# *This is mitochondrial disease.....*

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***University of Oxford***

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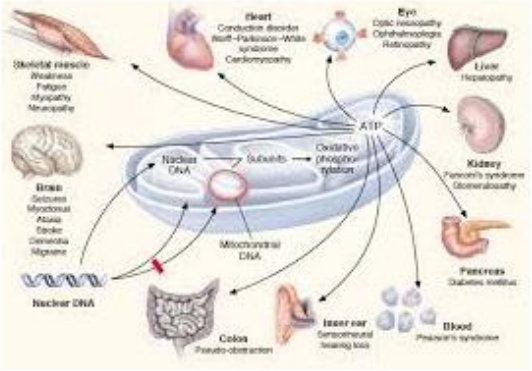
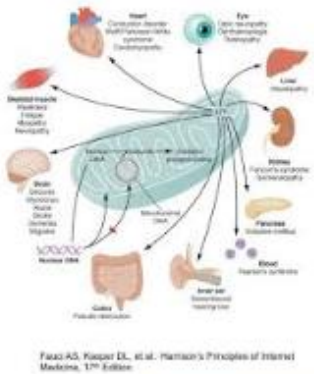
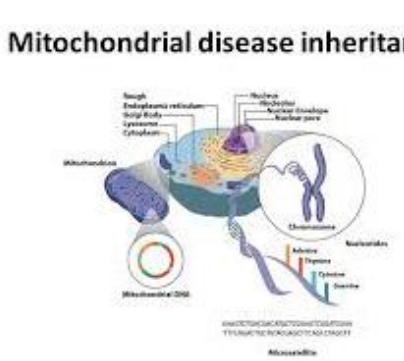
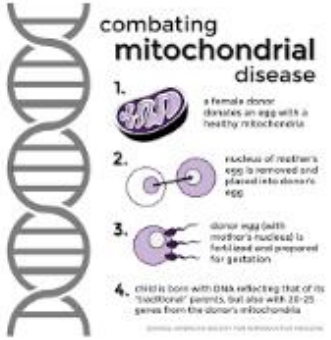
baby | mitochondria | human | mitochondrial dna | organ system | alpers | pearson syndrome | inheritance | mutation



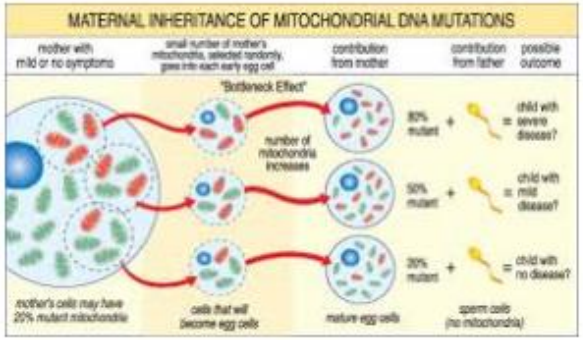





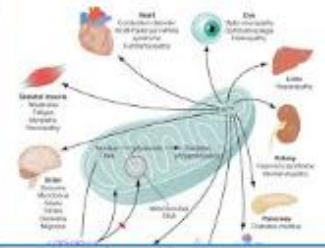


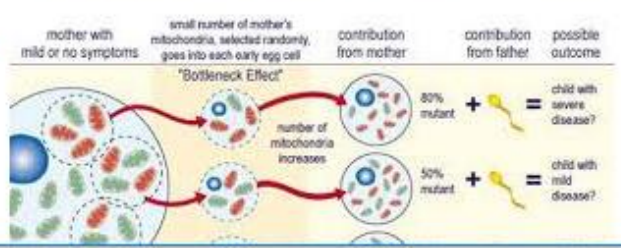













# *Hard to take in*

Lily

Fighting Mitochondrial Disease.
Fighting For Hope!

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# Join Our Around The World Challenge!


## Donate Now

Help improve the lives of people with mitochondrial disease today

## Need To Talk?

Have you or a loved one been diagnosed? We're here to help

## Join The Fight

Take part in an event, organise a fundraiser or become a partner

# *Mitochondrial diagnoses are rare*

The commonest type of MDS is Alpers syndrome (1 in 100,000)

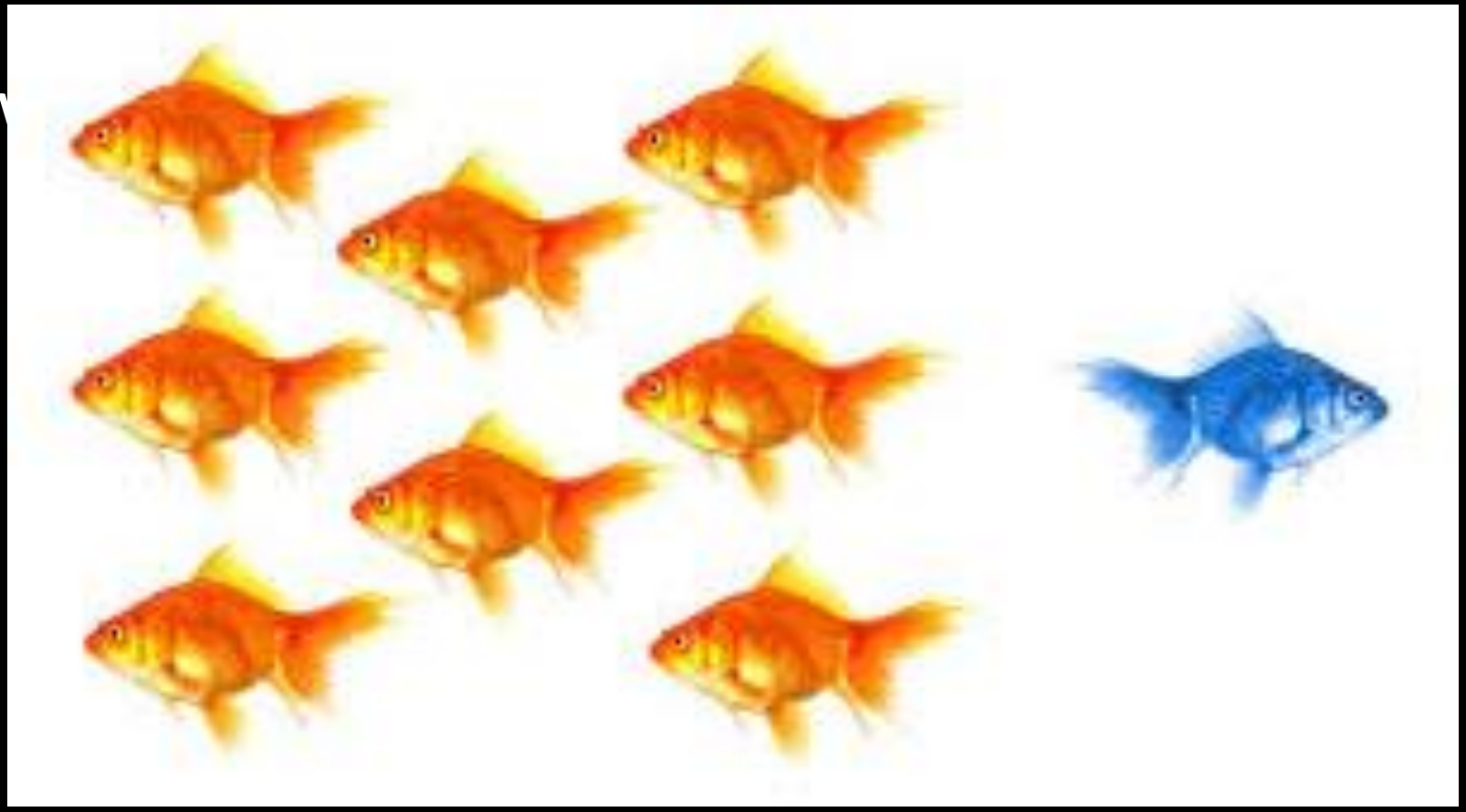
***But mitochondrial diseases are actually commoner***
***1 in 300***

