Treatment Discovery – From Bench To Bedside

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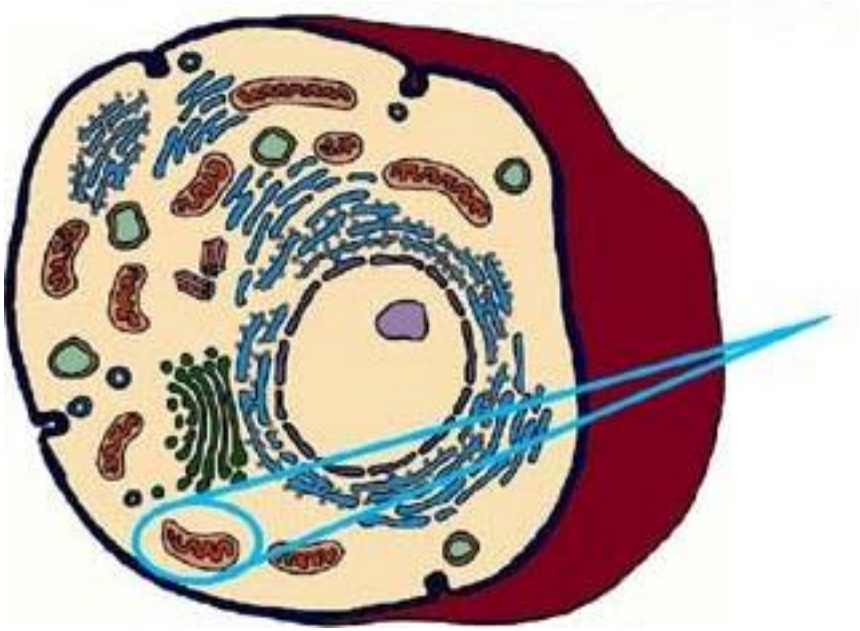
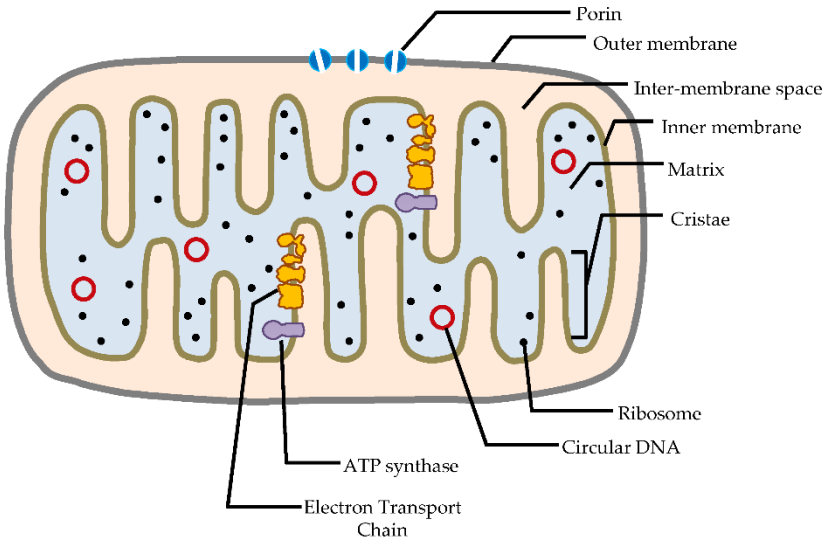
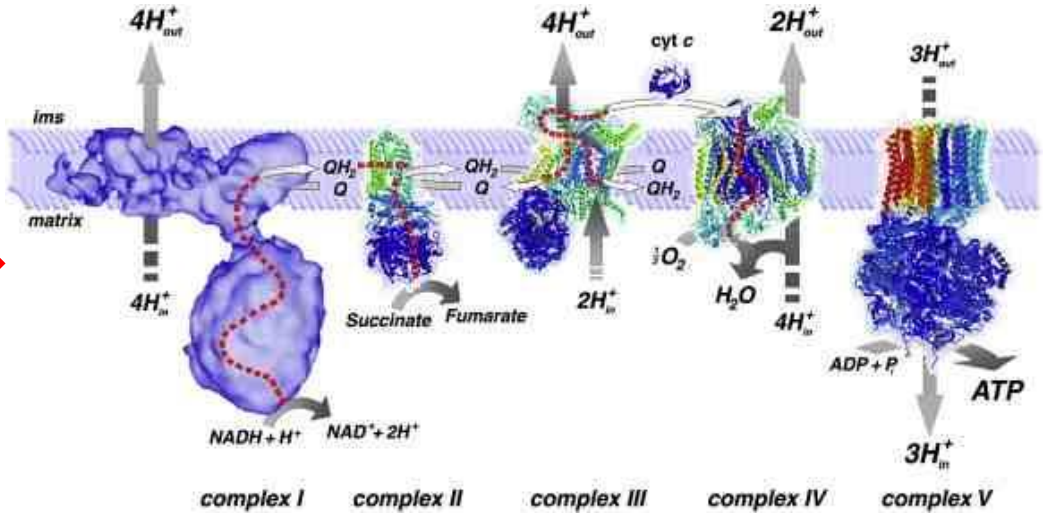
Lily Family Weekend




