



Drug repurposing as a strategy for rare disease charities

Dr Rick Thompson
CEO

findacure

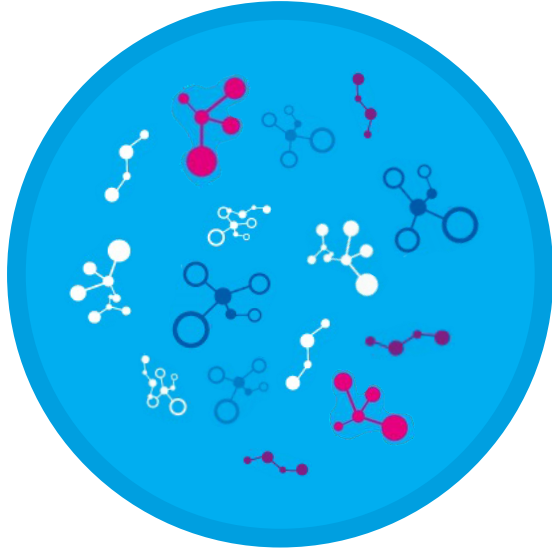
Registered charity number: 1149646

What is drug repurposing?

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

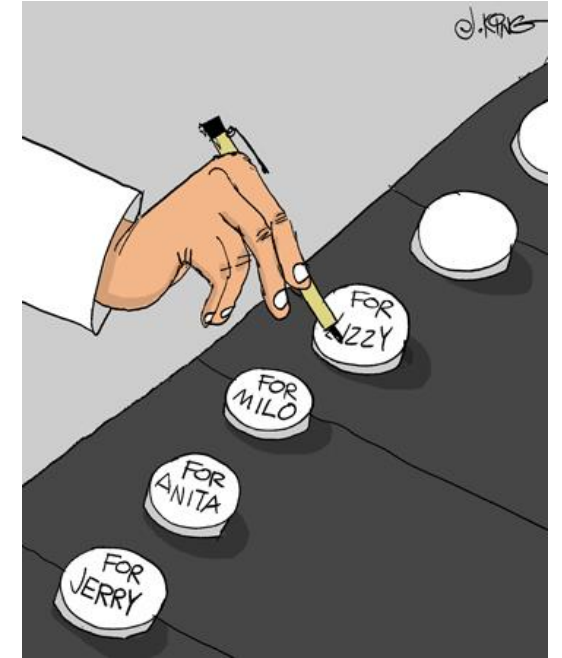


It is the act of taking a drug **intended to treat one patient population**, and demonstrating its efficacy in the **treatment of a completely different group of patients**.

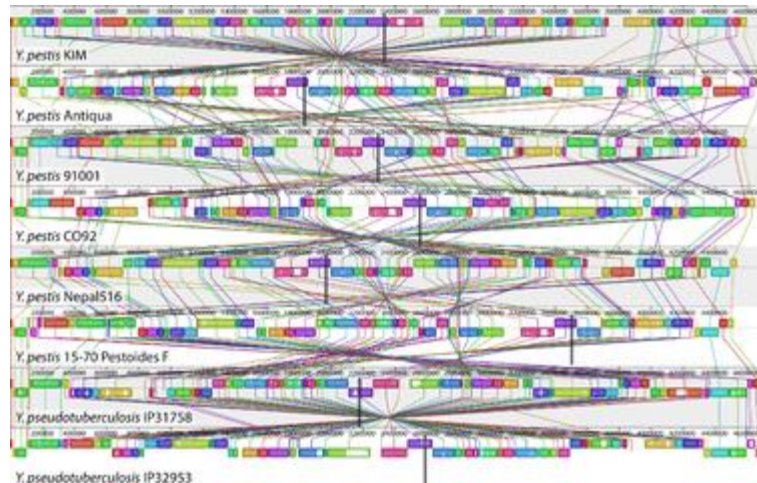


De novo
drug
discovery

Personalised
medicine



Genomics



Gene editing

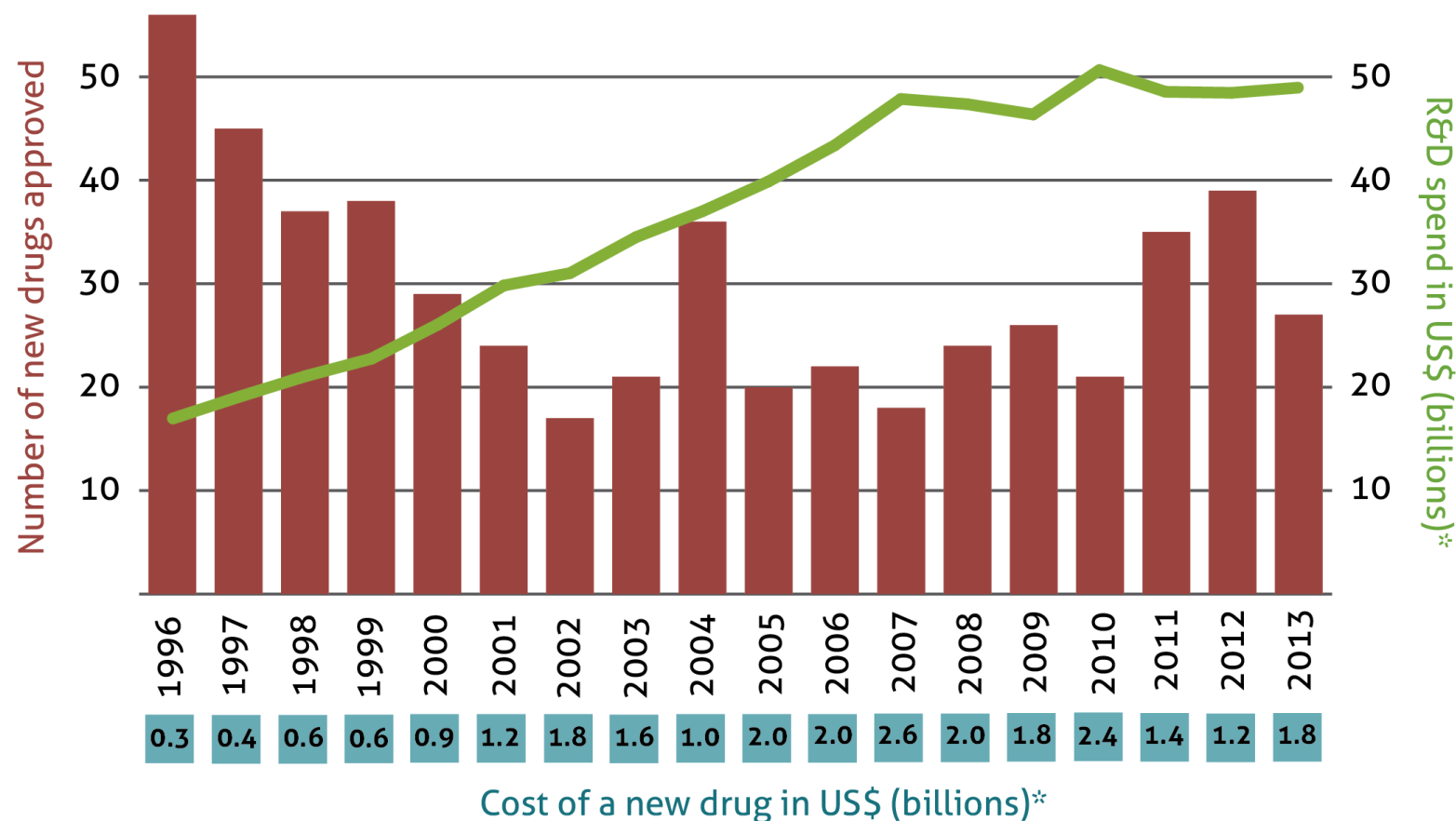
Repurposing – Why bother?