# *There are many types of Mitochondrial disease*

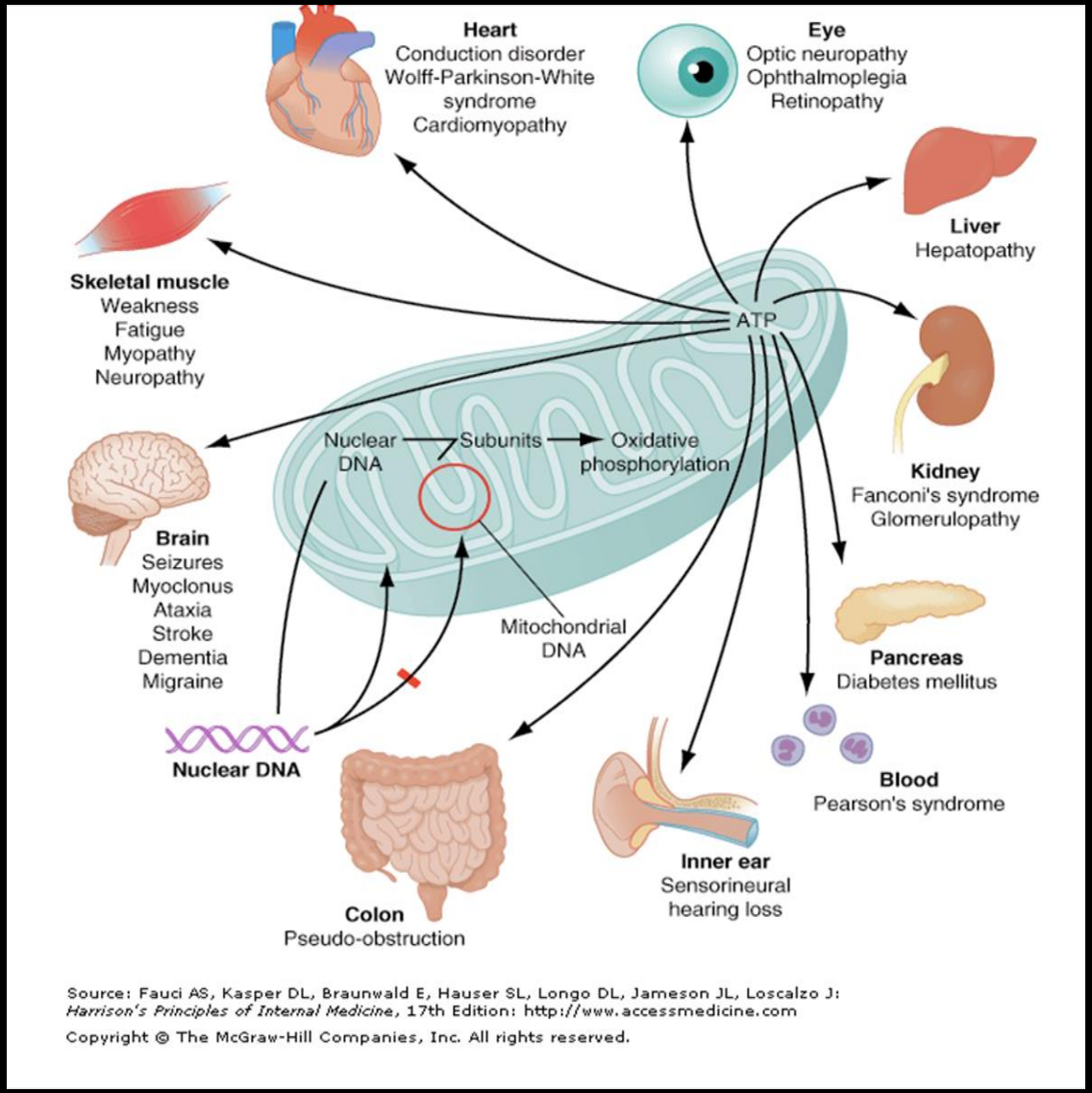
Hoping for the best

Planning for the worst

# *What kind of mitochondrial disease?*



# *Mitochondrial Diseases can be very different*

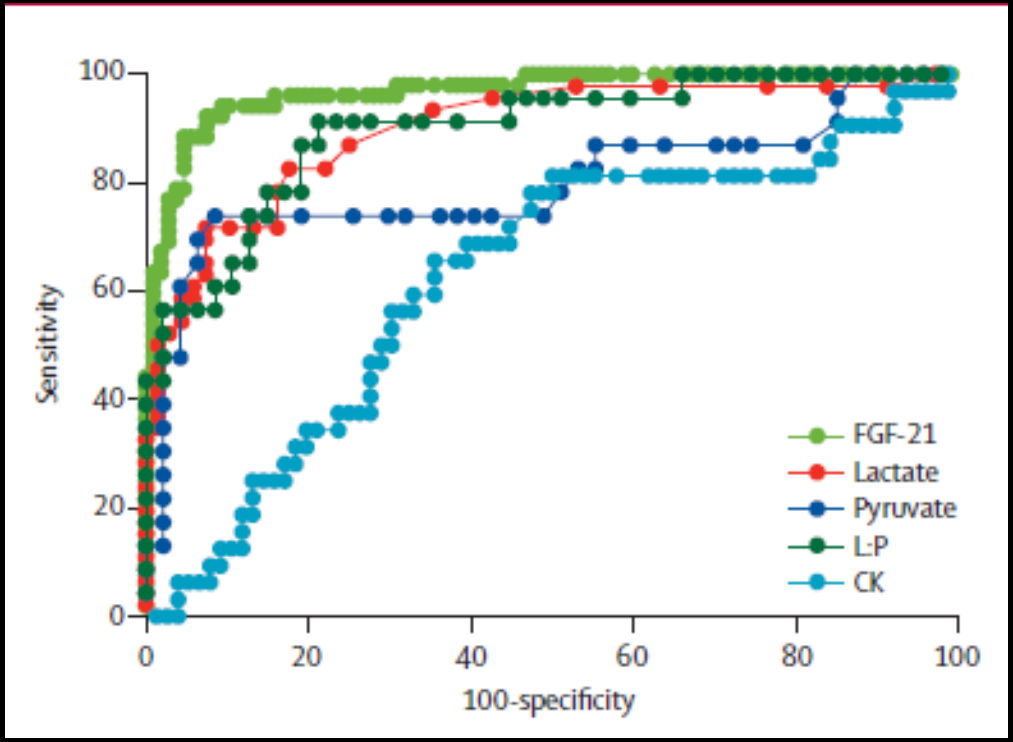



https://universe-review.ca/I10-05-mito02.gif

# ….or no diagnosis yet…?

# *Better diagnosis of mitochondrial disease*

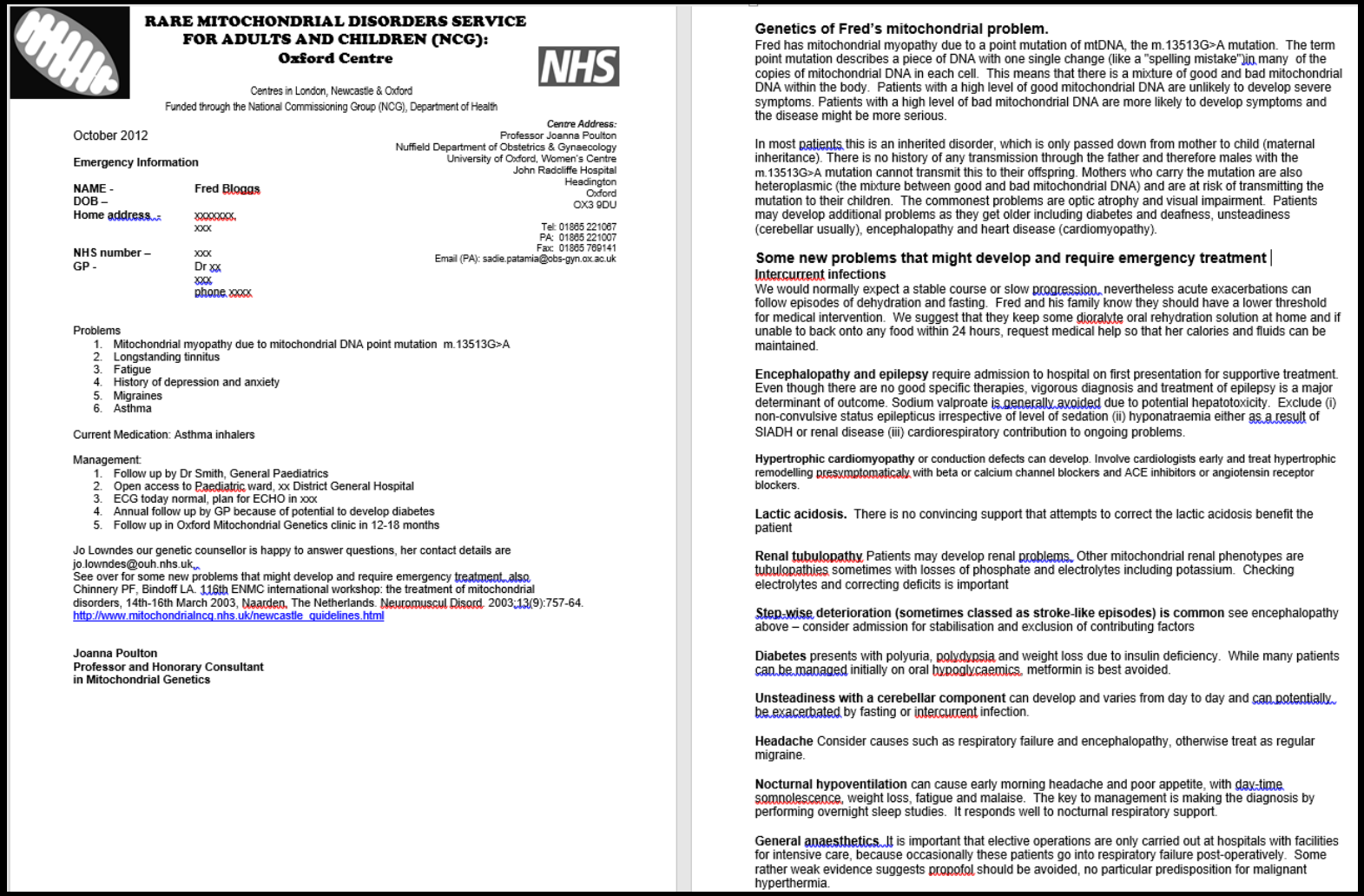
***FGF21 is better than***
***lactate,***
***pyruvate,***
***LP ratio***
***CK***




# *Mitochondrial Research has made big strides: better genetic diagnosis*

- Next Generation  Sequencing

# How can we treat mitochondrial disease?



**RARE MITOCHONDRIAL DISORDERS SERVICE FOR ADULTS AND CHILDREN (NCG): Oxford Centre**

NHS

Centres in London, Newcastle & Oxford

Funded through the National Commissioning Group (NCG), Department of Health

October 2012

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**Emergency Information**

**NAME -** Fred Bloggs
**DOB –**
**Home address -** xxxxxxx
xxx

**NHS number –** xxx
**GP -** Dr xx
xxx
phone xxxx

Problems
1. Mitochondrial myopathy due to mitochondrial DNA point mutation m.13513G>A
2. Longstanding tinnitus
3. Fatigue
4. History of depression and anxiety
5. Migraines
6. Asthma

Current Medication: Asthma inhalers

Management:
1. Follow up by Dr Smith, General Paediatrics
2. Open access to Paediatric ward, xx District General Hospital
3. ECG today normal, plan for ECHO in xxx
4. Annual follow up by GP because of potential to develop diabetes
5. Follow up in Oxford Mitochondrial Genetics clinic in 12-18 months

Jo Lowndes our genetic counsellor is happy to answer questions, her contact details are jo.lowndes@ouh.nhs.uk.
