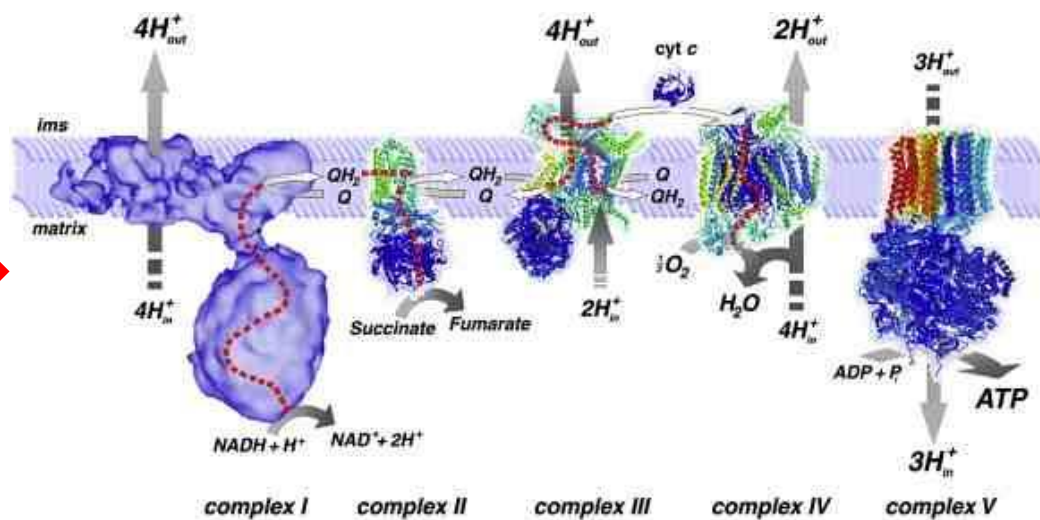
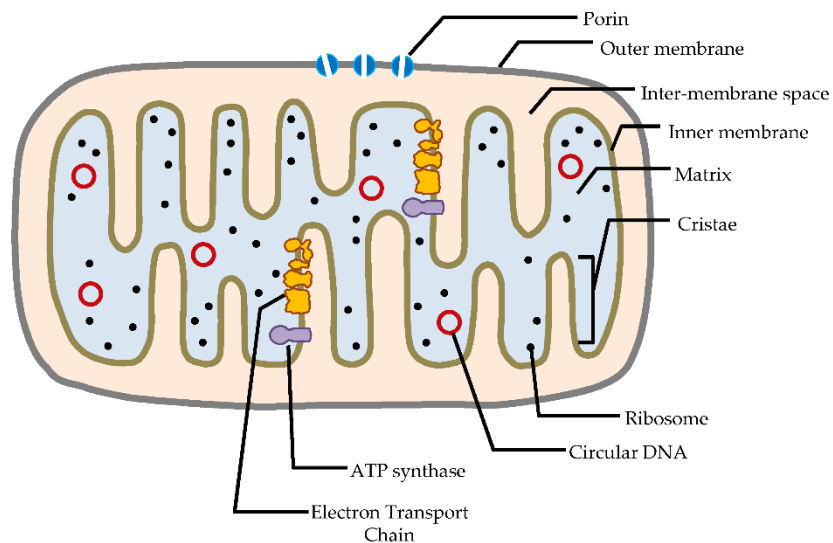
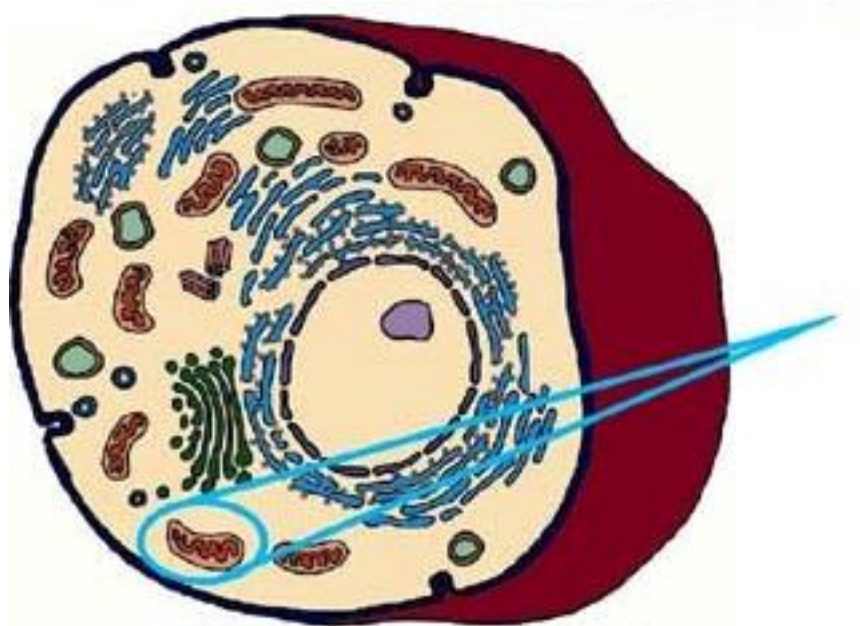