**I like my medicines new and
innovative!**



Productivity in the pharma industry

Finding the true cost of a new drug is complex and controversial...

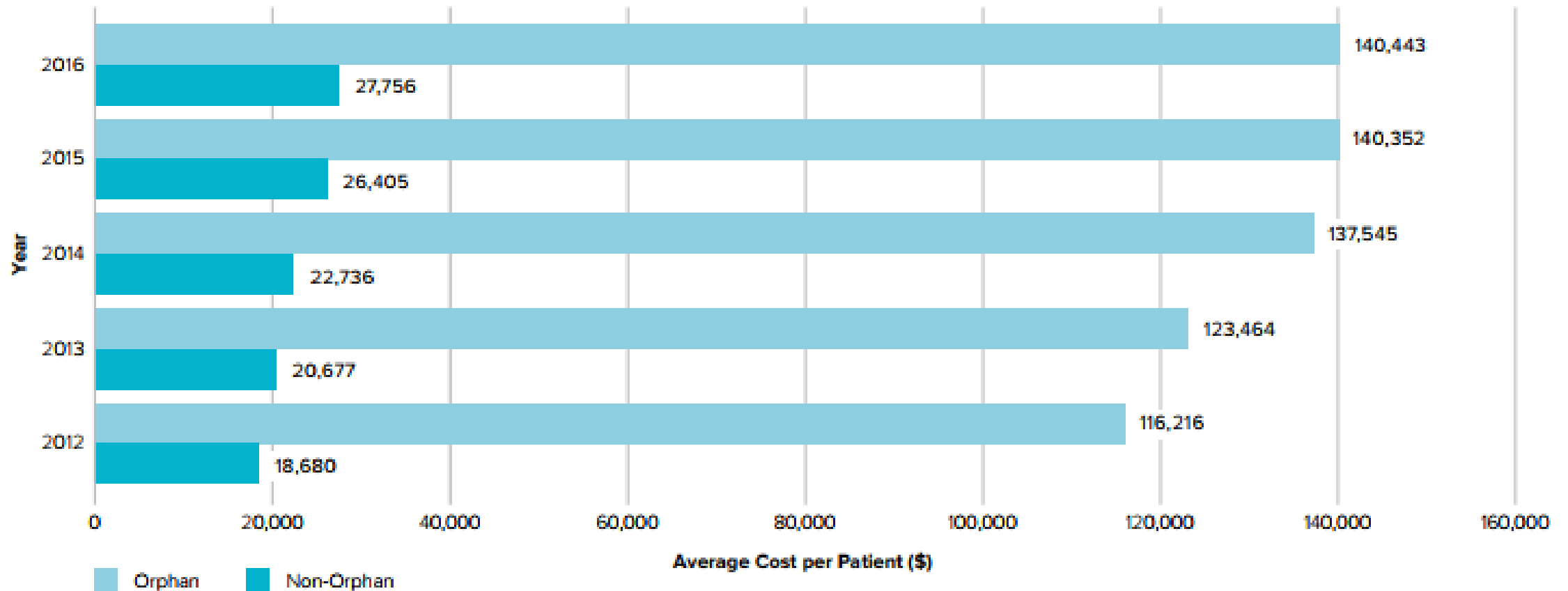


Data: USFDA, PhRMA

Pricing in rare diseases

Average Cost per Patient per Year 2012-2016

Source: EvaluatePharma* February 2017



A new model

The *de novo* drug discovery route is now struggling, leading to the search for a new model to accelerate the delivery of treatments to the clinic.

Drug repurposing is one possible model.

Possible targets

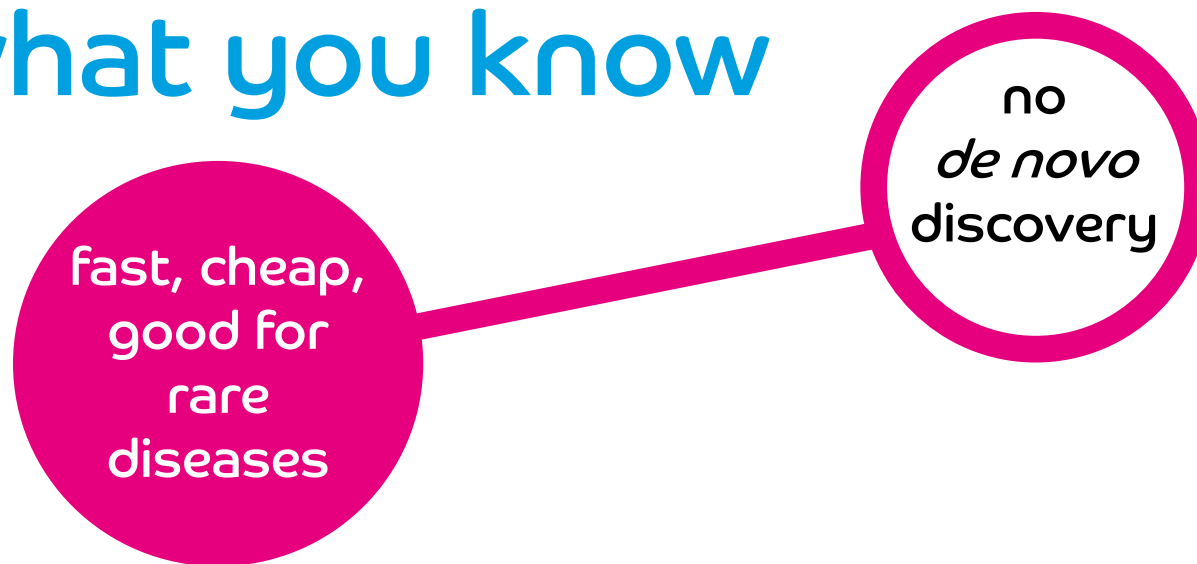
Existing **generic drugs** that are available on the market for one or more existing illnesses.

Current branded compounds – these are available on the market but remain protected by intellectual property.

Shelved compounds in pharmaceutical company libraries that proved to be **safe in humans**, but did not prove efficacious in their original targeted illness.