See over for some new problems that might develop and require emergency treatment, also
Chinnery PF, Bindoff LA. 116th ENMC international workshop: the treatment of mitochondrial disorders, 14th-16th March 2003, Naarden, The Netherlands. Neuromuscul Disord. 2003;13(9):757-64.
http://www.mitochondrialncg.nhs.uk/newcastle_guidelines.html

**Joanna Poulton**
**Professor and Honorary Consultant**
**in Mitochondrial Genetics**

**Genetics of Fred's mitochondrial problem.**
Fred has mitochondrial myopathy due to a point mutation of mtDNA, the m.13513G>A mutation. The term point mutation describes a piece of DNA with one single change (like a "spelling mistake") in many of the copies of mitochondrial DNA in each cell. This means that there is a mixture of good and bad mitochondrial DNA within the body. Patients with a high level of good mitochondrial DNA are unlikely to develop severe symptoms. Patients with a high level of bad mitochondrial DNA are more likely to develop symptoms and the disease might be more serious.

In most patients this is an inherited disorder, which is only passed down from mother to child (maternal inheritance). There is no history of any transmission through the father and therefore males with the m.13513G>A mutation cannot transmit this to their offspring. Mothers who carry the mutation are also heteroplasmic (the mixture between good and bad mitochondrial DNA) and are at risk of transmitting the mutation to their children. The commonest problems are optic atrophy and visual impairment. Patients may develop additional problems as they get older including diabetes and deafness, unsteadiness (cerebellar usually), encephalopathy and heart disease (cardiomyopathy).