Treatment Discovery – From Bench To Bedside

Yi Shiau Ng

NIHR Clinical Lecturer in Neurology

Lily Family Weekend



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”

Time to *flourish*

Inside innovation: the medicine development process

The pharmaceutical industry develops 90% of medicines¹

Re-investing profits from medicines enables companies to develop new medicines for patients

	4.5 years	5.5 years	7.0 years	8.5 years	11.0 years	12.5 years	
Average number of years taken to develop successful medicine ²							
Average cost to research and develop successful medicine ³	£436 million	£533 million	£710 million	£916 million	£1.1 billion	£1.15 billion	
Number of medicinal candidates tested to achieve one approved medicine ⁴	5,000 - 10,000 candidates	10-20 candidates	5-10 candidates	2-5 candidates	1-2 candidates	1 medicine	
Pre discovery Based on their disease focus, companies' scientists work to understand the disease	Drug discovery Researchers select a 'target', such as a gene or protein, then search for a molecule, or compound, that may act on the 'target' to alter the disease	Pre-clinical testing Early safety and efficacy tests are undertaken in computational models, cells and in animals	Phase 1 clinical trial The candidate medicine is tested in people for the first time. Studies are conducted with about 20 to 100 healthy volunteers	Phase 2 clinical trial Researchers evaluate the candidate medicine's efficacy in about 100 to 500 patients with the disease	Phase 3 clinical trial Researchers study the candidate medicine in about 1,000 to 5,000 patients to generate data about safety, efficacy and the overall benefit-risk relationship of the medicine	Licensing approval Information and results from all the studies is compiled and submitted to the regulatory agencies	Medicine available for patients The medicine is now licensed for use and patients may benefit from it, subject to value and cost-effectiveness assessments and local health budget availability

