for COA6</td>
</tr>
<tr>
<td>Disorders of mitochondrial non-vitamin cofactor metabolism</td>
<td>Coenzyme Q10 deficiency</td>
<td></td>
<td></td>
<td></td>
<td>Generally good in MoCD type A patients</td>
</tr>
<tr>
<td>Disorders of mitochondrial inorganic cofactor metabolism</td>
<td>Cytochrome c oxidase deficiency</td>
<td>SCO2</td>
<td></td>
<td></td>
<td>Unclear; only one patient reported; few patients treated so far</td>
</tr>
<tr>
<td>Disorders of mitochondrial non-vitamin cofactor metabolism</td>
<td>Molybdenum cofactor deficiency</td>
<td>MOCS1, MOCS2, GFHN</td>
<td>Infanile Leigh-like phenotype</td>
<td></td>
<td>Variable</td>
</tr>
<tr>
<td>Disorders of mitochondrial non-vitamin cofactor metabolism</td>
<td>3-Hydroxyisobutryl-CoA hydrolyase deficiency</td>
<td>HIBCH</td>
<td>Infanile Leigh-like phenotype</td>
<td></td>
<td>Variable</td>
</tr>
<tr>
<td>Disorders of mitochondrial non-vitamin cofactor metabolism</td>
<td>Enoyl-CoA hydratase deficiency</td>
<td>ECHS1</td>
<td>Infantile Leigh-like phenotype</td>
<td></td>
<td>Variable</td>
</tr>
<tr>
<td>Disorders of mitochondrial non-vitamin cofactor metabolism</td>
<td>Thioredoxin 2 deficiency</td>
<td>TXN2</td>
<td>Cerebellar atrophy, dystonia, seizures, peripheral neuropathy</td>
<td>Antioxidant treatment (e.g. idebenone up to 20 mg/kg/day)</td>
<td>Apparently good in one patient reported</td>
</tr>
<tr>
<td>Disorders of mitochondrial non-vitamin cofactor metabolism</td>
<td>Ethylmalonic encephalopathy</td>
<td>ETHE1</td>
<td>Severe, multisystem infantile disorder</td>
<td>Mercaptopirazole, N-acetyl cysteine as glutathione precursor, liver transplantation</td>
<td>Variable</td>
</tr>
</tbody>
</table>

"Benign" reversible mitochondrial myopathy

Acute liver failure in infancy (TRMU)

Exercise and diet
Exercise

• Important for general fitness: exercises muscles and keeps heart and circulation healthy

• If you become unfit can adversely affect muscles

• In many patients’ muscles there is a mixture of good and bad mitochondria; the hope is that exercise can increase the good mitochondria, boosting the level of ATP so avoiding symptoms

• This remains a theory and there are large trials looking at this idea

• Current advice is to exercise regularly at a level that is comfortable, but without pushing yourself to the point that the muscles become painful
Dietary modification

• Ketogenic (high fat / low carbohydrate) diet: promotes formation of ketone bodies (via FAO)
• Ketone bodies:
  – Alternative energy source for brain, heart and muscle
  – Associated with ↑OXPHOS gene expression (akin to starvation)
    – Possibly stimulate mitochondrial biogenesis
• No randomized, double-blinded trial data
• PDH deficiency
• Seizures
• Dietetic supervision!
Health surveillance and monitoring
Clinical variability

- Respiratory Failure
- Cardiomyopathy
- Conduction Defects
- Liver / Renal Failure
- Dysphagia
- Gut dysmotility
- Short stature
- Marrow Failure
- Diabetes
- Hypothyroidism
- Fatigue
- Myopathy
- Exercise intolerance

- Ptosis
- Optic Atrophy
- Retinitis Pigmentosa
- Cataracts
- Stroke / Seizures
- Developmental Delay
- Movement Disorders
- Deafness
- Peripheral neuropathy
Surveillance = early treatment

- Drugs
- PPM
- ICD
- Ablation
- Transplant

- Dietician
- SALT
- PEG
- Laxatives
- Microbiome
- Dialysis
- Transplant

- Growth hormone
- Transfusion
- Transplant

- Diet
- Drugs
- Insulin
- Enzymes

- Thyroxine
- Radioiodine
- Surgery

- CoQ10/exercise
- PT/OT/exercise
- Energy conservation

- Photocoagulation
- Ptosis surgery
- Eyelid props
- Cataract surgery
- Prisms

- AEDs
- Botox and drugs
- Tendon release
- DBS

- Hearing aids
- Cochlear implants

- Foot care
- Orthotics
- Surgery
Mitochondrial Diseases are an important group of inherited disorders that result in a defective mitochondrial respiratory chain.

Together they form an important group of inherited disorders, yet management of these conditions remains a poorly researched area and there is little expert advice available for the treatment of specific aspects of Mitochondrial Disease. Multi system involvement is also common and this can pose additional management dilemmas for doctors.