**Some new problems that might develop and require emergency treatment**
**Intercurrent infections**
We would normally expect a stable course or slow progression, nevertheless acute exacerbations can follow episodes of dehydration and fasting. Fred and his family know they should have a lower threshold for medical intervention. We suggest that they keep some dioralyte oral rehydration solution at home and if unable to back onto any food within 24 hours, request medical help so that her calories and fluids can be maintained.

**Encephalopathy and epilepsy** require admission to hospital on first presentation for supportive treatment. Even though there are no good specific therapies, vigorous diagnosis and treatment of epilepsy is a major determinant of outcome. Sodium valproate is generally avoided due to potential hepatotoxicity. Exclude (i) non-convulsive status epilepticus irrespective of level of sedation (ii) hyponatraemia either as a result of SIADH or renal disease (iii) cardiorespiratory contribution to ongoing problems.

**Hypertrophic cardiomyopathy** or conduction defects can develop. Involve cardiologists early and treat hypertrophic remodelling presymptomatically with beta or calcium channel blockers and ACE inhibitors or angiotensin receptor blockers.

**Lactic acidosis.** There is no convincing support that attempts to correct the lactic acidosis benefit the patient

**Renal tubulopathy** Patients may develop renal problems. Other mitochondrial renal phenotypes are tubulopathies sometimes with losses of phosphate and electrolytes including potassium. Checking electrolytes and correcting deficits is important

**Step-wise deterioration (sometimes classed as stroke-like episodes) is common** see encephalopathy above – consider admission for stabilisation and exclusion of contributing factors

**Diabetes** presents with polyuria, polydypsia and weight loss due to insulin deficiency. While many patients can be managed initially on oral hypoglycaemics, metformin is best avoided.

**Unsteadiness with a cerebellar component** can develop and varies from day to day and can potentially be exacerbated by fasting or intercurrent infection.

**Headache** Consider causes such as respiratory failure and encephalopathy, otherwise treat as regular migraine.

**Nocturnal hypoventilation** can cause early morning headache and poor appetite, with day-time somnolescence, weight loss, fatigue and malaise. The key to management is making the diagnosis by performing overnight sleep studies. It responds well to nocturnal respiratory support.

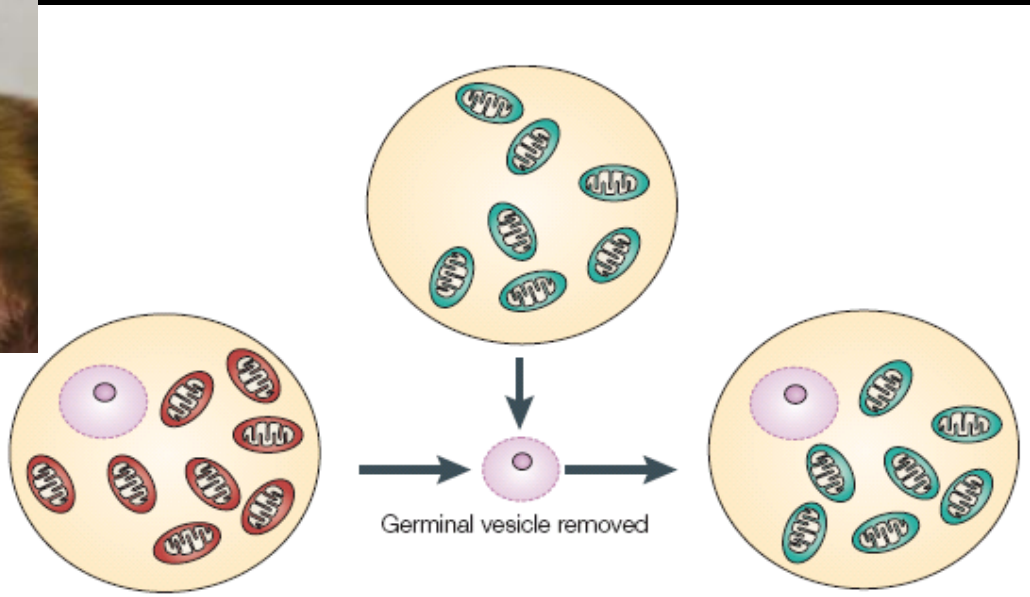
**General anaesthetics.** It is important that elective operations are only carried out at hospitals with facilities for intensive care, because occasionally these patients go into respiratory failure post-operatively. Some rather weak evidence suggests propofol should be avoided, no particular predisposition for malignant hyperthermia.

# *How can we treat mitochondrial disease?*

- Keep in touch with your team
- Enroll in the cohort

## *Three parent babies- Mitochondrial Replacement Therapy*

- Just starting in the UK
- Not a treatment, but a way of preventing passing mitochondrial disease to your children



# *Like changing a laptop battery…?*

Exciting basic science

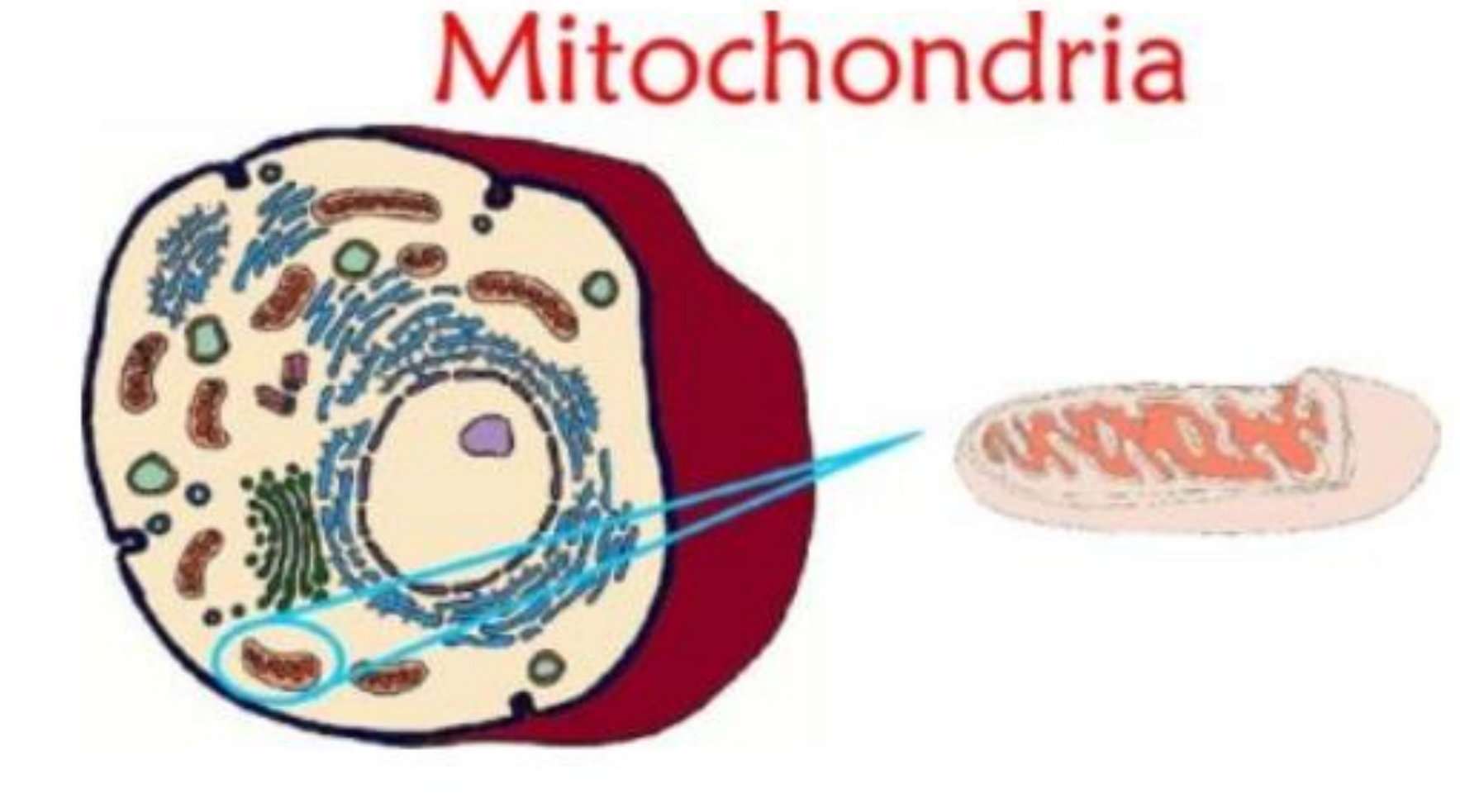
Not relevant for most families (such as MDS)