Porin
Outer membrane
Inter-membrane space
Inner membrane
Matrix
Cristae
Ribosome
Circular DNA
ATP synthase
Electron Transport Chain


ims
matrix
cyt c
Succinate
Fumarate
NADH + H+
NAD+ + 2H+
ADP + Pi
ATP
complex I
complex II
complex III
complex IV
complex V

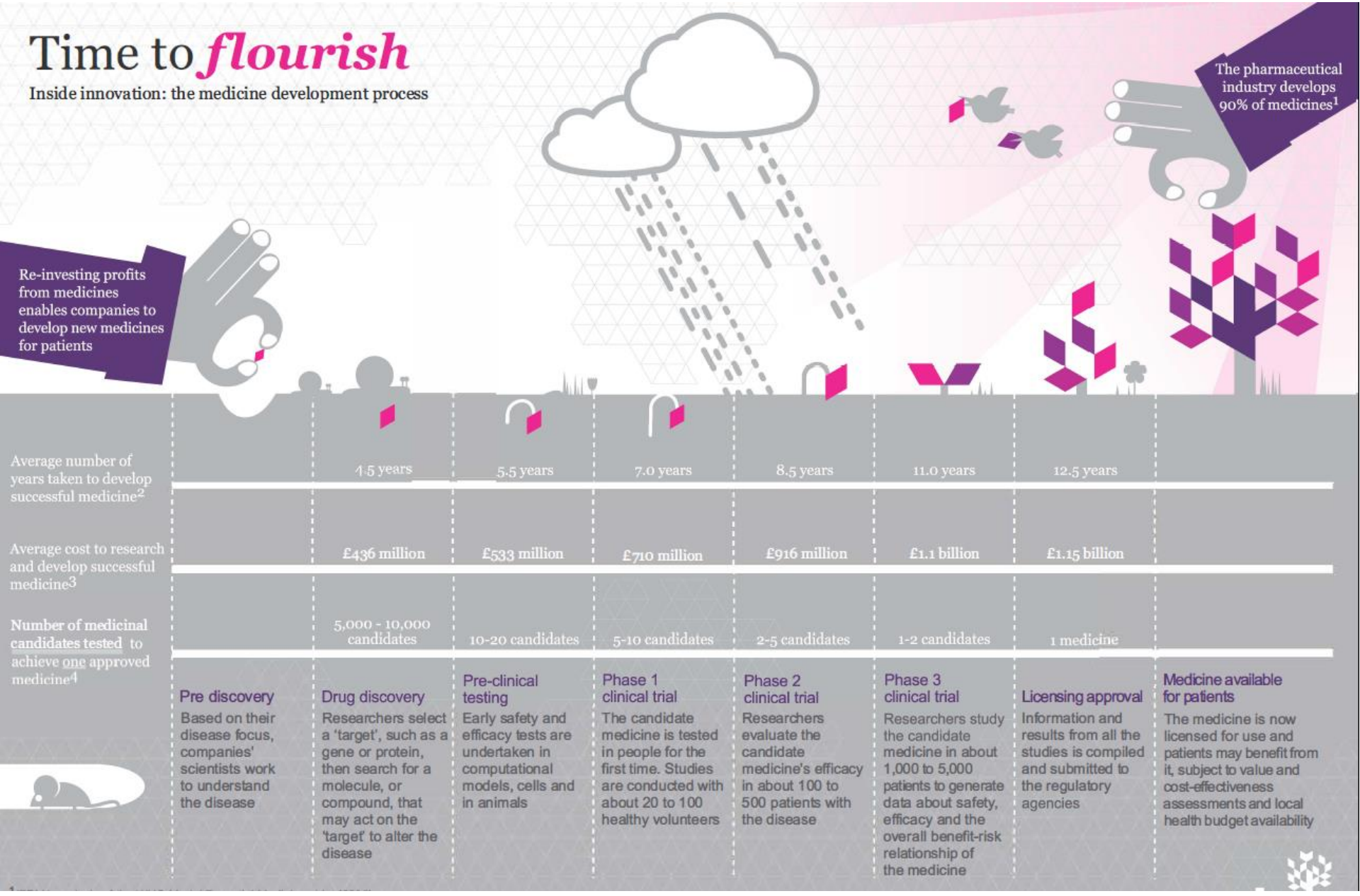
Treatment Approaches

Non-targeted approach

- Aims to improve generic mitochondrial functions
- Wider application
- Less expensive
- Biggest limitation: not leading to cure

Disease/mutation specific treatment

- Address the disease mechanism directly
- More efficacious
- More expensive
- “N = 1 approach”