drug
repositioning

Working with what you know



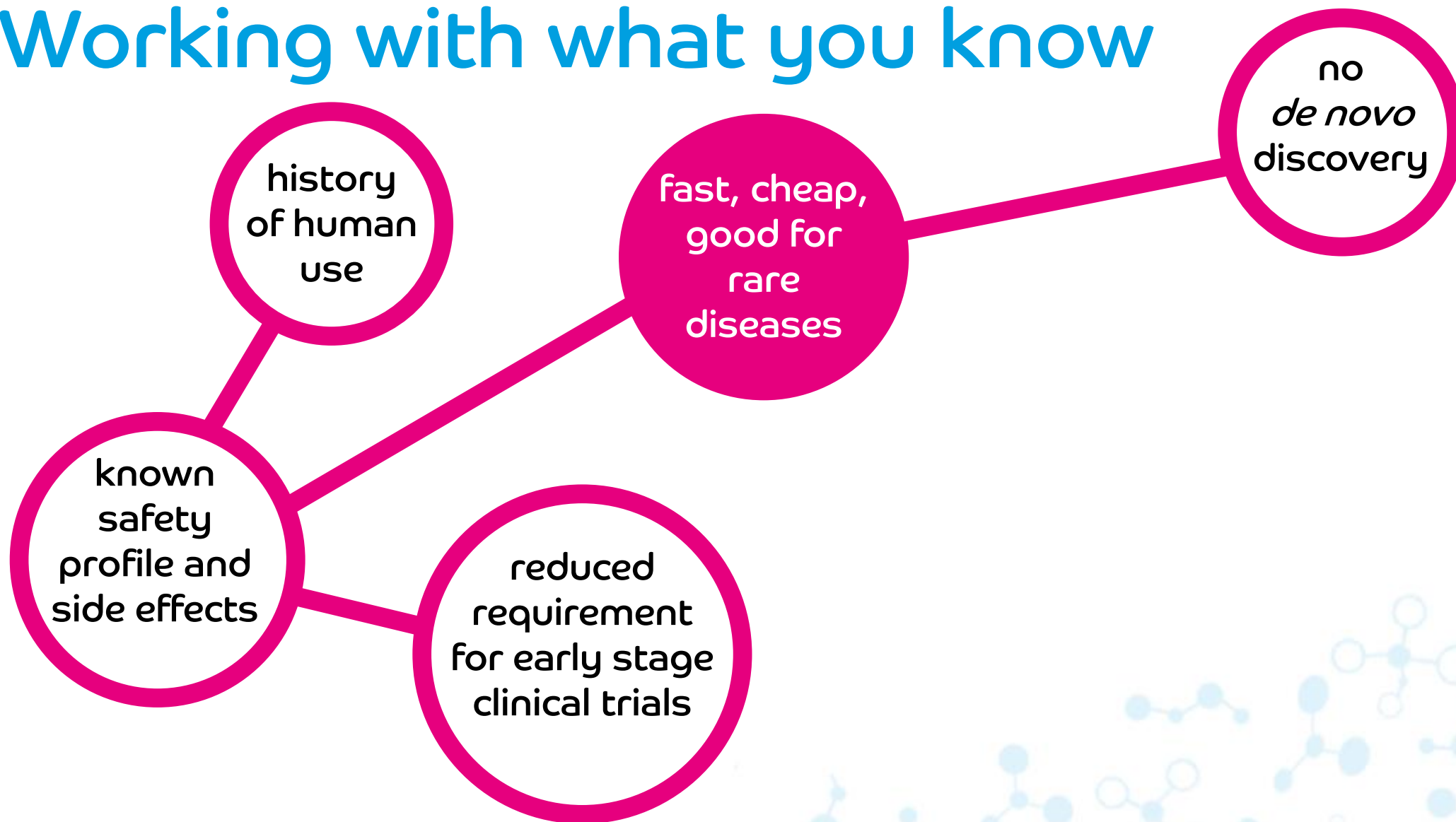
Working with what you know



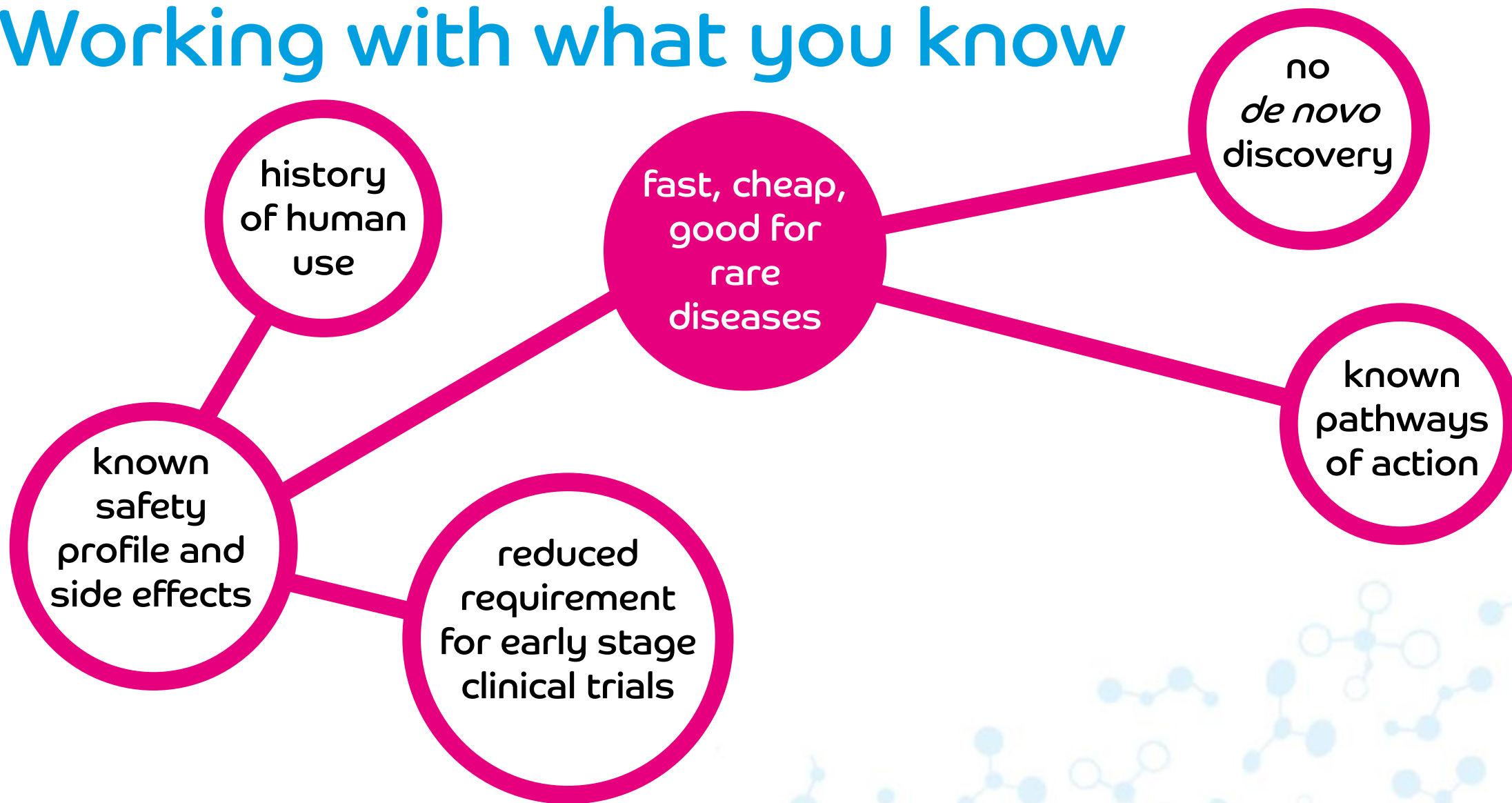
Working with what you know



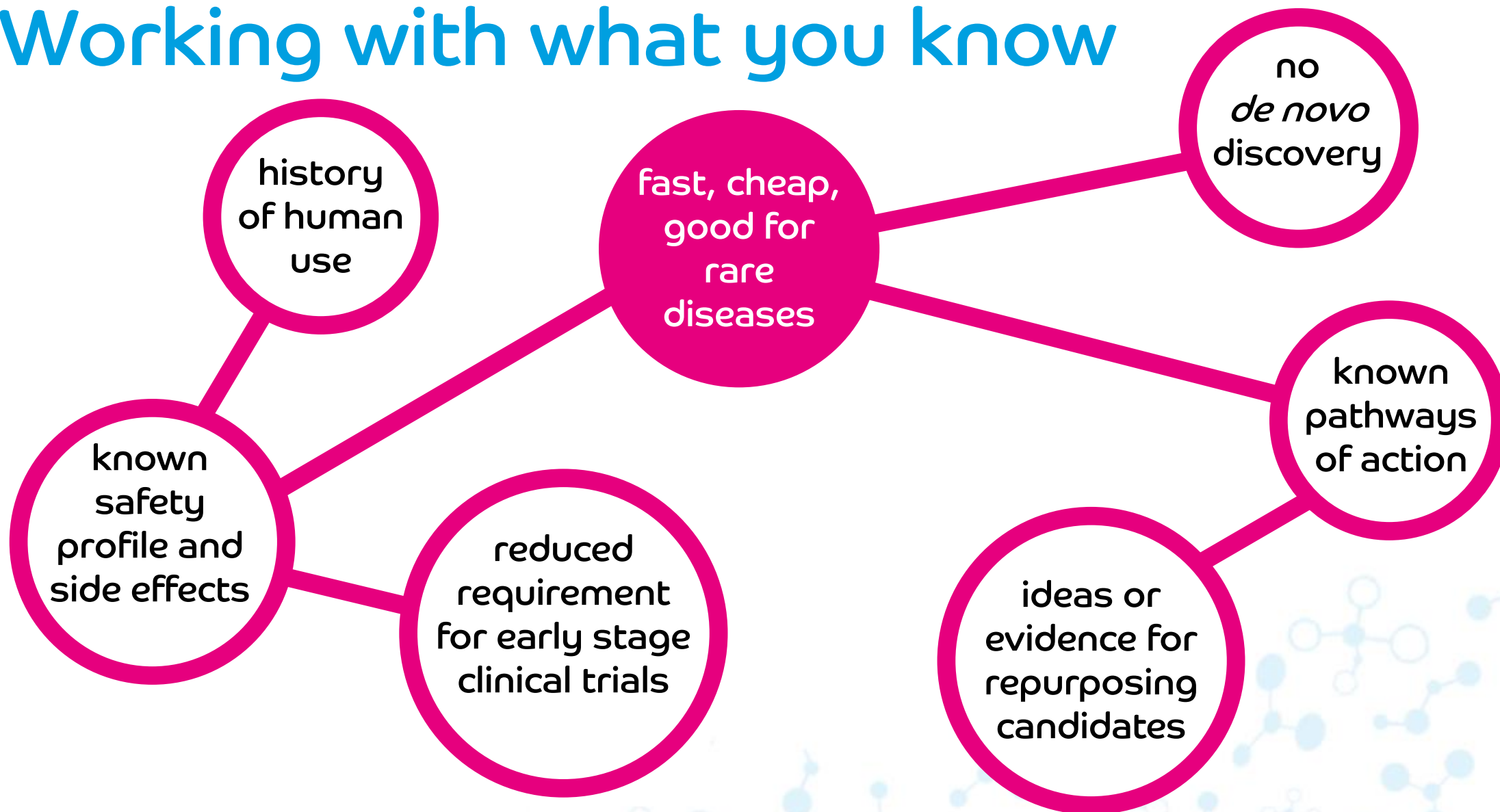
Working with what you know



Working with what you know



Working with what you know



Repositioning on the rise

Big
Pharma