Alternatives are available for all maternally inherited mtDNA disease

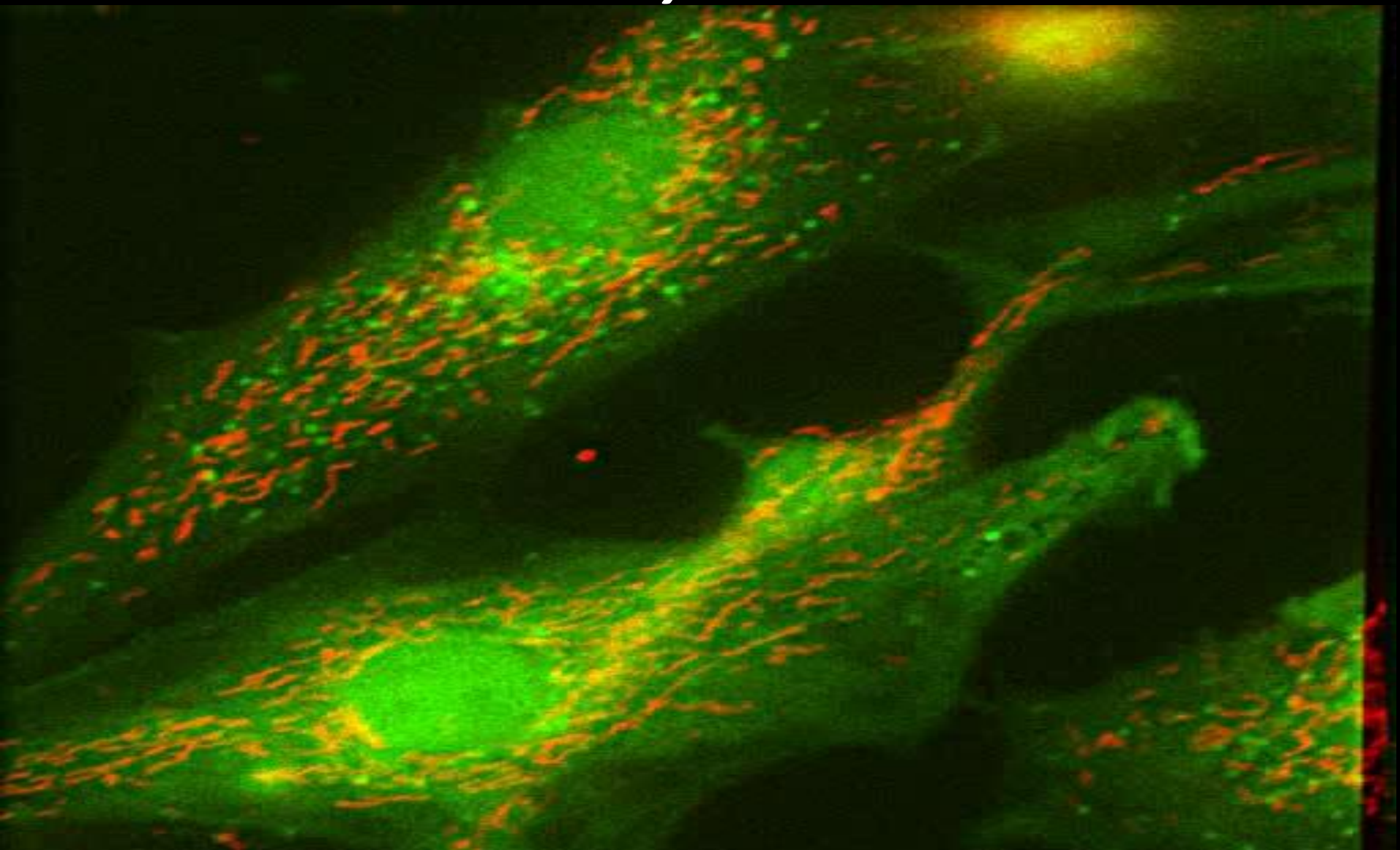
2010

… could be made available to women within the next three years"