Source: The Association of the British Pharmaceutical Industry (ABPI)

Pre clinical trials

Disease Understanding

- The genetic defect
- The function & pathway
- Creating cell lines, iPSC, animal models

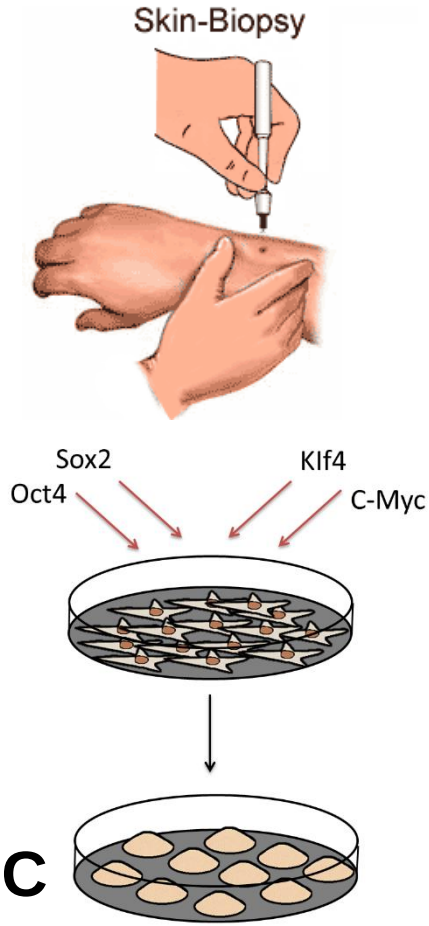
Target identification

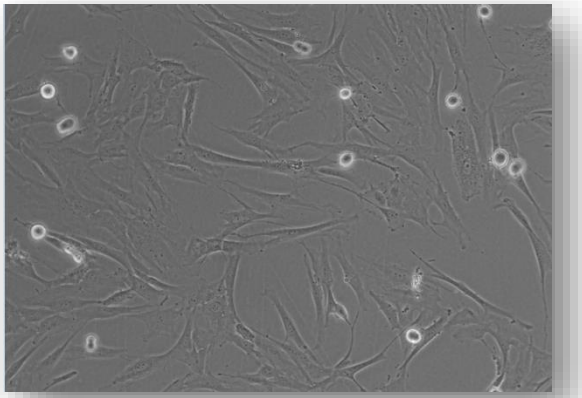
- Identifying potential drug targets
- Study the effect of a given compound in cells, tissues and animal models

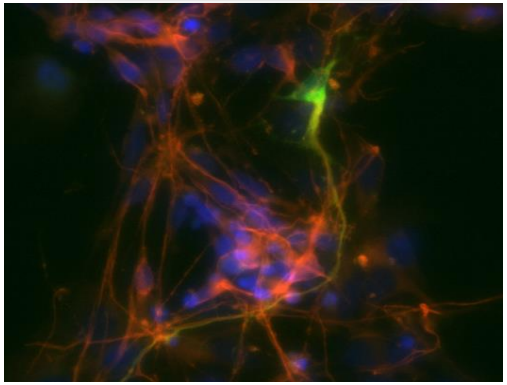
Drug discovery

- Finding the most promising compound (nature/synthetic)
- Formulation
- How to manufacture

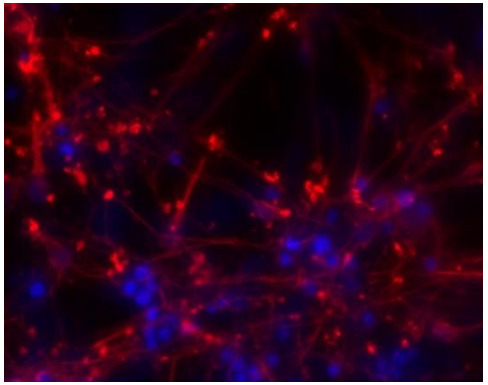
What is the skin biopsy for?