academic
institution



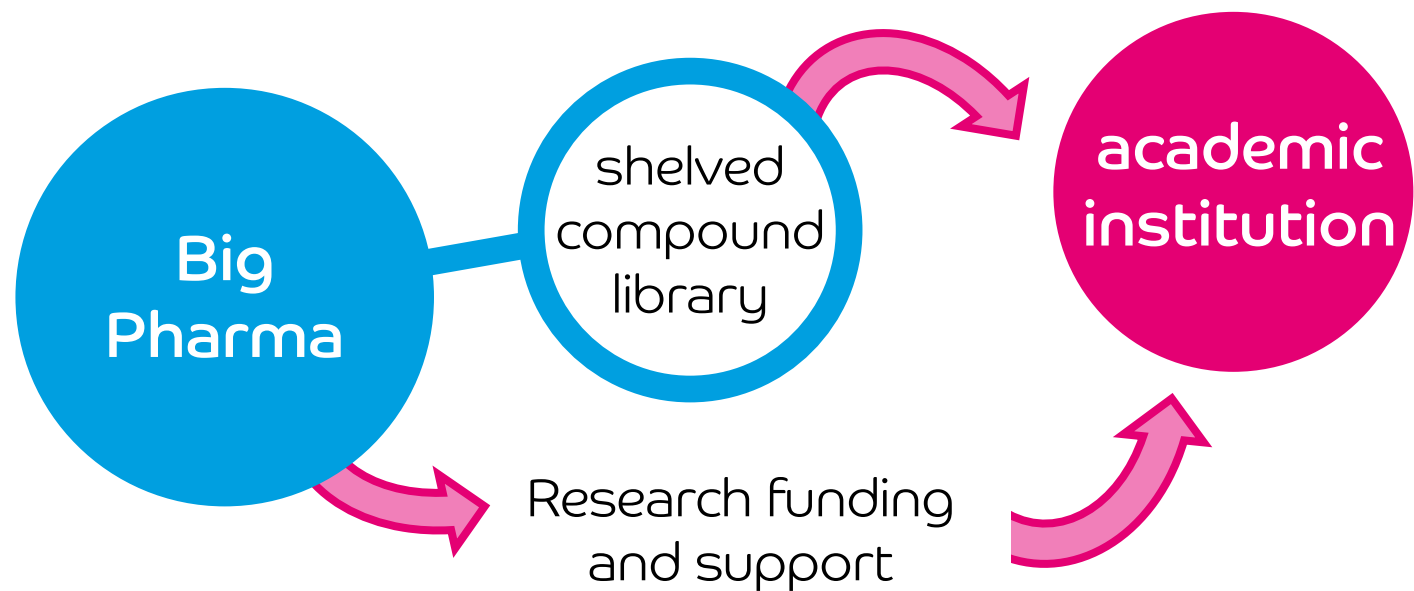
Repositioning on the rise



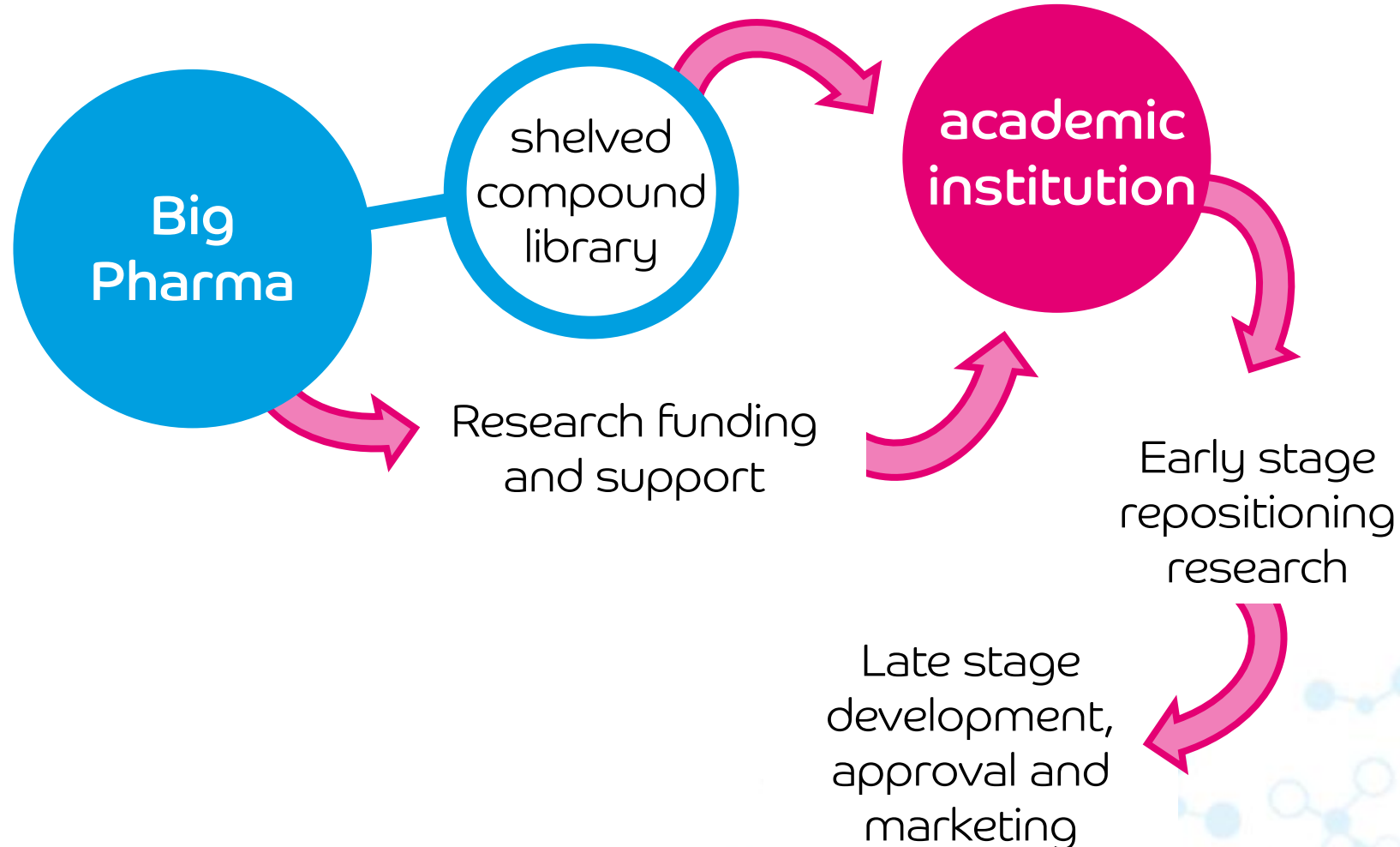
academic
institution



Repositioning on the rise

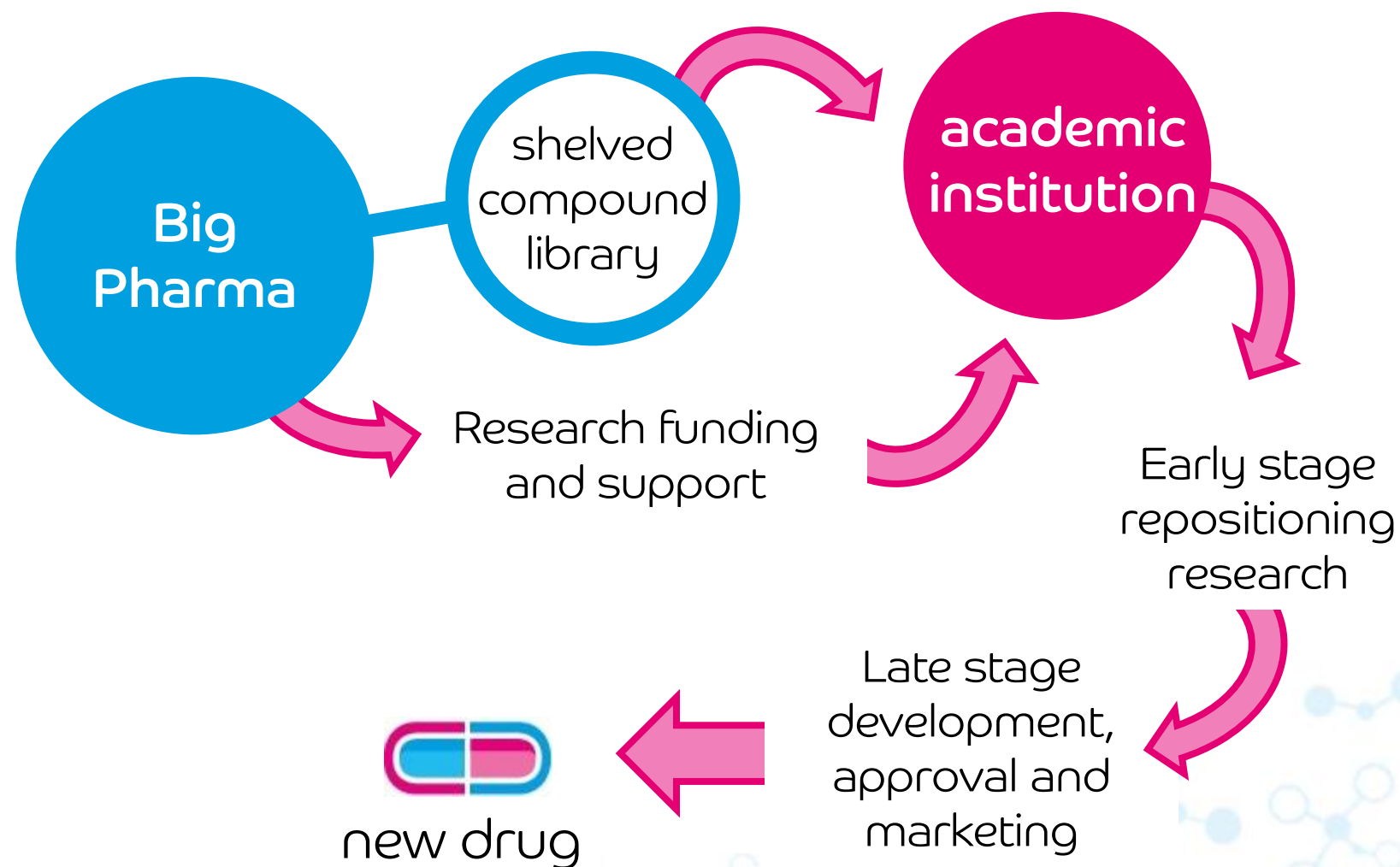


Repositioning on the rise



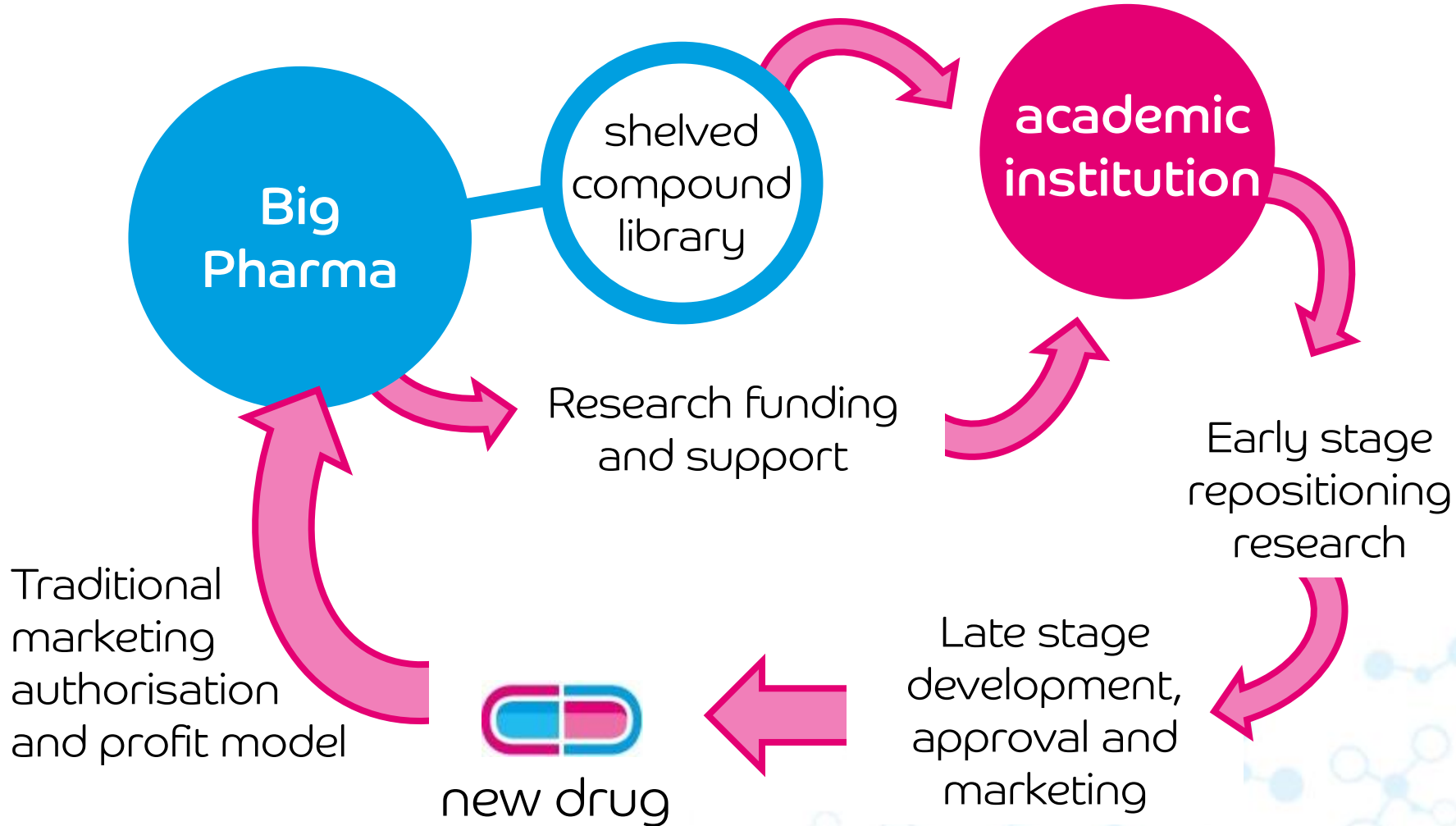
All research stages are collaborative, with increasing pharma involvement as development progresses