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



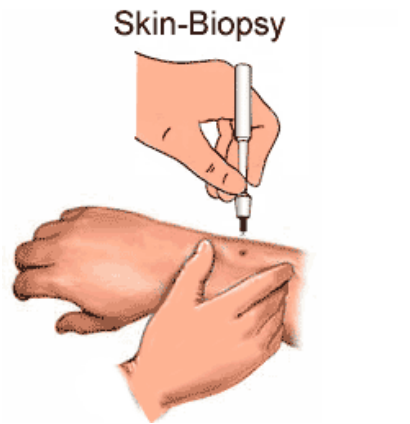
Drug discovery

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

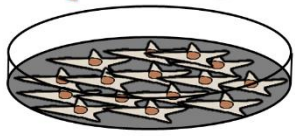




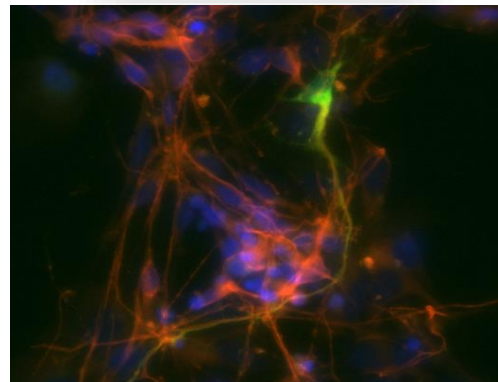
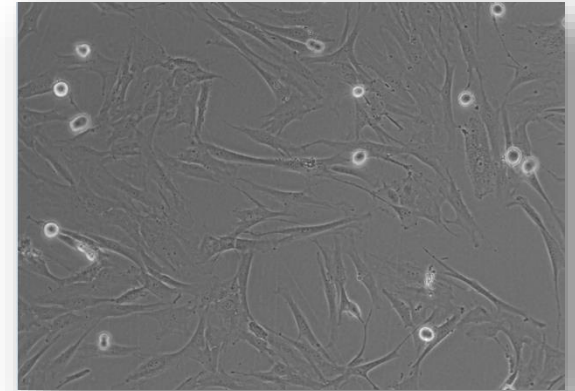
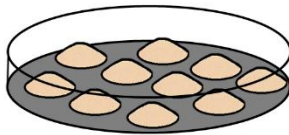
What is the skin biopsy for?



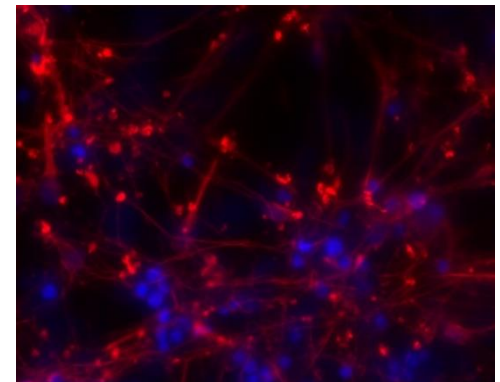
Sox2
Oct4
Klf4
C-Myc



iPSC



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

PHASE III

Confirmation
& side effects

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

PHASE IV

Long term
monitoring

- 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 paed)
 - Fees reduction
 - Compassionate use
- Currently, idebendone is the only orphan drug approved for primary mitochondrial disease (LHON)

Diagram illustrating the mitochondrial permeability transition pore (PTP) and its regulation. The diagram shows a cross-section of a mitochondrion with the PTP in the inner membrane. Various proteins are shown interacting with the PTP, including TAZ, AGK, SERAC1, TIMM8A, TIMM50, AIFM1, GFER, PMPCA, DNAJC19, XPNPEP3, MICU1, Ca²⁺, DNMI1, GDAP1, MFF, OPA1, SLC25A46, STAT2, YME1L1, HSPD1, CLPB, CLPP, HTRA2, LONP1, PITRM1, MIPEP, AFG3L2, SPG7, SACS, QIL1-C19orf70, APOPT1, CHCHD10, FBXL4, and OPA3. The diagram illustrates the PTP as a central hub for these regulatory proteins, which can either open or close the pore in response to various stimuli.

Q	ADCK3 ADCK4 COQ2 COQ4 COQ6	B	BTD HLCS	H	COX10 COX15 PPOX SLC25A38 CYCS HCCS	Fe	SFXN4
		T	SLC19A3 SLC25A19 TPK1			Cu	SCO1 SCO2 COA6
IS	BOLA3 FDX1L FXN GLRX5 IBA57 ISCA2	L	LIAS UPT1 DLD MECR	A	COASY PANK2 SLC25A42	M	SLC25A26
	COQ7 COQ9 PDSS1 PDSS2 ISCU LYRM4 NFU1 NF51 NUBPL			F	FLAD1 SLC25A32	N	NADK2 NAXE

ETHE1
IDH2*
D2HGDH
L2HGDH
SLC25A1
ECHS1
HIBCH
HTT
TXN2

The diagram illustrates the metabolic pathways of the TCA cycle and its associated enzymes and cofactors. The cycle is represented by a central circle containing the following components:

- Enzymes:** ACO2, FH, IDH3A, IDH3B, MDH2.
- Cofactors:** NADH (represented by a blue hexagon with 'N'), NAD⁺ (represented by a blue hexagon with 'N' and a '+' sign), and FAD (represented by a blue hexagon with 'F').

