Introduction to drug repurposing for rare diseases

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Head of Research, Findacure

#DrugRepo  #RareDiseaseDay  @findacure_fdn
A rare disease is defined by the EU as affecting fewer than 1 in 2,000 people.

In the UK, approximately 3.5 million people live with rare diseases, which can be chronic, life-threatening, and isolating.

75% of rare diseases affect children.

30% of rare disease patients will die before their 5th birthday.

Of the 7,000 recognised rare diseases, only 400 have licensed treatments.

The average rare disease patient waits 4 years before they receive their final diagnosis, during which time they consult with 5 doctors and receive 3 misdiagnoses.

2 in 3 patients and carers struggle to hold paid employment.

Similarly, 3 in 5 patients felt their rare disease affected their education.

The day-to-day challenges of managing conditions are often made worse by the absence of an effective treatment.

A third of patients do not have access to the medicine that they need and another third only have access after waiting years.

BUT: An informed patient population with the power and determination to deliver change.
What does findacure do?

empower patient groups

promote collaboration to develop new treatments
What is drug repurposing?

At its most basic level, drug repurposing can be likened to recycling.

It is the act of taking a drug **intended to treat one patient population**, and demonstrating its efficacy in the **treatment of a completely different group of patients**.
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
- No de novo discovery
- Known pathways of action
- Ideas or evidence for repurposing candidates
Repurposing of generics should be appealing due to the wealth of data available on their use in humans.

However:

- Hard to secure IP on generics
- Mode of use patents are hard to defend
  - Off-label prescription of alternative generics is hard to detect, and to prevent

Subsequently, it is more difficult for pharmaceutical companies to profit from their development of the drug.
CDKL5

- A rare x-linked condition.
- Results in early onset, difficult to control, seizures, and severe neuro-developmental impairment.
- Affects about 600 people worldwide.
- No current approved treatment.
Repurposing ideas - ‘Omics

‘Omics – understanding all of genes or proteins in an individual – is at the forefront of science, and can be used to find repurposing opportunities.

Expression levels of different genes in a disease affected cell.
Repurposing ideas - ‘Omics

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- Overexpressed
- Normal
- Underexpressed

Disease signature

Drug signature

Therapeutic result
CDKL5

- Data evaluation and curation: 1 month
- Develop treatment profile: 3.5 months
- Identify candidate compounds: 5 months
- In vitro validation

Identified appropriate existing datasets, treatment requirements, and developed disease profiles.

Identified a generic antidepressant that could benefit patients.

Showed that the drug counter-acted gene silencing on neurotransmitter receptors.
CureAccelerator™ aims to drive more treatments to more patients more quickly. It is an online platform to connect research funders with the researchers who have the best repurposing ideas.

“We knew that funders had trouble finding strong, vetted repurposing research, and researchers had no platform or funding source particularly interested in repurposing research. It seemed natural for us to create that platform and linkage.”

- Bruce Bloom, President and CSO, Cures Within Reach

Visit cureaccelerator.org to sign up and get involved.
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What is social finance?

An approach to managing money which delivers a benefit to society as well as economic return.

Socially financed projects are often completed by a third sector organisation. They will aim to provide an intervention to a social problem, and receive government funding based on the success of the intervention.
Rare Disease Drug Repurposing SIB

Social problem

Large number of rare disease patients with no treatment, and little hope of treatment. High burden of care.

Intervention

Find generic drugs with the potential to treat rare disease, and run clinical trials.

Success measure

The number of rare disease patients receiving repurposed treatments.

Where is the money?

A reduced burden of care.
Repurposing at findacure

1. £ Investment
2. £ Return on Investment
3. Successful trials → new treatments and £ savings
4. £ % of savings
5. Investors

Phase II clinical trials

Bond

Social Impact

NHS
Phase II clinical trials

Successful trials → new treatments and £ savings

£ Investment

£ Return on Investment

5

4

£ % of savings

Social Impact Bond

£ Investment

£ Return on Investment

5

4

Investors

£

1

2

3

4

5

6

Repurposing at findacure

SIB generates returns from healthcare savings

findacure

Phase II clinical trials

NHS
Proving the concept

- congenital hyperinsulinism
- wolfram syndrome
- friedreich’s ataxia
Proving the concept

We needed to present evidence on four major areas to the NHS and investors:

1. There is a high patient need for treatments
2. There are a number of viable generic drug repurposing projects out there for rare diseases that lack funding
3. Show that untreated rare diseases have a high cost to the NHS now
4. Show that repurposed generic drugs could save the NHS money through improving patient health

Reports available online
www.findacure.org.uk/focus-groups-2016
Cost of Illness models

Based on a detailed treatment pathway for each disease.

Cost for all UK patients in a year.

