Identifying Drug Repurposing Opportunities

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Historical Perspective
Retrospective Drug Repurposing Discovery
Historical Drug Repurposing Discovery

Serendipity

- Off-target effects in clinical practice
  - Colchicine for Gout → Oncology, Cardiology ...
- Off-target effects in a clinical trial
  - Sildenafil for Blood Pressure → Erectile dysfunction

Observation

- Clinician observation in practice from co-morbidity
  - Ketamine for Pain and Mental Health
- Side effects yield a new indication
  - Tylenol PM contains drowsiness inducing Benadryl

Physician Desperation

- Thalidomide for leprosy
  - 1964 Jacob Sheskin, despite a ban, prescribes drug for a patient with acute leprosy
Current Perspectives
Proactive Drug Repurposing Discovery
Translational path to discovering treatments

The underlying workflow that drives discovery and development of new treatments.

Key processes in the workflow. Others exist and certain paths may be context specific.

- **Discovery**
  - Basic Research to understand biology of disease, generate and collate research data

- **Candidate selection**
  - Hypothesis generation, target and compound selection

- **Preclinical**
  - Show compound activity in disease model systems

- **Clinical**
  - Phase 1 – safety
  - Phase 2 – Dose & efficacy
  - Phase 3 – Population efficacy
  - Phase 4 – Post market surveillance

- **Market Authorisation**
  - Receive regulatory approval to market drug
Four drug repurposing strategies

1. Investigator-led innovation
   • Clinician Scientist proposes a repurposing opportunity, e.g. an academic

2. Experimental laboratory screening
   • High throughput laboratory experimental screens

3. Big data approaches
   • Data-driven “in silico” approaches ... like Healx!

4. Patient-led innovation
   • Inspired and driven by patient groups like you! e.g. Sirolimus for autoimmune lymphoproliferative syndrome.
1. Investigator-led innovation

MD/PhD interested in clinical care and academic research
- Probably has both a clinical practice & research lab
- Strongest candidate to drive therapy to patients
- Mentality is to start with clinical management

PhD connected to a disease
- Often very strong discovery and preclinical
- Sometimes cannot find a clinical partner
- Likely will be driven by establishing disease understanding

Clinician connected to a disease
- Often tries off-label first
- May or may not then work with a PhD

Applies translational path from basic research to clinical
- Seeks market authorization or off-label use

Dr. David Teachey, Children’s Hospital of Philadelphia

Treatment with sirolimus results in complete responses in patients with autoimmune lymphoproliferative syndrome, 2009
2. Experimental laboratory screening

**Contract Research Organization or Academic Group**
- GLP/GMP facilities to perform wet work
- Access to available clinical material or resources that recapitulate biology of the disease
- Can be High or Low throughput screening

**Generic workflow mirroring translational path**
- Develop an assay that reports modulation of the disease process, implies efficacy biomarker exists
- Test available drugs, nutraceuticals, or other candidate biologicals
- Assay results drive lead candidate selection
- Assess preclinical activity
- Define pharmacological safety profile (ADME analysis)
- Clinical evaluation through human trials
- Seek off-label use, or follow market approvals route
2. Experimental laboratory screening cont.

Outcomes

- Lots of leads
- Not many clinical successes
- Assays may not fully represent diseases
- Assays are being improved
- Some think that AI/”In Silico” might be better
3. Big data approaches

Natural language processing
• All published / private unstructured text-based data (scientific articles, EHRs ...)
• Computer reads, remembers, connects data
• Humans review/retrain computer models
• Apply models to predict new treatment connections

Multi-omic approaches
• Genomics, transcriptomics, metabolomics of drugs and disease
• Explored biological networks to drive mechanism-based approaches
• Use data unsupervised to find connections, e.g. Connectivity Mapping

Synthetic pharmacology
• Start with a target, then use structural modelling to build a molecule to modulate it
3. Big data approaches & AI powered drug discovery

Artificial Intelligence/Machine Learning
- AI: computer simulates human processing
- Faster/better memory, not as smart
- Reads and “understands” massive data
- Finds obvious/non-obvious connections
- Humans curate data in/results out
- ML: train/retrain computer to be smarter
- Many AI companies validating approach
4. Patient-led innovation

- Patient voice crucial and increasingly heard
- Patients and carers are disease world experts
- Creating knowledge/expertise/networks
  - Registries
  - -Omics data
  - Cellular/animal models
  - Clinical networks
  - Day to day learning/living tools
- Resources increasingly valuable to industry

Many Success Stories

- Sarizotan, antipsychotic
- PBI4050, antifibrotic
- Nitisinone, Herbicide
Fragile X Case Study
Proactive Drug Repurposing Discovery
Fragile X Syndrome