The Newcastle Mitochondrial Disease Guidelines aim to provide expert guidance to health professionals on the management of specific aspects of Mitochondrial Disease.

These guidelines have been developed using consensus expert opinion sourced from the NHS Rare Mitochondrial Disorders Service in Newcastle with associated experts from other hospitals.

Anaesthesia & Peri-Operative Guidelines
Cardiology Guidelines
Diabetes Guidelines
Epilepsy Guidelines
Gastrointestinal Guidelines
Neuropathy Guidelines
Ophthalmology Guidelines
Pregnancy Guidelines
Respiratory Guidelines
Stroke Like Episode Guidelines
Emergency plans and acute management
Emergency plan

University College London Hospitals
NHS Foundation Trust

The National Hospital for Neurology and Neurosurgery
Queen Square
London WC1N 3BG

Our Ref:
NHS No:
Clinic:
Date:

MEDICAL IN CONFIDENCE

Emergency and anaesthetic plan

Patient details:

Next of kin details:

Diagnosis: Mitochondrial disease, m.3243A>G mutation

Problems: bilateral hearing loss

Medication: Co Enzyme Q10 200mg BD

Contact details for the mitochondrial team:

Consultants: Professor M. G Hanna, Consultant Neurologist, Dr Quinlivan, Consultant in Neuromuscular Disorders
Contact via Marcia Forde PA to Professor Hanna on 0203 448 8014 or at Marcia.forde@uclnhs.uk
Clinical Nurse Specialist: Direct line 0203 448 8009
Specialist Registrar for the muscle team via the hospital switchboard on 0845 155 5000, bleep 6211 (during working hours 08.30 - 16.00)
For out of hours advice please contact the on-call registrar for the National Hospital for Neurology via the UCLH switchboard on 0845 155 5000.
Acute management

• Early recognition of warning signs:
  – Nausea and vomiting
  – Confusion, sleepiness or irritability
  – Weakness, numbness or speech problems
  – Visual or hearing disturbance
  – Seizures
  – Severe headaches
  – Sudden bowel problems
Acute management

• Seek medical attention early (GP or A&E)
• Ensure any infection treated and well hydrated
• Review medications
• Admit to hospital for:
  – Intravenous fluids
  – Intravenous antibiotics
  – Correction of acidosis
  – Wide bore NGT, enemas, fluids +/- TPN for IPO
  – Stroke-like episodes = seizure control
QS Mitochondrial Disease
Research studies
Lower urinary tract symptoms and sexual dysfunction in mitochondrial disease – completed
Background

Mitochondrial disease can affect bowel function
Mitochondrial disease can affect bowel function

**We asked:**
Can mitochondrial disease cause lower urinary tract symptoms (LUTS) and sexual dysfunction too?
Methods

- Questionnaire study
- Comparing
  - 58 people with genetically confirmed mitochondrial disease
  - 19 unaffected individuals
Results: LUTS

- Adults with genetically confirmed mitochondrial disease frequently experience LUTS (84%)

- Overactive bladder symptoms (*urinary urgency, the sudden compelling urge to urinate*) most common 82%

- Overactive bladder symptoms and low stream symptoms (*weak urine stream, difficulty starting urination*) are more common in patients than in unaffected individuals (*)
Results: Sexual Dysfunction

• Sexual dysfunction is more common in females with mitochondrial disease than unaffected females

• Sexual dysfunction is very common in those with m.3243A>G mutation (66.7%)
Conclusions

- LUTS are common in individuals with mitochondrial disease.
- Despite several effective treatments available for LUTS, most were untreated.
- Sexual dysfunction is common in female mitos and those with m.3243A>G.
- This work will help ensure physicians and patients are aware of LUTS and sexual dysfunction symptoms in mitochondrial disease, so they are identified and treated, improving quality of life.
Vestibular dysfunction: a frequent problem in adult mitochondrial disease – completed
Method

- Genetic diagnosis of mitochondrial disease (n=36)
- Clinicopathological diagnosis of mitochondrial disease (n=4)

Patients with suspected balance disorder seen in specialist mitochondrial clinic (n=40)

- Referred to specialist neuromuscular physiotherapist to complete vestibular and neurological assessment (n=40)

- Non-vestibular causes of dizziness and imbalance (n=7)
  - Cerebellar syndrome (n=5)
  - Biomechanical falls (n=2)

- Referred to Neuro-Otology for full audiovestibular assessment (n=33)
  - Genetic diagnosis of mitochondrial disease (n=29)
  - Clinicopathological diagnosis of mitochondrial disease (n=4)

JNNP in press
Results

- Suspected balance disorder: 91% (30/33)
- Minimum prevalence of vestibular abnormality: 26% (30/114)
Results

- Peripheral vestibulopathy: 77% (23/30)
Importance – treatment available!