Repositioning on the rise



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Repositioning on the rise



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Funding generic drug repurposing

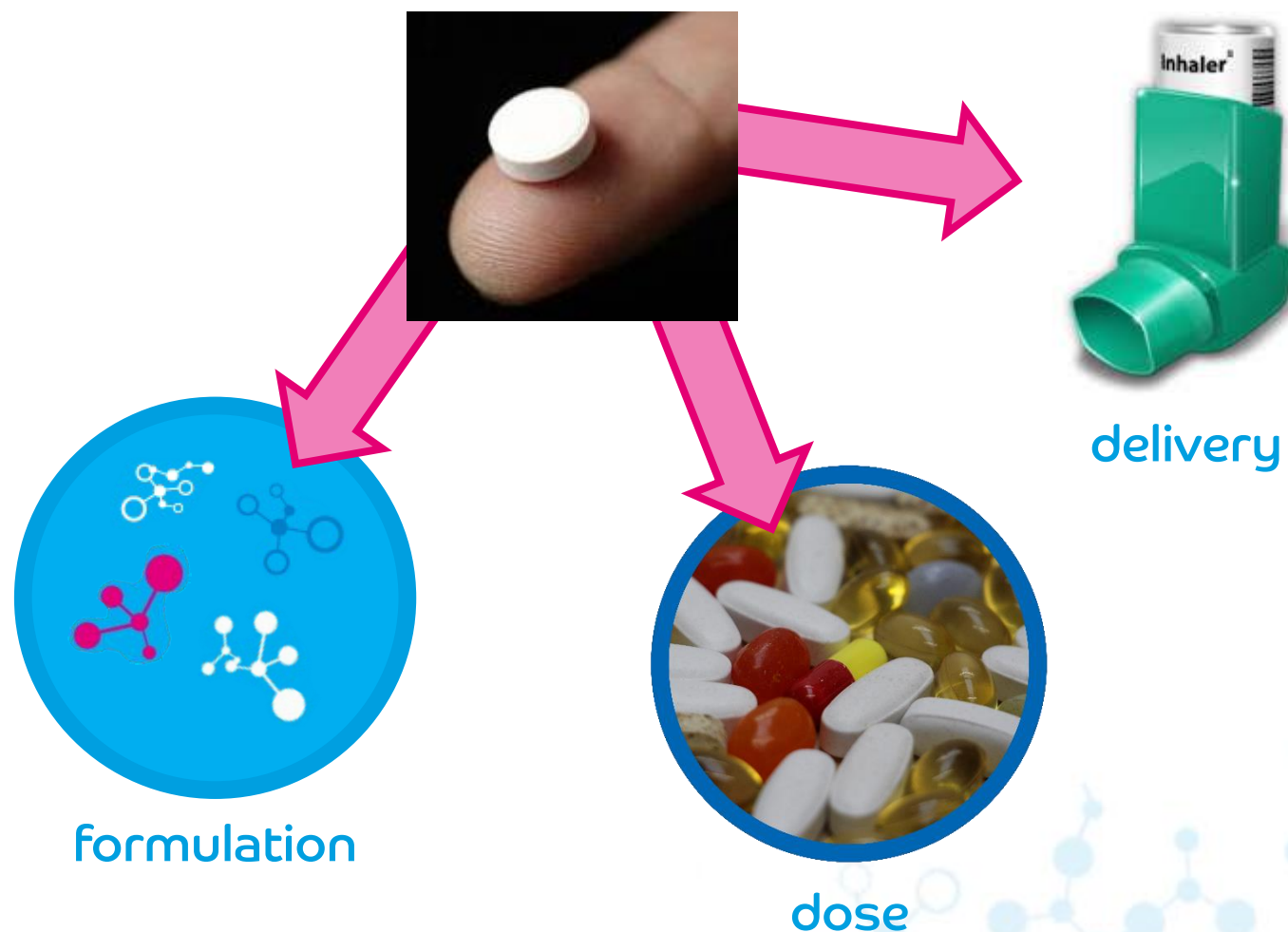
Repurposing of generics should be appealing due to the wealth of data available on their use in humans.

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.

Repurposing for pharma



Gain IP

BUT...

Requires new
safety data for
human use.

Repurposing without
reformulation work can
appeal to academia and
patient groups.

Review of repurposing

A literature review of published examples of drug repurposing for rare diseases is underway.