Example: Wolfram syndrome
Cost of treating the 64 patients known to the specialist services in Birmingham.
<table>
<thead>
<tr>
<th><strong>Optic Atrophy and general visual impairment</strong></th>
<th><strong>Diabetes Mellitus</strong></th>
<th><strong>Hearing Loss/Deafness</strong></th>
<th><strong>Neurological Development Problems</strong></th>
<th><strong>Psychiatric Problems</strong></th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Testing</strong></td>
<td>Testing</td>
<td>Testing</td>
<td>Testing</td>
<td>Testing</td>
</tr>
<tr>
<td>• Hormone level tests</td>
<td>Coeliac serology: IgA tTG and EMA tests</td>
<td>Audiological examination and annual review</td>
<td><strong>Clinical psychology assessment</strong></td>
<td>Mental health care assessment</td>
</tr>
<tr>
<td><strong>Management</strong></td>
<td>Duodenal biopsy</td>
<td>Auditory brain response (ABR) testing</td>
<td><strong>Brain or spine MRI scan</strong></td>
<td><strong>Inpatient psychiatric treatment</strong></td>
</tr>
<tr>
<td>• Desmopressin acetate</td>
<td>Severe hypoglycaemia</td>
<td><strong>Nerve conduction studies</strong></td>
<td><strong>Sleep studies</strong></td>
<td><strong>Community mental health care</strong></td>
</tr>
<tr>
<td>• Testosterone injections</td>
<td>Coeliac disease</td>
<td><strong>Bronchoscoppy</strong></td>
<td><strong>Speech and language therapist</strong></td>
<td></td>
</tr>
<tr>
<td>• Estradiol tablets</td>
<td><strong>Multiple daily injections</strong></td>
<td><strong>Wheelchair</strong></td>
<td><strong>Wheelchair</strong></td>
<td></td>
</tr>
<tr>
<td>• Desogestrel tablets</td>
<td><strong>Continuous subcutaneous insulin infusions</strong></td>
<td><strong>Walking aids</strong></td>
<td><strong>Walking aids</strong></td>
<td></td>
</tr>
<tr>
<td><strong>Symptoms</strong></td>
<td><strong>Dietician</strong></td>
<td><strong>Physiotherapy</strong></td>
<td><strong>Physiotherapy</strong></td>
<td></td>
</tr>
<tr>
<td>• Ketoacidosis</td>
<td><strong>Secondary Complications due to Diabetes Mellitus</strong></td>
<td><strong>Occupational therapy sessions</strong></td>
<td><strong>Occupational therapy sessions</strong></td>
<td></td>
</tr>
<tr>
<td>• Severe hypoglycaemia</td>
<td>• Cardiac events</td>
<td><strong>Podiatry appointments</strong></td>
<td><strong>Podiatry appointments</strong></td>
<td></td>
</tr>
<tr>
<td>• Coeliac disease</td>
<td>• Visual complications</td>
<td><strong>Rehabilitation services</strong></td>
<td><strong>Rehabilitation services</strong></td>
<td></td>
</tr>
<tr>
<td><strong>Management</strong></td>
<td>• Renal complications</td>
<td><strong>Additional referrals may be made to a gastroenterologist and/or orthopaedic consultant</strong></td>
<td><strong>Tracheostomy</strong></td>
<td></td>
</tr>
<tr>
<td>• Multiple daily injections</td>
<td>• Ulcers</td>
<td><strong>Tracheostomy</strong></td>
<td><strong>Tracheostomy</strong></td>
<td></td>
</tr>
<tr>
<td>• Continuous subcutaneous insulin infusions</td>
<td>• Amputations</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>• Dietician</td>
<td></td>
<td></td>
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</tr>
</tbody>
</table>

**Renal/Neurogenic Bladder**

**Testing**

• Urodynamic studies
• Urine dipstick

**Symptoms and Management**

• Intermittent self-catheterisation
• Indwelling catheter
• Urinary tract infection treatment
Data from NHS reference costs, clinician interviews, national formulary, published literature, patient experience.

Cover the whole MDT costs, and support staff.

Cost of treating the 64 patients currently known to the adult and paediatric specialist services in Birmingham each year.

Cover the whole MDT costs, and support staff.

Over £990,000 per annum.
Budget Impact Modelling

Modelling the impact of a drug on a disease:

- MUST be conservative but fair
- Evidence based, and clinician driven
- Conservative in price as well as effect

**Example:** Nicotinamide for Friedreich’s ataxia

*Slowing disease progression.*

Estimated to save over £200,000 per annum.
## Overall results

<table>
<thead>
<tr>
<th>Condition</th>
<th>Cost of Illness (per annum)</th>
<th>Budget Impact (per 5 years)</th>
<th>SIB projected returns (after repaying costs)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Congenital hyperinsulinism</td>
<td>£4,561,827.58</td>
<td>£477,693.12</td>
<td>£840,800</td>
</tr>
<tr>
<td>Wolfram syndrome</td>
<td>£990,588.45</td>
<td>£672,772</td>
<td>£61,782</td>
</tr>
<tr>
<td>Friedreich’s ataxia</td>
<td>£7,560,471.81</td>
<td>£1,148,493.99</td>
<td>£300,000</td>
</tr>
</tbody>
</table>

A SIB can work as a tool to fund phase II proof of concept clinical trials into repurposed generic medicines for rare diseases.

Our current examples are not the most lucrative, but the principle is sound.
Next steps

We are talking to the NHS about using a SIB as a way to fund drug repurposing based on our work.

Looking for investors into a social impact bond project.

Possibly building a single disease pilot study, looking at centre of excellence partnerships.

An open call for new repurposing ideas.

If we succeed this will be a new way to quickly develop new treatments for any rare disease.

Watch this space for progress.
Rare Repurposing Open Call

Do you know of a drug repurposing project for a rare disease that is struggling to reach the clinic?

The call, hosted online by CureAccelerator™, is open to ideas from clinicians, researchers, and patient groups worldwide. It aims to raise the profile of drug repurposing in the rare disease community, find new research projects for Findacure’s innovative Social Impact Bond, and connect projects with funders and professionals with the skills to move them to the clinic.

www.findacure.org.uk/open-call