Mitochondrial Diseases
Patient Engagement Day
London

Dr Robert Pitceathly
Saturday 13th October 2018
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
The mitochondrion
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

Each child has 1 in 4 chance of disease

Dominant

Each child has 1 in 2 chance of disease

- Red: Disease
- Blue: Unaffected
- Pink: Unaffected carrier
Mitochondrial DNA
mitochondrial disease

Not ‘Yes’ or ‘No’?

But how much?

Nuclear:
 e.g. Dominant inheritance

Mitochondrial:
 Maternal inheritance
So things are complicated...

Inheritance:
- Nuclear DNA disease: Dominant, Recessive, X-linked
- MtDNA disease: Maternal
Less mitochondria – less energy

Human Cell (the machine)

Nucleus containing Chromosomes (blueprint)

Mitochondria (batteries)
Genetic variability

- mtDNA
- nDNA
- mtDNA maintenance
- mtDNA transcription
- mtDNA translation

13 polypeptide subunits

Complex assembly and remaining 76 subunits

- Complex I: 7/44
- Complex II: 0/4
- Complex III: 1/11
- Complex IV: 3/14
- Complex V: 2/16
Clinical variability

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

Respiratory chain dysfunction

Female

Male

Food and drink icons
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
From clinical assessment to genetic diagnosis

I. **Age, Phenotype, Pedigree**

II. **BLOOD**
   - Nuclear maintenance panel (21 genes)
   - Targeted exome (300 mito genes)
   - Common mtDNA point mutations (3243, 8344, 8993)
     - RFLP >1%
   - Full mtDNA Sequencing
     - NGS >10%
     - NGS >10%
   - Large scale rearrangements
     - LPCR, SB >5%

III. **MUSCLE**
   - Histopathology (COX/SDH, RRF)
   - Biochemistry (RCEA, BN-PAGE)
   - Full mtDNA Sequencing
     - NGS
   - Large scale rearrangements
     - LPCR, SB

IV. **BLOOD**
   - Novel mutations/genes
   - Exome/Genome (Research)
   - Functional studies
     - Modelling
     - Additional families
   - mtDNA copy number
     - RT-PCR
Current treatment strategies
Exciting times!

Gene transfer

Drugs

Stem cells

New proteins

Targeted nucleases

mtDNA

Peptide nucleic acid

tRNA enzymes
What about now!
Pharmacological agents, vitamins and related substances
Vitamins, cofactors and food supplements

- CoQ10
- Idebenone
- Succinate
- L-Arginine/Citrulline
- Folate/Folinic acid
- Vitamin C/E
- α-lipoic acid
- Carnitine
- Creatine
- Riboflavin
- Thiamine
Pharmacological agents and vitamins

Cochrane Database of Systematic Reviews

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

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<th>Disease</th>
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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.
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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.

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<tr>
<th>During the past week, I have found that ...</th>
<th>Never</th>
<th>Hardly any time</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>
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<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>
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<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>
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<td>6</td>
<td>7</td>
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Mitochondrial diseases with specific treatment options