Normal dopaminergic neuron



Disease

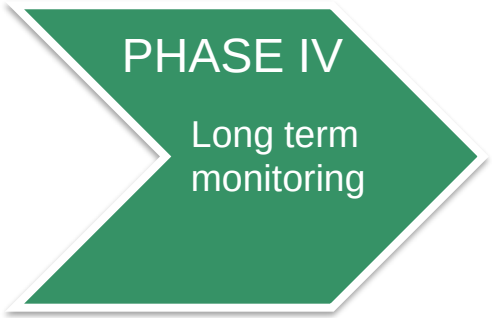
Steps of Clinical Trial

- Healthy volunteers
- Can the drug be tolerated
- Severe side effects?
- Low numbers, typically young males
- 64.5% drugs make it through

- Patients
- Does the drug actually work?
- What is the best way to administer?
- Are there patient specific side effects?
- Low numbers – up to 100 patients
- 32% drugs make it through

Steps of Clinical Trial

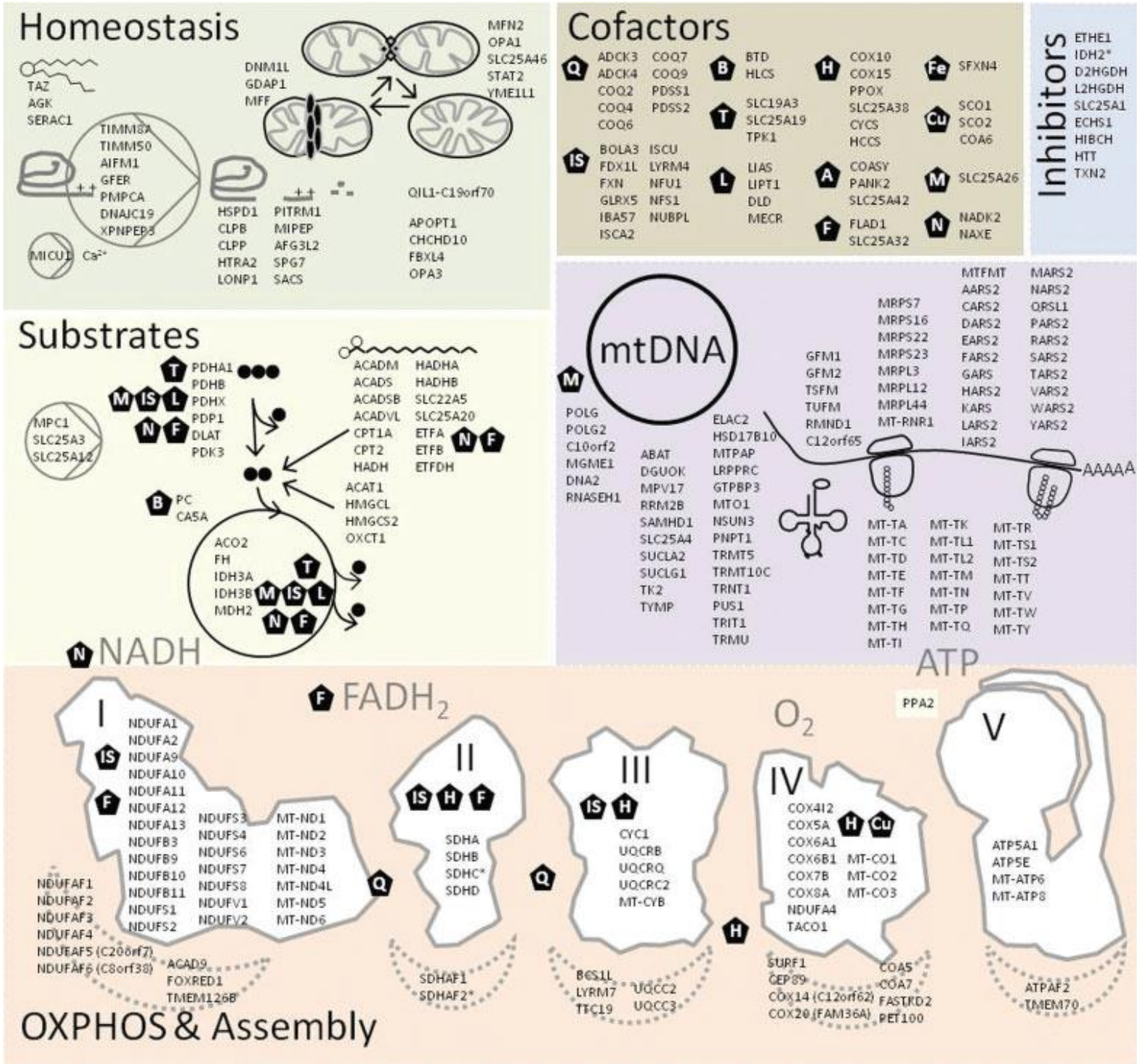
- Large numbers of patients
- Look for rare side effects
- Confirm efficacy of drug