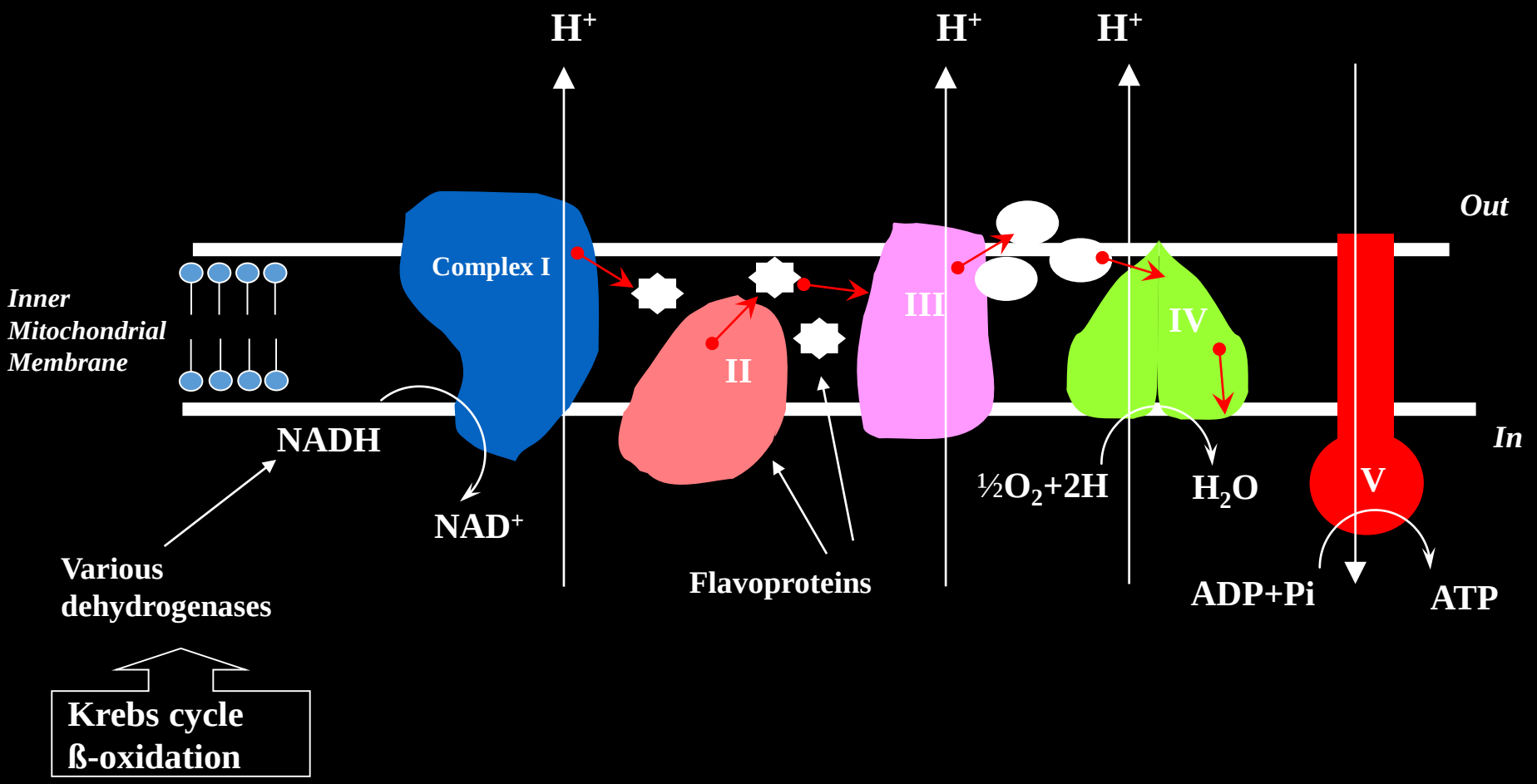
***Mitochondria are small parts of cells that are needed for making energy***



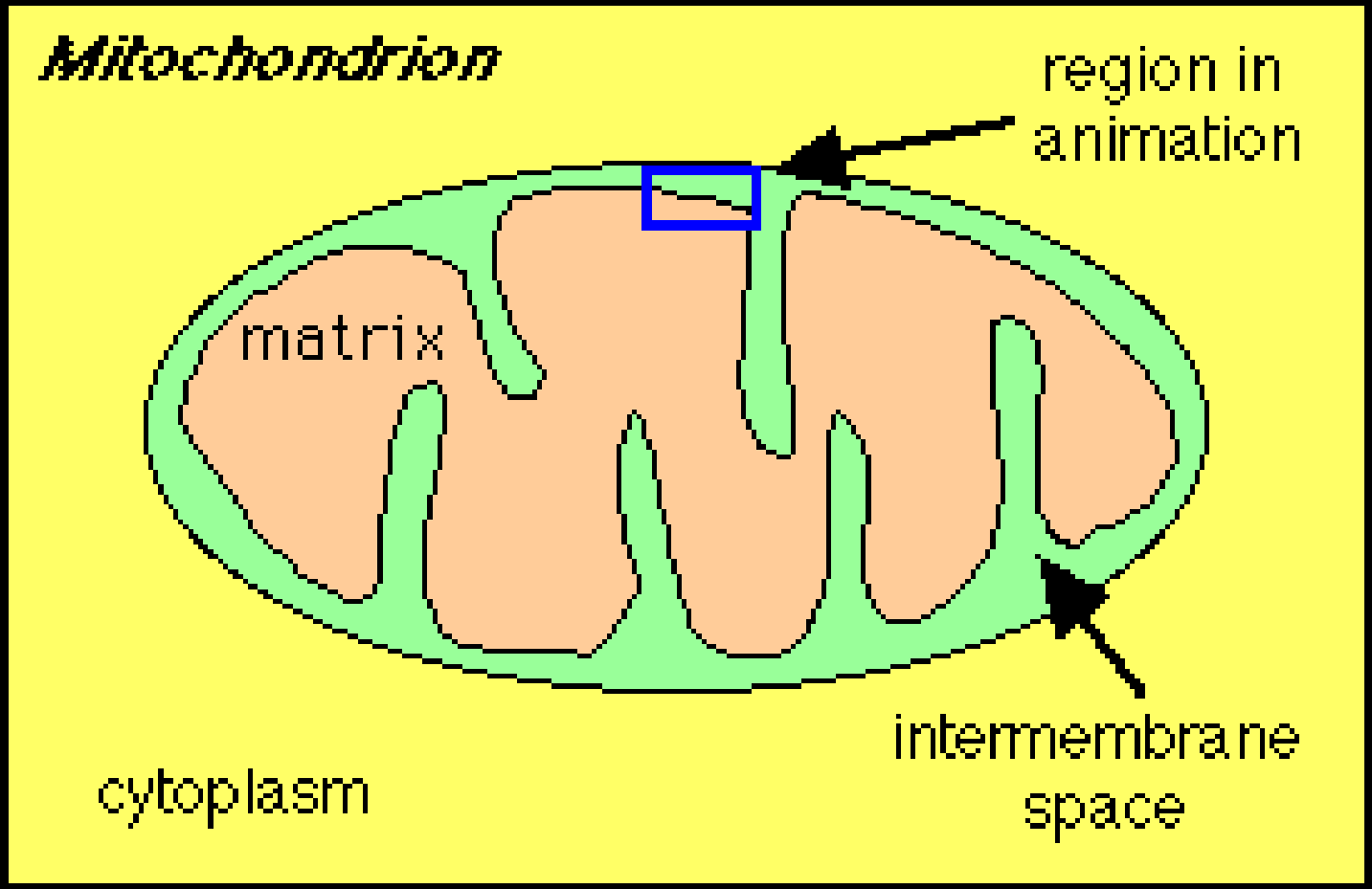
***Mitochondria are DYNAMIC***
***Splitting and joining, relocating to the part of the cell where they are needed***