Surrounding the cycle are various other components:

- Top Left:** A circle containing MPC1, SLC25A3, and SLC25A12.
- Top Center:** A cluster of enzymes: PDHA1, PDHB, PDHX, PDP1, DLAT, and PDK3. Above them are cofactors T (blue hexagon), M (blue hexagon), I (blue hexagon), S (blue hexagon), L (blue hexagon), and F (blue hexagon).
- Top Right:** A list of enzymes: ACADM, ACADS, ACAD5B, ACADVL, CPT1A, CPT2, HADH, ACAT1, HMGCL, HMGCS2, and OXCT1.
- Right Side:** A list of cofactors: HADHA, HADHB, SLC22A5, SLC25A20, ETFA, ETFB, and ETFDH. Above them are cofactors N (blue hexagon) and F (blue hexagon).
- Bottom Left:** A blue hexagon labeled B, with PC and CASA written next to it.

Arrows indicate the flow of metabolites and cofactors between these components and the central TCA cycle.

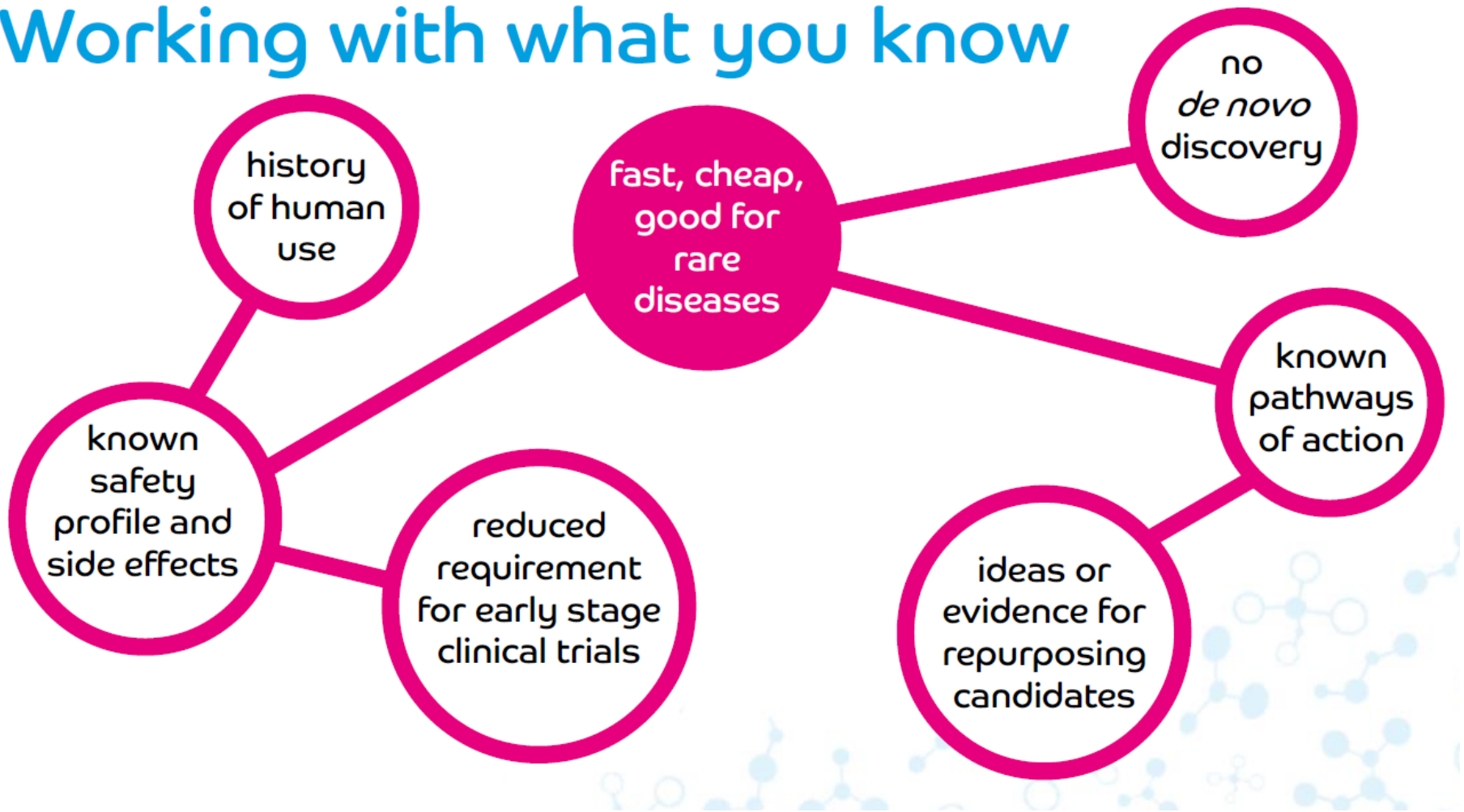
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Is there a quicker and cheaper way of finding treatment for rare diseases?