- Drug on general sale
- Licensed for use by FDA
- 10% drugs in phase 1 get to this stage
- Continuous monitoring by drug company for rare side effects eg. Vioxx

Orphan Drug Status

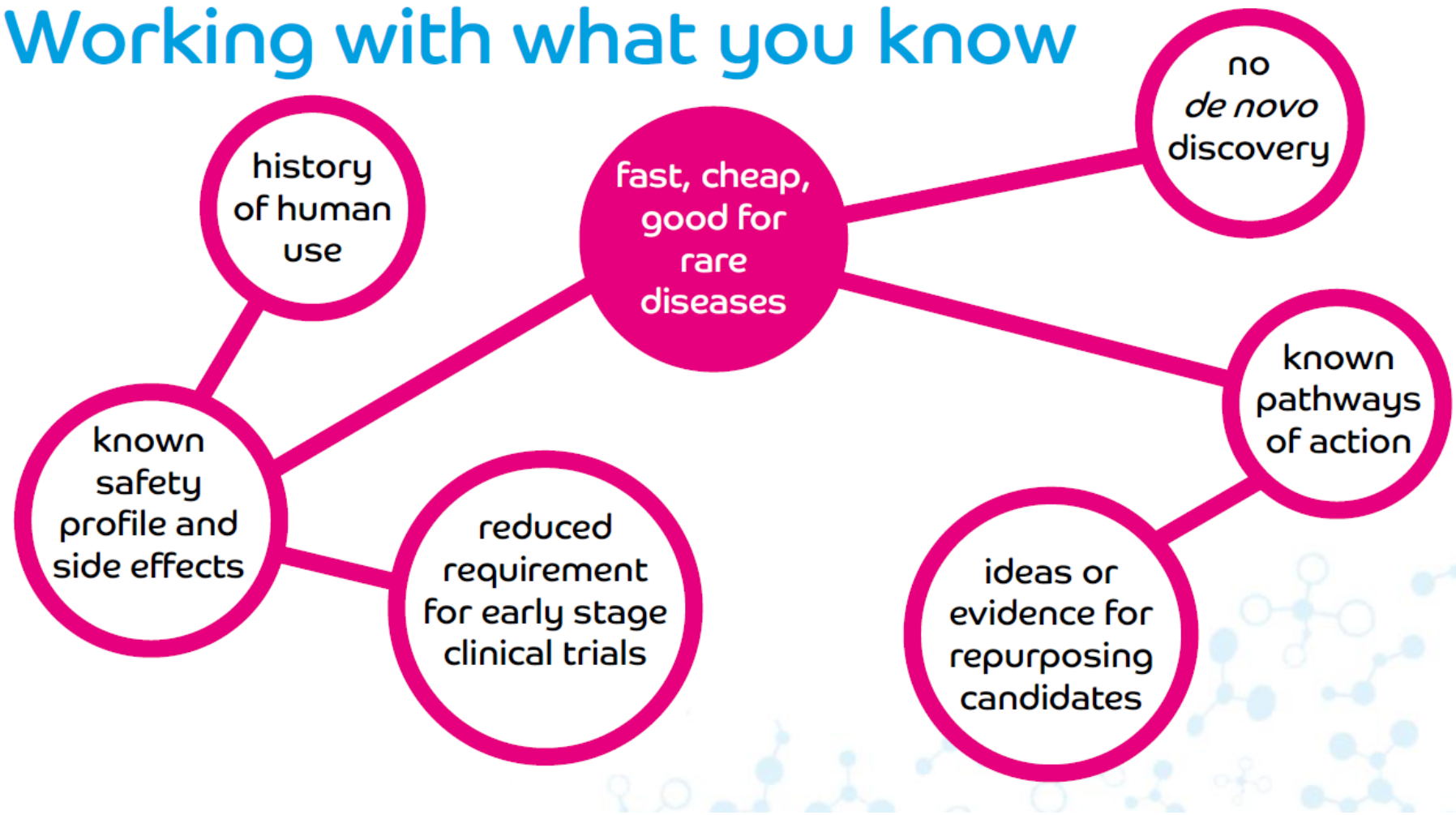
- Rare disease = 5 in 10,000
- European Medicines Agency (EMA) Incentives for drug companies to develop treatment for rare diseases:
  - Free of charge protocol assistance
  - Marketing exclusivity (10 yrs + 2 if paeds)
  - Fees reduction
  - Compassionate use
- Currently, idebendone is the only orphan drug approved for primary mitochondrial disease (LHON)