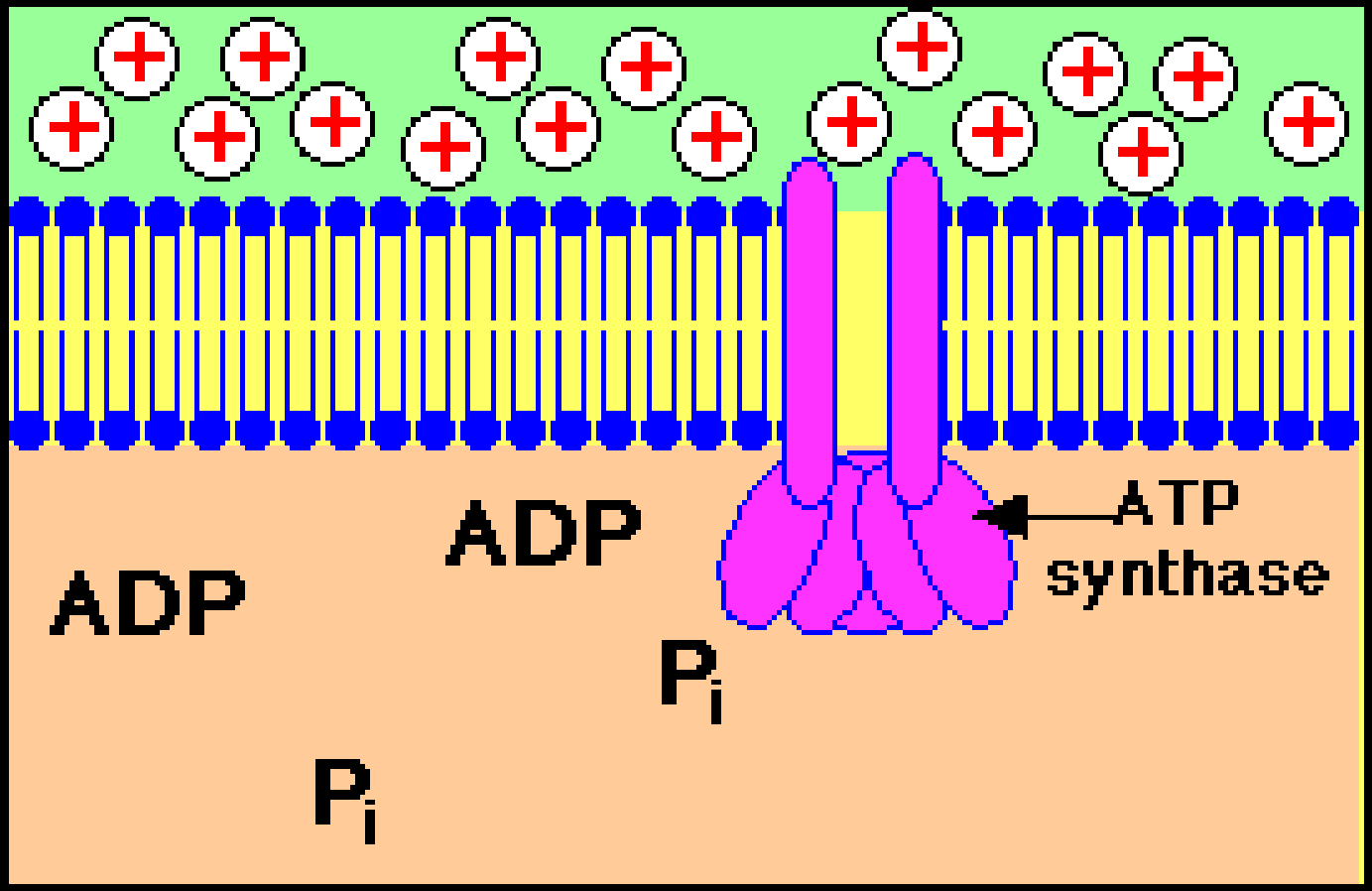
# Production line for energy



# *The energy production line charges up the outside of the mitochondria*



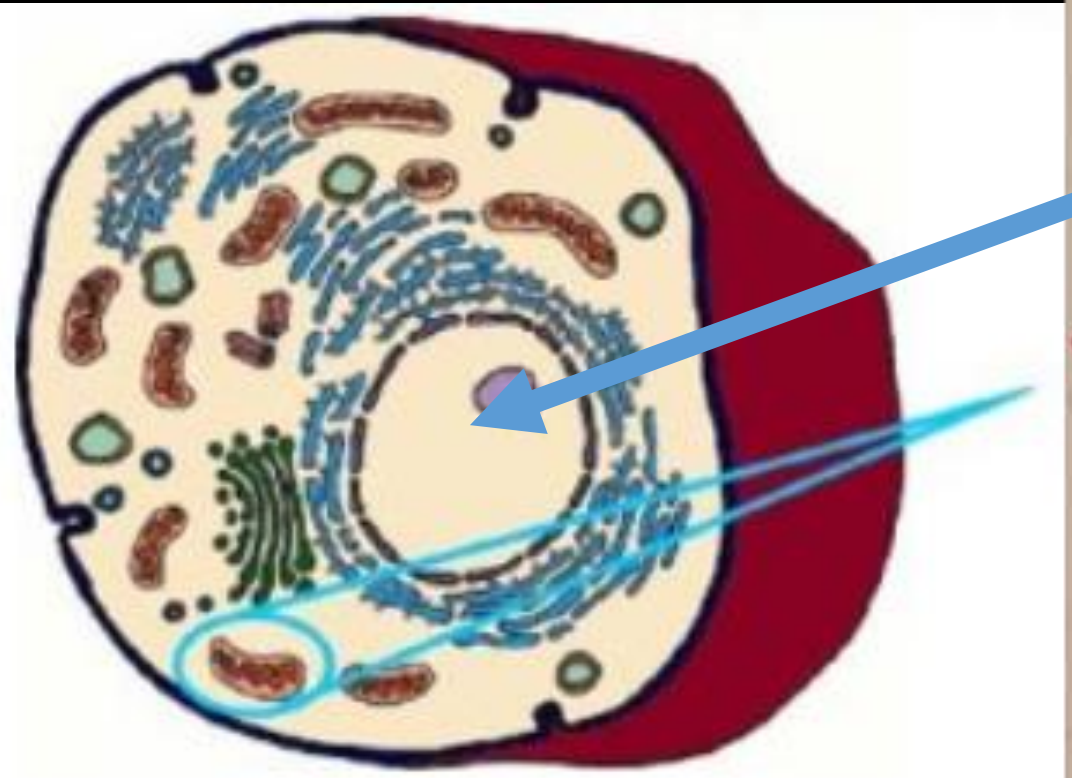
# *The charge powers the mitochondrial rotor, generating ATP, the energy currency*