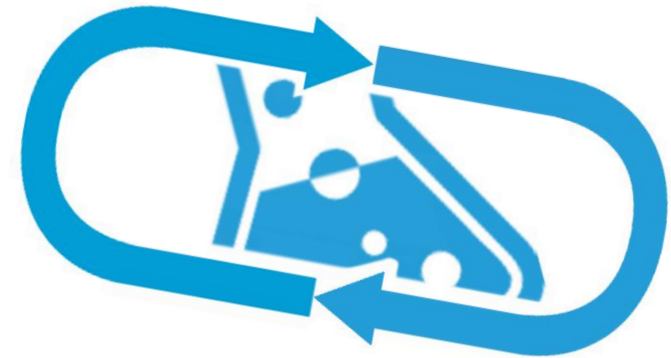
167 different cases identified so far

47 are paediatric

70 report off label use
in rare conditions

11 are based on case reports




Only **3** are reported through
full clinical trials, and **4** are
retrospective analyses



Open call results

38 different proposals

Including for some better known conditions such as:

-  cystic fibrosis
-  sickle cell anaemia
-  Duchenne muscular dystrophy

Excitingly, many ultra-rare conditions were also represented, including:

-  epidermolysis bullosa
-  adult polyglucosan body disease
-  PTEN syndrome

Of the proposed open call projects:



20 are **US** based
5 are **UK** based
4 are based in **Europe**
1 Canadian, 1 Australian
& 1 South African



Of those beyond the UK

21 have a **UK collaborator**



29 target rare genetic conditions



3 target common conditions



12 conditions have no treatment



11 proposals target a condition with a prevalence no higher than

1 in 50,000

6 treat rare cancers



17 proposals include **patient group** collaboration



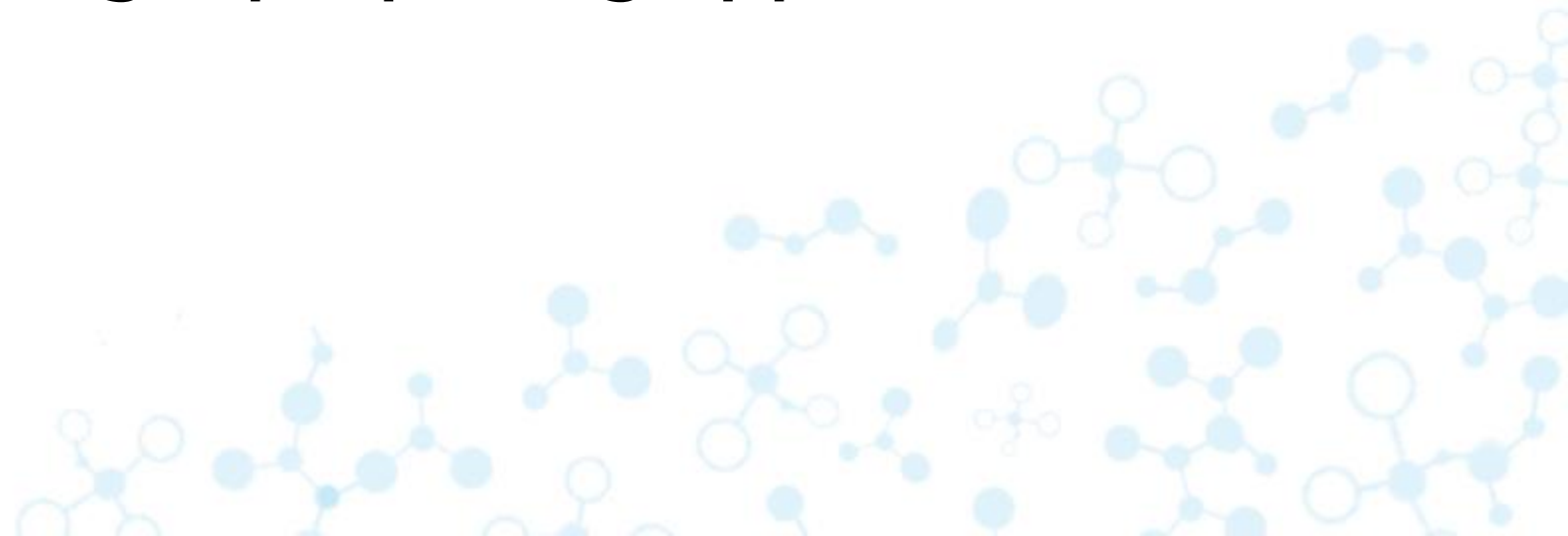
3 preclinical studies
6 phase I studies
24 phase II or III studies



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Repurposing is an ideal patient group or
academic led collaborative model

How do we identify repurposing opportunities?



Serendipity – thalidomide for leprosy

Traditionally repurposing has been driven by serendipity, or clinical insight.

Thalidomide was originally prescribed to pregnant women for nausea and insomnia, with horrific consequences for the development of their children in the 60's.

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In 1964 Dr Jacob Sheskin, a dermatologist working with leprosy patients in Jerusalem, prescribed a patient Thalidomide to help them sleep through the unbearable pain and discomfort of his skin lesions.

After only four tablets he noted a dramatic response in his condition, leading him to treat another six patients and recording the same dramatic result.



Screening compound libraries

This is an experimental approach that essentially tests multiple different drugs with the aim of finding some with a positive impact on your target biological pathway.

Screening requires:

- A model system, possibly a cell system of your condition of interest
- A collection of different drugs that could have an effect on the condition.
- A way to measure the effect on the pathway that you are trying to target in the cells. This could be a change in the form of the cell, the excretion or uptake of a specific protein or compound, the production of a specific protein, or even the cessation or acceleration of cell death.

Generally high-content screening is used allowing multiple drugs to be tested on a system at a time, while measuring multiple outcomes.

When repurposing, the selection of the compounds screened can be focussed on a target biological pathway, thus reducing the number of compounds used.

Screening – Wolfram syndrome

- ❖ A rare genetic condition that affects young children from around the age of 5.
- ❖ Patients exhibit diabetes and visual impairment, which progresses into blindness and deafness, along with other neurological complications.
- ❖ Affects about 60 people in the UK



- ❖ No current approved treatment
- ❖ Prof Tim Barrett has worked to secure a specialist centre for Wolfram syndrome, and now identified a repurposing candidate for the condition.
- ❖ The first trial is starting this year.

Screening – Wolfram syndrome

Model system: cells where the WFS1 gene is knocked out – a model cell system

Drugs screened: Compounds known to increase p21cip expression – this was found to be under expressed in wolfram syndrome cells leading to cell death.

Drugs already licensed for use in children (Wolfram is a paediatric condition)

Drugs that cross blood brain barrier (Wolfram is caused by degeneration of the brain stem)

Marker: p21cip expression was measured in the screen. Cells can be modified to tag this substance with a glowing green protein. This makes it simple to visualise how much p21cip the cell is producing. Those drugs that cause cells to appear the greenest should have the most impact on Wolfram syndrome.

Sodium valproate, a generic anti-convulsant drug, was shown to have the biggest impact on p21cip. Later shown to have an impact on the blood sugar regulation of Wolfram mice. Now on verge of phase II clinical trial in UK.

Literature mining

PubMed comprises more than **28 million** citations for biomedical literature from MEDLINE, life science journals, and online books.

Literature mining approaches seek to extract as much relevant information from this huge body of science as possible. It supposes that no one person can have connect all of the science relevant to a condition.

Approaches can be as simple as searching for a word in a database....