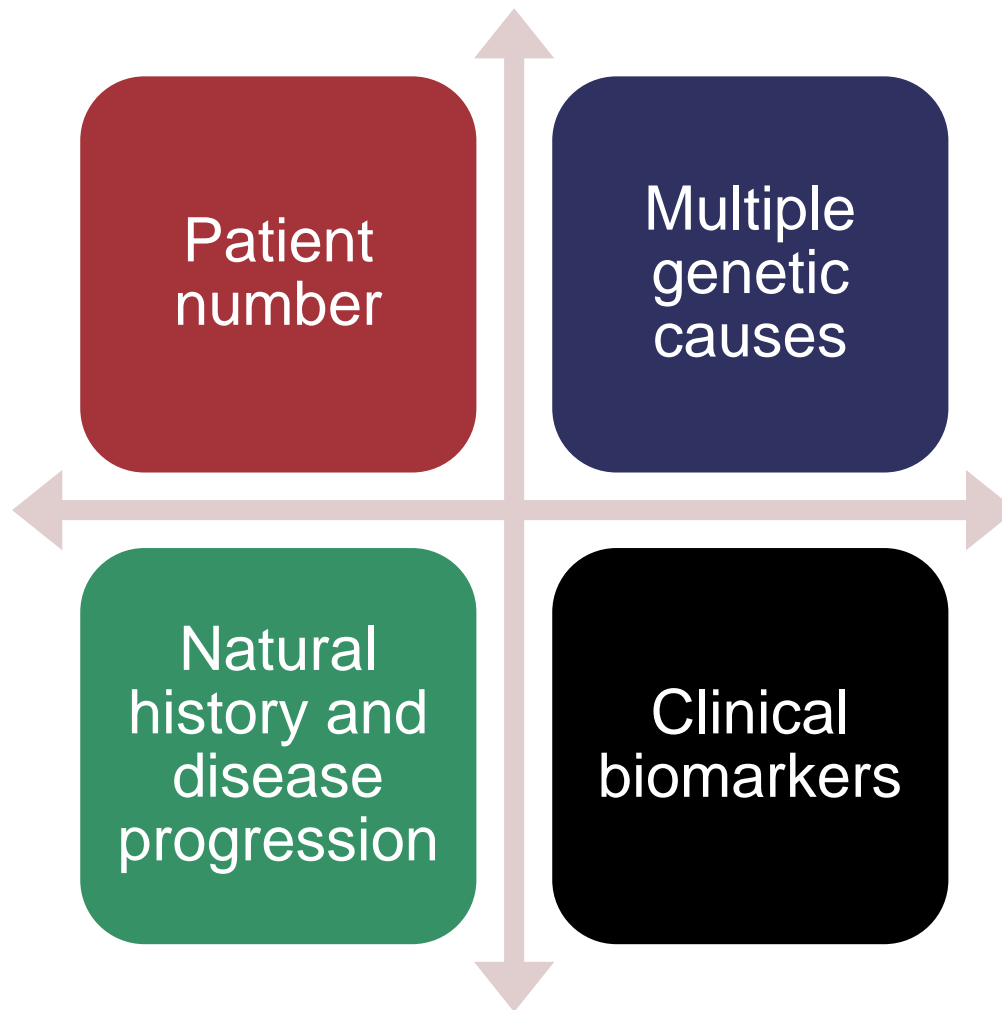
Drug Repurposing = Drug Recycling

Drug Repurposing

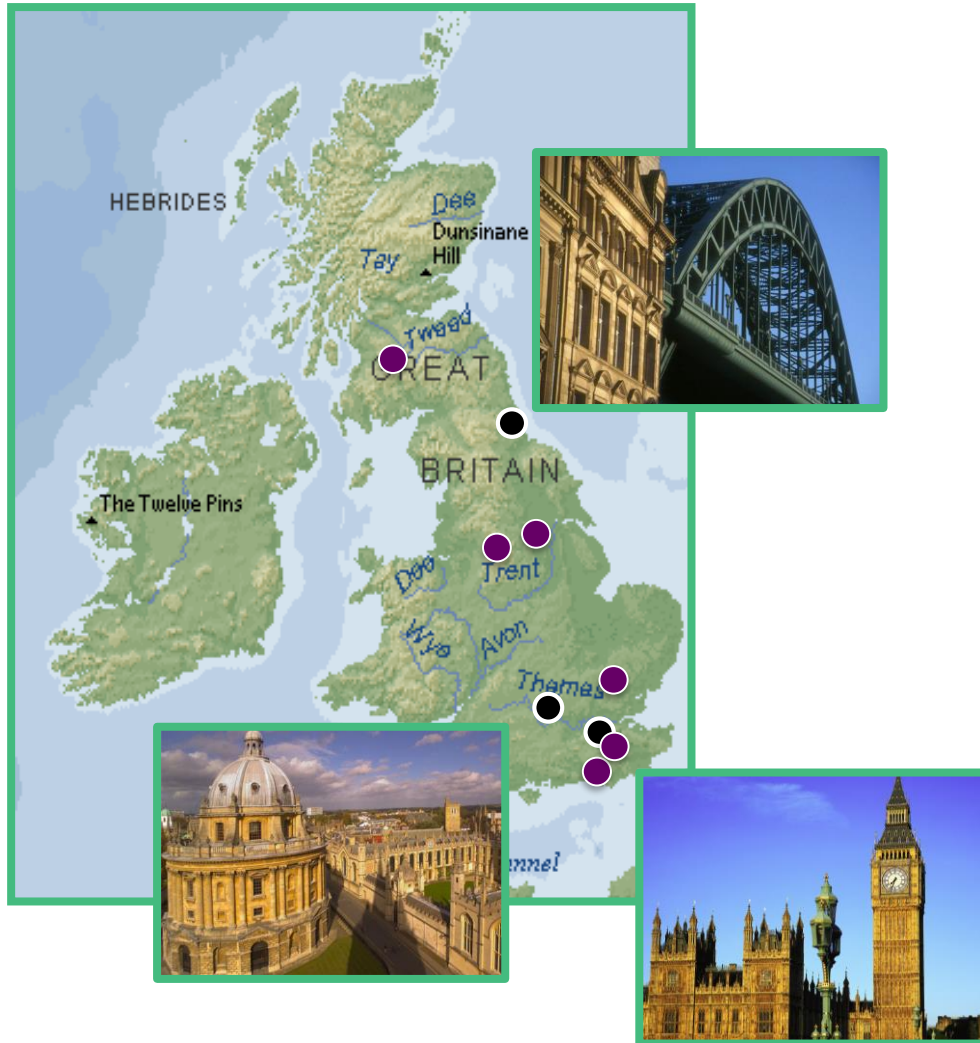
Working with what you know



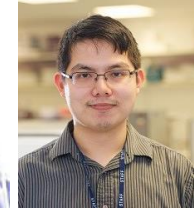
Challenges for drug studies in mitochondrial disease



Mitochondrial Disease Patient Cohort (UK)



The Newcastle upon Tyne Hospitals **NHS**
NHS Foundation Trust



Oxford Radcliffe Hospitals **NHS**
NHS Trust



Thank you

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