Homeostasis
TAZ
AGK
SERAC1
TIMM8A
TIMM50
AIFM1
GFER
PMPCA
DNAJC19
XPNPEP3
MICU1
Ca2+
DNM1L
GDAP1
MFF
MFN2
OPA1
SLC25A46
STAT2
YME1L1
HSPD1
CLPB
CLPP
HTRA2
LONP1
PITRM1
MIPEP
AFG3L2
SPG7
SACS
QIL1-C19orf70
APOPT1
CHCHD10
FBXL4
OPA3
Cofactors
Q
ADCK3
ADCK4
COQ2
COQ4
COQ6
COQ7
COQ9
PDSS1
PDSS2
B
BTD
HLCS
T
SLC19A3
SLC25A19
TPK1
IS
BOLA3
FDX1L
FXN
GLRX5
IBA57
ISCA2
ISCU
LYRM4
NFU1
NFS1
NUBPL
L
LIAS
LIPT1
DLD
MECR
H
COX10
COX15
PPOX
SLC25A38
CYCS
HCCS
A
COASY
PANK2
SLC25A42
F
FLAD1
SLC25A32
Fe
SFXN4
Cu
SCO1
SCO2
COA6
M
SLC25A26
N
NADK2
NAXE
Inhibitors
ETHE1
IDH2*
D2HGDH
L2HGDH
SLC25A1
ECHS1
HIBCH
HTT
TXN2
Substrates
T
PDHA1
PDHB
M IS L
PDHX
PDP1
N F
DLAT
PDK3
MPC1
SLC25A3
SLC25A12
ACADM
ACADS
ACADSB
ACADVL
CPT1A
CPT2
HADH
HADHA
HADHB
SLC22A5
SLC25A20
ETFA
ETFB
N F
ETFDH
ACAT1
HMGCL
HMGCS2
OXCT1
B
PC
CA5A
ACO2
FH
IDH3A
IDH3B
MDH2
T
M IS L
N F
N NADH
mtDNA
M
POLG
POLG2
C10orf2
MGME1
DNA2
RNASEH1
ABAT
DGUOK
MPV17
RRM2B
SAMHD1
SLC25A4
SUCLA2
SUCLG1
TK2
TYMP
ELAC2
HSD17B10
MTPAP
LRPPRC
GTPBP3
MTO1
NSUN3
PNPT1
TRMT5
TRMT10C
TRNT1
PUS1
TRIT1
TRMU
GFM1
GFM2
TSFM
TUFM
RMND1
C12orf65
MRPS7
MRPS16
MRPS22
MRPS23
MRPL3
MRPL12
MRPL44
MT-RNR1
MTFMT
AARS2
CARS2
DARS2
EARS2
FARS2
GARS
HARS2
KARS
LARS2
IARS2
MARS2
NARS2
QRSL1
PARS2
RARS2
SARS2
TARS2
VARS2
WARS2
YARS2
AAAAA
MT-TA
MT-TC
MT-TD
MT-TE
MT-TF
MT-TG
MT-TH
MT-TI
MT-TK
MT-TL1
MT-TL2
MT-TM
MT-TN
MT-TP
MT-TQ
MT-TR
MT-TS1
MT-TS2
MT-TT
MT-TV
MT-TW
MT-TY
ATP
F FADH2
O2
PPA2
I
IS
F
NDUFA1
NDUFA2
NDUFA9
NDUFA10
NDUFA11
NDUFA12
NDUFA13
NDUFB3
NDUFB9
NDUFB10
NDUFB11
NDUFS1
NDUFS2
NDUFS3
NDUFS4
NDUFS6
NDUFS7
NDUFS8
NDUFV1
NDUFV2
MT-ND1
MT-ND2
MT-ND3
MT-ND4
MT-ND4L
MT-ND5
MT-ND6
Q
NDUFAF1
NDUFAF2
NDUFAF3
NDUFAF4
NDUFAF5 (C20orf7)
NDUFAF6 (C8orf38)
ACAD9
FOXRED1
TMEM126B
II
IS H F
SDHA
SDHB
SDHC*
SDHD
Q
SDHAF1
SDHAF2*
III
IS H
CYC1
UQCRB
UQCRQ
UQCRC2
MT-CYB
Q
BCS1L
LYRM7
TTC19
UQCC2
UQCC3
H
IV
COX4I2
COX5A
COX6A1
COX6B1
COX7B
COX8A
NDUFA4
TACO1
H Cu
MT-CO1
MT-CO2
MT-CO3
SURF1
CEP89
COX14 (C12orf62)
COX20 (FAM36A)
COA5
COA7
FASTKD2
PET100
V
ATP5A1
ATP5E
MT-ATP6
MT-ATP8
ATPAF2
TMEM70
OXPHOS & Assembly