Patient reported symptoms:
Dizziness, light-headedness, loss of balance, unsteadiness, falls

Additional questions:
- Dizzy on turning over in bed?
- Dizzy/loss of balance when bending or moving head down or up?
- Head or neck pain?
- Visual aura?
- Light/sound sensitivity?
- Nausea?
- Dizziness or blurry vision when moving head or body?
- Bobbing vision when walking?
- Imbalance?
- Imbalance in the dark?
- Dizzy or imbalance in crowds, escalators, supermarkets?

Potential cause of balance disorder:
- BPPV
- Migraine
- Peripheral vestibular disorder
- Visual dependence

Management:
- Positional tests and repositioning manoeuvres
- Refer for vestibular rehabilitation (as required)
- Manage migraine
- Refer for vestibular rehabilitation (as required)
- If positive head thrust test, refer for neuro-otological investigations
- Refer for vestibular rehabilitation
- Refer for neuro-otological investigations
- Refer for vestibular rehabilitation
Mood in mitochondrial disease – ongoing
Mood and quality of life in mitochondrial diseases

We started evaluating carefully the presence of subtle mood alterations in mitochondrial diseases

**WHY:** early identification of mood alterations may lead to appropriate management

**HOW:** set of questionnaires exploring different aspects of mood involvement
Mood and quality of life in mitochondrial diseases

Pilot study

• Evaluate which questionnaires are the most appropriate for evaluating mood
• Evaluate the frequency of mood alterations and how they relate to clinical symptoms

To better understand the role of mitochondria on mood alterations
To improve clinical management of mitochondrial diseases
QS Mitochondrial Disease
Clinical Trials
Elamipretide / Bendavia
- UCL and Newcastle (UK)
Elamipretide / Bendavia

Peroxidation Disrupts the Inner Mitochondrial Membrane Structure and Supercomplexes

ROS \rightarrow + \text{Bendavia}
An Observational Study of Patients With Primary Mitochondrial Disease (SPIMM-300)

**Inclusion Criteria**

- Genetic diagnosis of mitochondrial disease
- Patient can provide informed consent
- Patient $\geq 16$ and $\leq 65$ years of age
- Signs or symptoms of mitochondrial myopathy (fatigueability, exercise intolerance, muscle pain)
- Ambulatory and can walk for 6 minutes
An Observational Study of Patients With Primary Mitochondrial Disease (SPIMM-300)

**Patient visits and procedures**
- 2 questionnaires: fatigue (8Qu) and PMD symptom assessment (9Qu)
- 6MWT
- 3TUG
- 5XSST
- 6 month follow up telephone call
SPIMM-301: Phase 3 Randomized, Double-Blind, Parallel-Group, Placebo-Controlled Trial to Evaluate the Efficacy and Safety of Daily Subcutaneous Injections of Elamipretide in Subjects with Primary Mitochondrial Myopathy Followed by an Open-Label Treatment Extension
PART 1 Objectives/Endpoints

Primary Objective

- To evaluate the effect of single daily SC doses of 40 mg elamipretide administered with the elamipretide delivery system for 24 weeks on the:
  - Distance Walked (meters) on the 6MWT
  - Total Fatigue score on the Primary Mitochondrial Myopathy Symptom Assessment (PMMSA)
PART 1 Objectives/Endpoints

Secondary Objectives:

• To evaluate the effect of single daily SC doses of 40 mg elamipretide administered with the elamipretide delivery system for 24 weeks as measured by changes in the:
  – Fatigue During Activities score on the PMMSA
  – Neuro-QoL Fatigue score
  – Most bothersome symptom score on the PMMSA
PART 1 Objectives/Endpoints

Secondary Objectives:
• To evaluate the safety and tolerability of single daily SC doses of 40 mg elamipretide administered with the elamipretide delivery system for 24 weeks:
  – Adverse Events (AEs)/Adverse Device Effects (ADEs)
  – Vital Signs
  – Electrocardiograms (ECGs)
  – Clinical laboratory evaluations
  – Columbia-Suicide Severity Rating Scale (C-SSRS)
SPIMM-301 PART 1

Elamipretide 40 mg SC daily for 24 weeks

Placebo SC daily for 24 weeks

Screening Visit  Baseline Visit  Week 4 Visit  Week 12 Visit  Week 24 Visit  Week 28 Visit (PART 1 EOT*/Early D/C Visit)

Screening  PART 1 Treatment Period  PART 1 Follow-Up Period

*only applicable if subject and/or Investigator decide not to continue subject into Part 2 (SPIMM-301 OLE)
PART 2 Objectives/Endpoints

Primary Objective

• To assess the long-term safety and tolerability of single daily SC doses of 40 mg elamipretide administered with the elamipretide delivery system for up to 144 weeks.