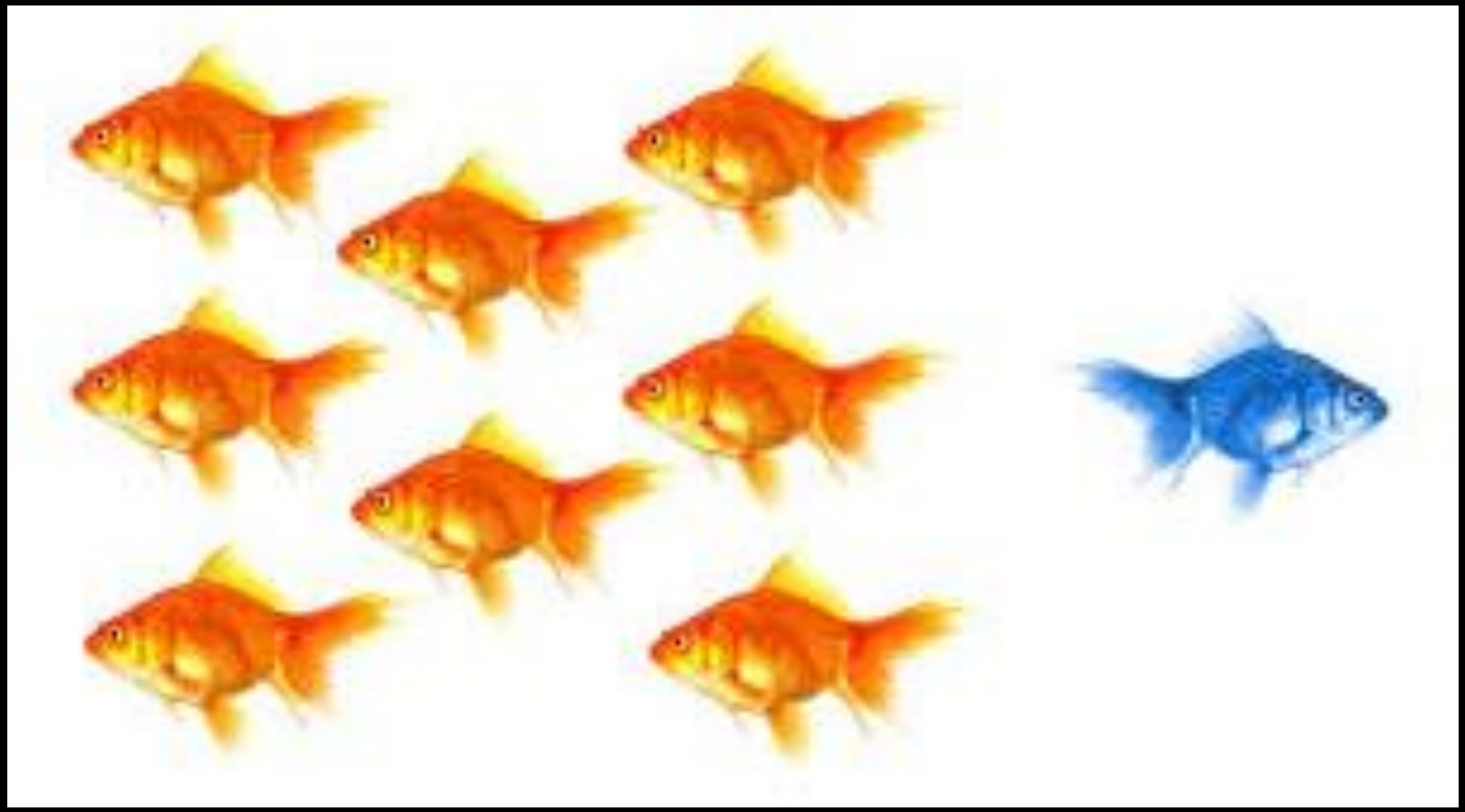
# *Mitochondria are complex*

*DNA the blue print for how to make this machinery*

*2 sets of instructions*
*Nuclear DNA*
*Mitochondrial DNA*



# *Is it mtDNA or nuclear DNA?*

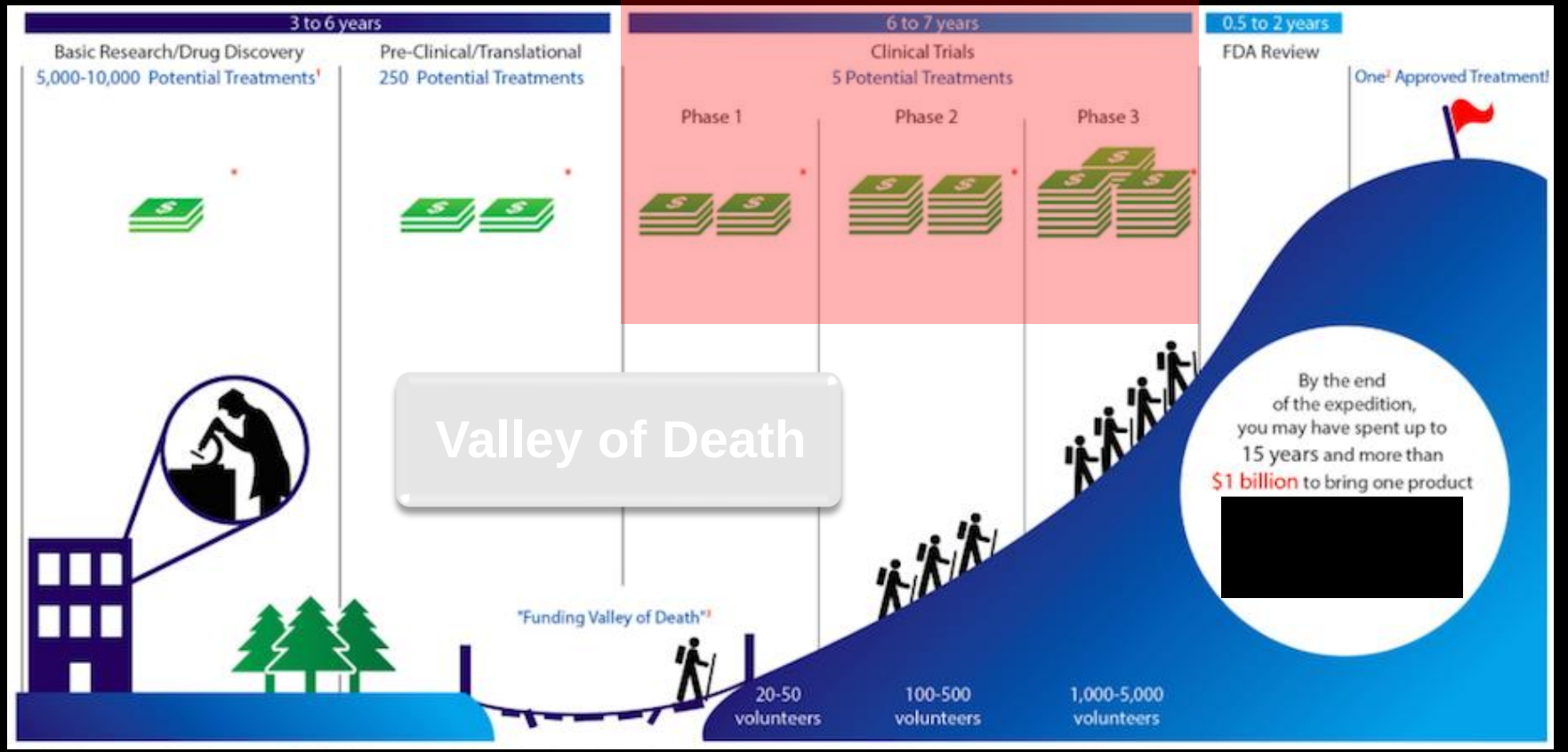


# *Mitochondrial Research*

## Mitochondrial diseases are rare

- MRC, NIHR and Wellcome trust give money to
  - Common diseases- obesity
  - Glitzy research- 3 parent babies
- Lily Foundation are making a big difference to the smaller groups!

# *Clinical Trials – Challenges*




**Basic Research** → **A Cure!!!**

# *Lily have funded us to seek a treatment for mtDNA depletion syndrome*

# *For further strides we need YOU!*