Treatment Discovery – From Bench To Bedside

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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

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<th>Pre discovery</th>
<th>Drug discovery</th>
<th>Pre-clinical testing</th>
<th>Phase 1 clinical trial</th>
<th>Phase 2 clinical trial</th>
<th>Phase 3 clinical trial</th>
<th>Licensing approval</th>
<th>Medicine available for patients</th>
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<tr>
<td>Based on their disease focus, companies' scientists work to understand the disease.</td>
<td>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.</td>
<td>Early safety and efficacy tests are undertaken in computational models, cells and in animals.</td>
<td>The candidate medicine is tested in people for the first time. Studies are conducted with about 20 to 100 healthy volunteers.</td>
<td>Researchers evaluate the candidate medicine's efficacy in about 100 to 500 patients with the disease.</td>
<td>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.</td>
<td>Information and results from all the studies is compiled and submitted to the regulatory agencies.</td>
<td>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.</td>
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### Average number of years taken to develop successful medicine

- 4.5 years
- 5.5 years
- 7.0 years
- 8.5 years
- 11.0 years
- 12.5 years

### Average cost to research and develop successful medicine

- £436 million
- £533 million
- £710 million
- £916 million
- £1.1 billion
- £1.15 billion

### Number of medicinal candidates tested to achieve one approved medicine

- 5,000 - 10,000 candidates
- 10-20 candidates
- 5-10 candidates
- 2-5 candidates
- 1-2 candidates
- 1 medicine

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**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?
Steps of Clinical Trial

**PHASE I**

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

**PHASE II**

- Efficacy testing
- 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
- 10% drugs in phase 1 get to this stage
- Continuous monitoring by drug company for rare side effects, e.g., Vioxx

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, e.g., 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)
Is there a quicker and cheaper way of finding treatment for rare diseases?

Drug Repurposing = Drug Recycling
Drug Repurposing

Working with what you know

- Fast, cheap, good for rare diseases
- History of human use
- Known safety profile and side effects
- Reduced requirement for early stage clinical trials
- Known pathways of action
- Ideas or evidence for repurposing candidates
- No de novo discovery

Source: Findacure
Challenges for drug studies in mitochondrial disease

- Patient number
- Multiple genetic causes
- Natural history and disease progression
- Clinical biomarkers
Mitochondrial Disease Patient Cohort (UK)
Thank you

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