  – Adverse Events (AEs)/Adverse Device Effects (ADEs)
  – Vital Signs
  – Electrocardiograms (ECGs)
  – Clinical laboratory evaluations
  – Columbia-Suicide Severity Rating Scale (C-SSRS)
SPIMM-301 PART 2

Elamipretide 40 mg SC daily

- 4 weeks
- 8 weeks
- 12 weeks
- 28 days

- Week 24 Visit (PART 1)
- Week 28 Visit
- Week 36 Visit
- Week 48 Visit
- Weeks 60, 84, 108, 132, 156 (phone call)
- Week 72, 96, 120, 144, 168 Visits
- Part 2 EOT/Early D/C Visit

PART 2 Treatment Period

Part 2 Follow-Up Period
PART 2 Continuation Criteria

A subject must meet all of the following PART 2 Continuation Criteria at the Week 24 Visit in SPIMM-301 to be eligible for PART 2:

1. Subjects must continue to be able and willing to adhere to the trial requirements.
2. Subject is appropriate to continue in PART 2 (i.e. subject was compliant in SPIMM-301), in the opinion of the Investigator.
3. Subject has not had a serious adverse event (SAE)/serious adverse device effect (SADE) attributed to the elamipretide delivery system.
4. Subject has not permanently discontinued the elamipretide delivery system.
Nicotinamide Riboside
- Cambridge and UCL
Less mitochondria = less energy
More mitochondria = more energy
The role of Nicotinamide Riboside in Mitochondrial Biogenesis

*What’s the study about?*
Aim of this study is to investigate if Nicotinamide Riboside, a modified B vitamin, can increase energy production and reduce symptoms in humans with mitochondrial disease.

*Who’s running the study?*
Professor Patrick Chinnery and his research team in Cambridge

*What’s involved?*
6 visits to Addenbrooke’s Hospital, Cambridge:

- **Visit 1:** MRI scan, muscle biopsy, 6 minute walk test, timed up and go, grip strength, questionnaires.
- **4 weeks** of Nicotinamide Riboside supplementation
- **Visits 2-5:** blood samples and progress check.
- **Visit 6:** MRI scan, muscle biopsy, 6 minute walk test, timed up and go, grip strength, questionnaires.

*Who’s eligible?*
Men and women aged 18-70 years, with a confirmed diagnosis of:

- Mitochondrial disease caused by the *m.3243A>G* mutation in mitochondrial DNA
- Progressive external ophthalmoplegia (PEO) plus exercise intolerance/fatigue, caused by a single deletion of mitochondrial DNA

Zoe McIntyre  
01223 331506  
zm276@medschl.cam.ac.uk  
mitopatients@mrc-mbu.cam.ac.uk  
@cam_mito
2-Deoxyglucose
- UCL
Less healthy mitochondria = less energy
More healthy mitochondria = more energy
2-Deoxyglucose experimental medicine study

- Modified sugar molecule
- Reduces mutant 3243G in patient skin cells
- Has been used in humans in cancer and epilepsy

Study design

- **Stage I** (4 patients) → 8 weeks escalating dose
- **Stage II** (6 patients) → 12 week study to measure whether 2DG reduces 3243G levels in humans (will involve muscle biopsies pre- and post-treatment)
Summary

• Diagnosing mitochondrial disease can be challenging; multidisciplinary approach crucial

• No evidence from trials for current treatments apart from specific scenarios – but lots we can still do

• Surveillance and treatment of complications and recognising warning signs early essential

• Lots of active research studies and preclinical and early phase clinical trials ongoing
Acknowledgments

- Prof M Hanna
- Prof H Houlden
- Prof M Reilly
- Dr R Quinlivan
- Dr C Turner
- Dr M Parton
- Dr O Poole
- Dr E Bugiardini
- Ms S Holmes
- Ms N James
- Ms M Skorupinska
- Ms I Skorupinska
- Ms L Germain
- Mr D Kozyra
- Dr J Holton
- Dr R Phadke
- Dr J Polke
- Ms C Woodward
- Dr R Labrum
- Prof S Heales
- Dr A Lam
- Dr I Hargreaves
- Dr A Chalasani
- Dr M Madej
- Dr A Male
- Dr D Kaski
- Dr G Ramdharry
- Prof D Turnbull
- Prof R Taylor
- Dr R McFarland
- Dr A Schaefer
- Dr G Gorman
- Dr Yi Ng
- Prof J Poulton
- Dr V Nesbitt
- Dr C Fratter
- Dr C Smith
- Dr G Brown
Lots of exciting research and trials in mitochondrial disease – speak to Louise, Iwona or Mariola to register your interest!

l.germain@nhs.net       iwona.skorupinska@nhs.net       mariola.skorupinska@nhs.net