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<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>
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<td>Primary disorders of mitochondrial vitamin cofactor metabolism</td>
<td>Brown-Viallette-Van Laere syndrome / Fazio-Londe disease</td>
<td>SLC52A2, SLC52A3, SLC52AJa</td>
<td>Sensorineural hearing loss, cranial nerve palsies</td>
<td>Riboflavin (oral: 10–50 mg/kg/day)§</td>
<td>Generally good</td>
</tr>
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<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) §</td>
<td>Generally good</td>
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<td>Biotinidase deficiency</td>
<td>BTD</td>
<td>Dermatitis, muscular hypotonia, developmental regression</td>
<td>Thiamine (oral: 10–20 mg/kg/day) §</td>
<td>Generally good</td>
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<td>Holocarboxylase synthetase deficiency</td>
<td>HLCS</td>
<td>Skin lesions, metabolic acidosis, seizures, developmental delay</td>
<td>Biotin (oral: 5–10 mg/kg/day)±</td>
<td>Variable but generally good</td>
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<td>Thiamine pyrophosphokinase deficiency</td>
<td>TPK1</td>
<td>Episodic encephalopathy, dystonia, spasticity</td>
<td>Biotin (oral: 10–15 mg/kg/day)±</td>
<td>Variable</td>
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<td>Disorders with indirect response to mitochondrial vitamin cofactor supplementation</td>
<td>ACAD9 deficiency</td>
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<td>Encephalopathy, myopathy, hypertrophic cardiomyopathy</td>
<td>Thiamine (oral: ~20 mg/kg/day)§</td>
<td>Variable</td>
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<td>Multiple acyl-CoA dehydrogenase deficiency</td>
<td>ETF4, ETFB, ETFDH, SLC25A32, FAD1</td>
<td>Early childhood multisystem disease or late-onset form with muscle weakness, hepatopathy, etc.</td>
<td>Riboflavin (oral: 10–20 mg/kg/day) §</td>
<td>Variable</td>
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<td>Thiamine-responsive pyruvate dehydrogenase deficiency</td>
<td>PDHA1</td>
<td>Neonatal lactic acidosis, seizures, developmental regression, spasticity</td>
<td>Thiamine (oral: 30–40 mg/kg/day)</td>
<td>Variable</td>
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<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>Generally good</td>
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<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)§</td>
<td>Unclear; only one COQ2 patient treated; only in vitro evidence for COA6</td>
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<td>Molybdenum cofactor deficiency</td>
<td>MOCS1, MOCS2, GPHN</td>
<td>Infantile-onset epileptic encephalopathy, progressive brain damage</td>
<td>Cyclic pyranopterin monophosphate (intravenous: 80–320 μg/kg/day)§</td>
<td>Generally good in MoCD type A patients</td>
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<td>‘Inhibitors’ of mitochondrial metabolism</td>
<td>3-Hydroxyisobutyryl-CoA hydrolase deficiency</td>
<td>HIBCH</td>
<td>Infantile Leigh-like phenotype</td>
<td>Valine-restricted diet≤</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≤</td>
<td>Unclear; only few patients treated</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)≤</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>Metronidazole, N-acetyl cysteine as glutathione precursor, liver transplantation≤</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 Biotin-thiamine-responsive basal ganglia disease</td>
<td>SLC52A2, SLC52A3, SLC52A1 (SLC52A1) SLC19A3</td>
<td>Sensorineural hearing loss, cranial nerve palsies Episodic encephalopathy, dystonia, seizures</td>
<td>Riboflavin (oral: 10-50 mg/kg/day) Thiamine (oral: 10-20 mg/kg/day), biotin (oral: 10-15 mg/kg/day) Biotin (oral: 5-10 mg/kg/day)</td>
<td>Generally good</td>
</tr>
<tr>
<td>Disorders with normal response</td>
<td></td>
<td></td>
<td></td>
<td>Biotin (oral: 10 mg/kg/day)</td>
<td>Generally good</td>
</tr>
<tr>
<td>Coenzyme Q10 supplementation</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Variable but generally good</td>
</tr>
<tr>
<td>Disorders of mitochondrial non-vitamin cofactor metabolism</td>
<td>Coenzyme Q10 deficiency</td>
<td></td>
<td></td>
<td></td>
<td>Variable</td>
</tr>
<tr>
<td>Disorders of mitochondrial inorganic cofactor metabolism</td>
<td>Molybdenum cofactor deficiency MOCS1, MOCS2, GPHN</td>
<td></td>
<td></td>
<td></td>
<td>Highly variable depending on the underlying defect</td>
</tr>
<tr>
<td>‘Inhibitors’ of mitochondrial metabolism</td>
<td>3-Hydroxyisobutryl-CoA hydrolase deficiency EC2H</td>
<td></td>
<td></td>
<td>Copper-histidine (dose unclar; subcutaneous injection of up to 500 µg daily)</td>
<td>Unclear, only one SO2 patient treated; only in vitro evidence for COA6, generally good in MCD type A patients</td>
</tr>
<tr>
<td></td>
<td>Enoyl-CoA hydratase deficiency EC5H1</td>
<td></td>
<td></td>
<td></td>
<td>Unclear, only few patients treated; apparently few patients so far</td>
</tr>
<tr>
<td></td>
<td>Thioredoxin 2 deficiency TXN2</td>
<td></td>
<td></td>
<td></td>
<td>Variable</td>
</tr>
<tr>
<td></td>
<td>Ethylmalonic encephalopathy ETHE1</td>
<td></td>
<td></td>
<td></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
- Ptosis
- Optic Atrophy
- Retinitis Pigmentosa
- Cataracts
- Stroke / Seizures
- Developmental Delay
- Movement Disorders
- Deafness
- Cardiomyopathy
- Conduction Defects
- Liver / Renal Failure
- Dysphagia
- Gut dysmotility
- Short stature
- Marrow Failure
- Diabetes
- Hypothyroidism
- Fatigue
- Myopathy
- Exercise intolerance
- Peripheral neuropathy
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.
Emergency plans and acute management
Emergency plan

University College London Hospitals

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. O 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@uclh.nhs.uk

Clinical Nurse Specialist: Direct line 0203 448 8009
Specialist Registrar for the muscle team via the hospital switchboard on 0845 155 5000, bleep 8211 (during working hours 08.30 – 18.00)
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
Mitochondrial disease can affect bowel function
Background

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

• Overactive bladder symptoms (*uninary 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: LUTS
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)

Genetic diagnosis of mitochondrial disease (n=29)

Clinicopathological diagnosis of mitochondrial disease (n=4)

Referred to Neuro-Otology for full audiovestibular assessment (n=33)
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 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

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

**HOW:** set of questionnaires exploring different aspects of mood involvement

We started evaluating carefully the presence of subtle mood alterations in mitochondrial diseases
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 $\downarrow$ + Bendavia

Complex I  IMS  C

Complex III  IMS  C

Complex IV  matrix

CL  PC  CLOOH
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

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

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@cam_mito
2-Deoxyglucose
- UCL
Less healthy mitochondria = less energy

Human Cell (the machine)

Nucleus containing Chromosomes (blueprint)

Mitochondria (batteries)
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
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- Prof M Reilly
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- 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!

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