Is there a quicker and cheaper way of finding treatment for rare diseases?

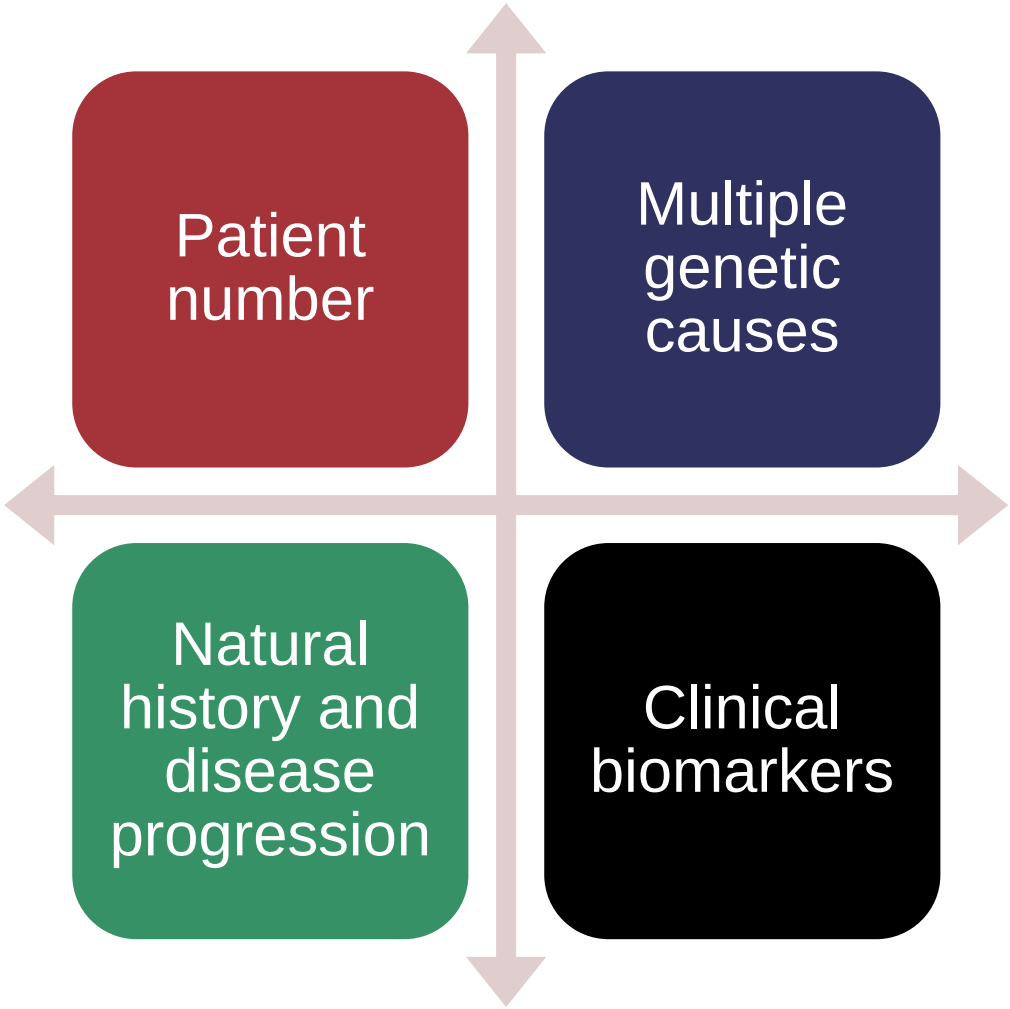
Drug Repurposing = Drug Recycling

Drug Repurposing

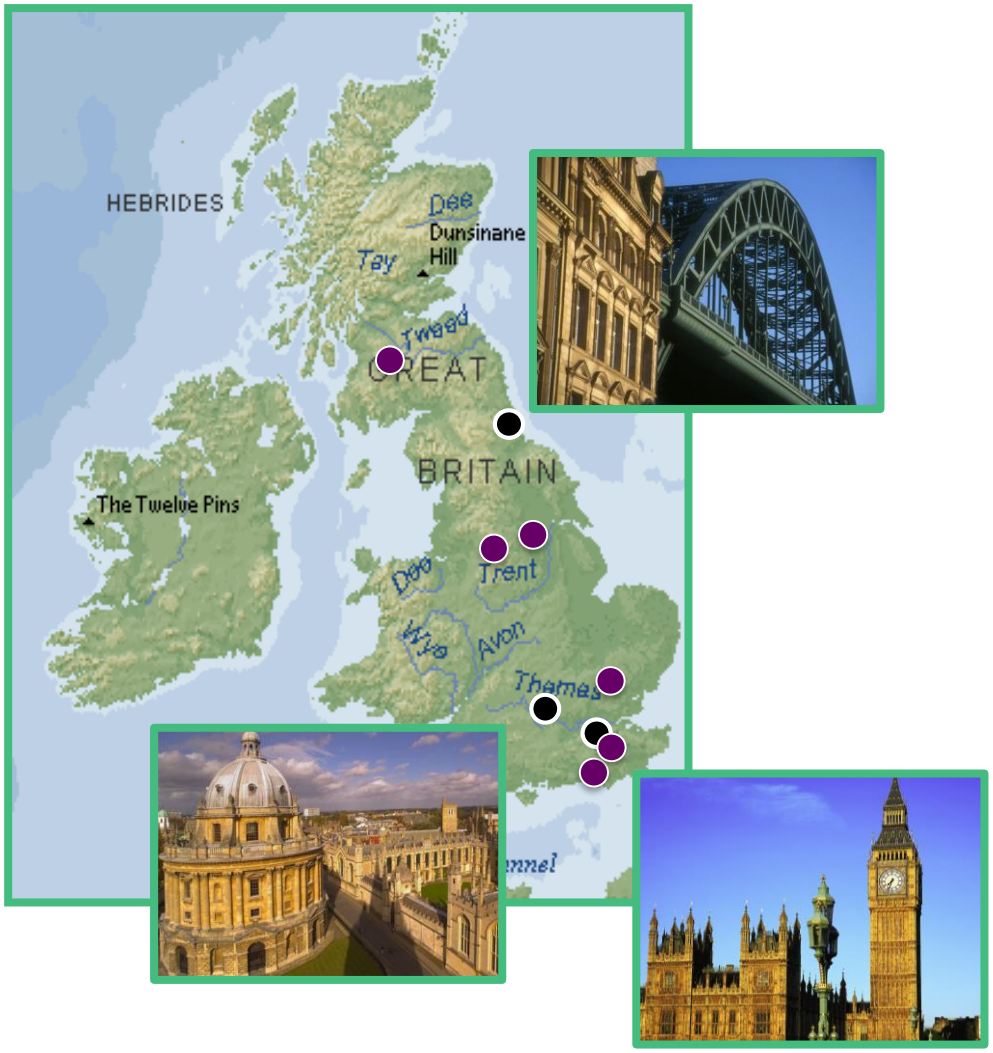


Source: Findacure

Challenges for drug studies in mitochondrial disease



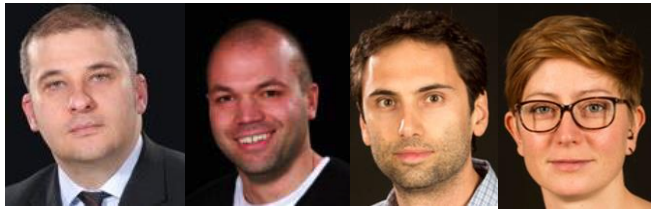
Mitochondrial Disease Patient Cohort (UK)



Newcastle University

The Newcastle upon Tyne Hospitals NHS
NHS Foundation Trust

UCL



Oxford Radcliffe Hospitals NHS
NHS Trust

Thank you

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wellcome centre mitochondrial research