Case study

Symptoms

- Intellectual disability
- ADHD, hyperactivity
- Anxiety, sensory issues
- Autistic behaviours
- Seizures (~25%)
- Boys more affected than girls

DNA repeat in FMR1 gene
(chromosome X)

Affects 1/6,000 people

Image by: Peter Saxon
Preclinical testing combinations predictions in Fragile X

# combinations of 18 shown to fully rescue four key mouse behaviours in disease model

Number of mouse behaviours fully rescued

- 0/4: 1
- 1/4: 3
- 2/4: 1
- 3/4: 4
- 4/4: 9

94% (17/18)

Full rescue of at least one behaviour

50% (9/18)

Fully rescued all 4 behaviours tested
Announcing Rare Treatment Accelerator

Getting involved
Rare Treatment Accelerator

Healnet platform and drug discovery expertise

Public launch: 18 November, 2019

Submission: 10 January, 2020

Initial Partnerships Announcement: Rare Disease Day 29th February, 2020

Website: healx.io/rare-treatment-accelerator
Email: accelerate@healx.io
Every rare disease patient deserves a treatment

info@healx.io
Working Group Activities

Assessing your readiness to deliver a drug repurposing project
Workgroup Activity: Assessing a disease readiness for repurposing

Objectives:
- Understand how to become Repurpose Ready in your disease
- Revisit the Clinical Pathway
  - Identify outputs and decision points in key translational processes
- Review key Drug Repurposing Data
  - Understand how certain data unblocks and enable drug repurposing

Group Activity, Each group ...
- Task 1
  - builds a translational path and define key processes and decision boundaries (15 min)
  - Feedback & discussion
- Task 2
  - Lists datatypes that inform treatment discovery and development (15 min)
  - Feedback & discussion
Clinical pathway to discovering treatments

The underlying workflow that drives discovery and development of new treatments.

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**Clinical**

**Market Authorisation**
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Key processes in the workflow. Others exist and certain paths may be context specific.
Task 1: Clinical Pathway (15 min to discuss)

- How do I enable repurposing in my disease?
- What might the outputs from each process look like?
- What are the critical decision points?
- What resources maybe required?
- Who can help me succeed?

- Lead Candidate Selection
- Preclinical Testing
- Clinical Trials Testing
- No wrong answers, discuss this pathway in your team. Share experiences, concerns and expectations

healx
How do I enable repurposing in my disease?

- Clinical unmet need
- Disease mechanism of action
- Candidate targets
- Clinical network
- SAB, KOLs
- Natural history studies
- Patient registries
- Real World Evidence

Lead Candidate Selection

- Compound screening libraries
- Target product profile (desirable drug properties)

Preclinical Testing

- Bioassays
- Biomarkers of efficacy
- Models of human disease (in vitro / in vivo)
- ADME data

Clinical Trials Testing

- Clinical endpoints
- Regulatory engagement
- Trial sites, patients
- Study design
- Expert panels
Task 2: Types of data that enable drug repurposing

- What types of information will you put in these boxes?

- No wrong answers, discuss in your team. Share experiences, concerns and expectations about collating resources.
Task 2: Types of data that enable drug repurposing - Feedback

- Clinical Challenge
- Pharmacology, treatments, Off-label
- Disease Biology
- Community Effort
- Preclinical Biological Resources
- Preclinical data
- Clinical Trials
- Clinical Benefits
### Key Processes in the Translational Path

<table>
<thead>
<tr>
<th>Process Stage</th>
<th>Description</th>
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<tbody>
<tr>
<td>Basic Research</td>
<td>A rare disease mechanism serves as a target for modulation with a drug.</td>
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<tr>
<td>Candidate Selection</td>
<td>A compound – disease relationship is proposed, and likely drug selected for progression.</td>
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<tr>
<td>Preclinical Evaluation</td>
<td>Compound is tested in a recognised model of human disease and shows activity.</td>
</tr>
<tr>
<td>Clinical Evaluation</td>
<td>Compound is trialled in humans and shown to be efficacious, meeting requirements of regulatory authorities.</td>
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We’ve given you some process stages and the outputs that enable progression, but in many cases the path taken will be specific to the disease. What other stages and decisions do you propose to be essential?
1. What are the key process stages that enable discovery and development of new treatments?
2. What is the output of each stage that informs a Go / No-Go decision to progress?

Use the information provided to get started, then add your own thoughts …
We’ve given you some data types and examples of knowledge necessary to minimise risk in a translational programme, what other data types could assist?
Data Types to Inform Treatment Translation

Basic Research

Market Authorisation

Clinical Benefit

Suggest critical datatypes & rank their importance on progressing a treatment

Advancing treatments for rare diseases