Best matches for Congenital hyperinsulinism:

[A syndrome of congenital hyperinsulinism and rhabdomyolysis is caused by KCNJ11 mutation.](#)

Albaqumi M et al. J Med Genet. (2014)

[Congenital hyperinsulinism.](#)

Petrailienė I et al. Medicina (Kaunas). (2014)

[Congenital hyperinsulinism.](#)

Dillon PA et al. Curr Opin Pediatr. (2013)

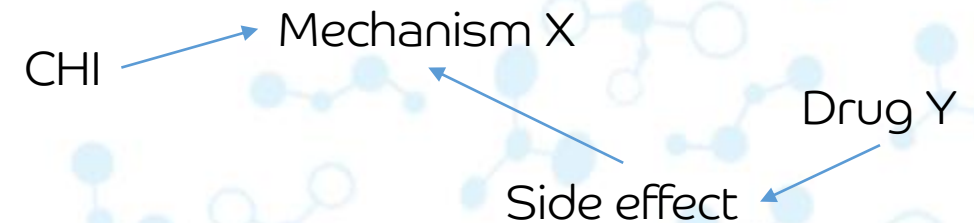
[Switch to our new best match sort order](#)

Search results

Items: 1 to 20 of 910

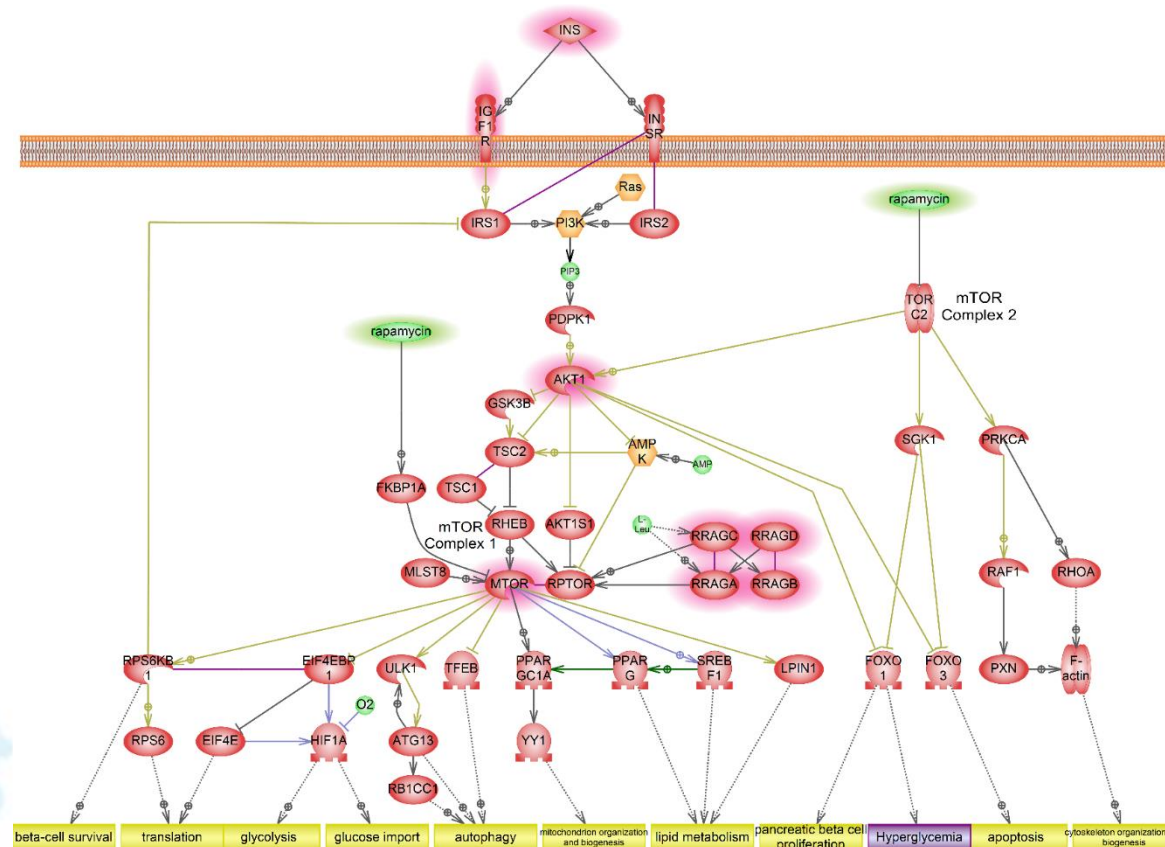
<< First < Prev Page 1 of 46 Next > Last >>

... or use artificial intelligence to infer connections between otherwise unconnected studies.







Literature mining – CHI

- Structured list of papers that are about CHI
- A full and detailed disease pathway, including associated mutations
- A list of key authors and institutions looking into the condition
- A list of proteins involved in CHI
- A list of diseases and cell processes linked to CHI
- A list of small molecules that could potentially effect the disease



'Omic approaches: 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

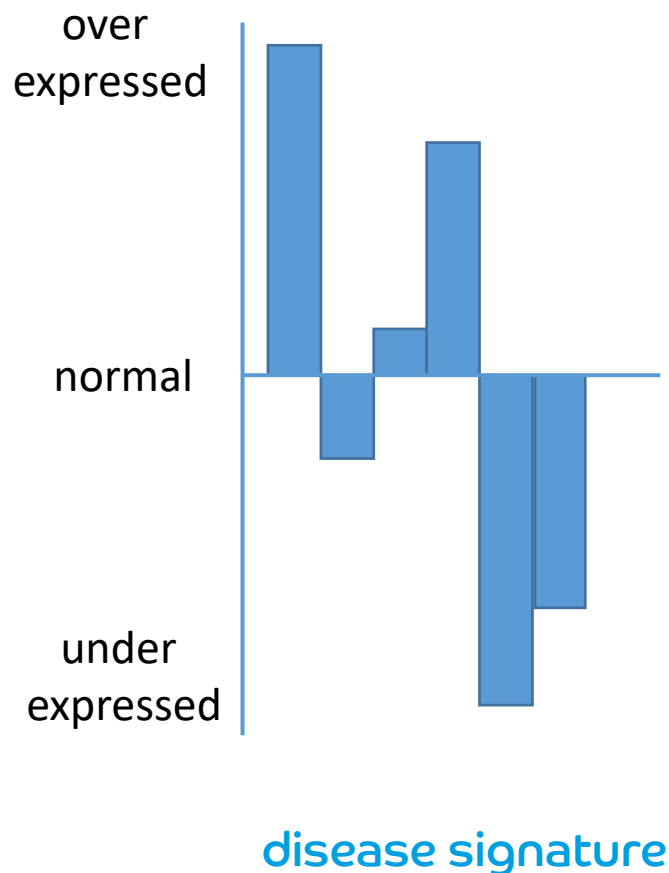


healx



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.

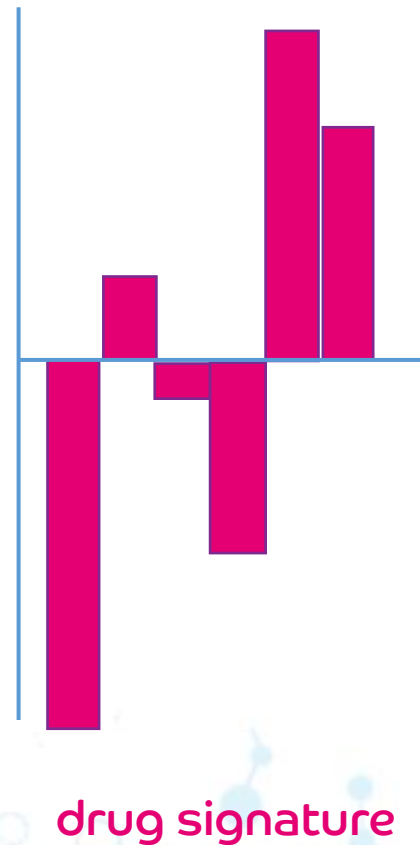
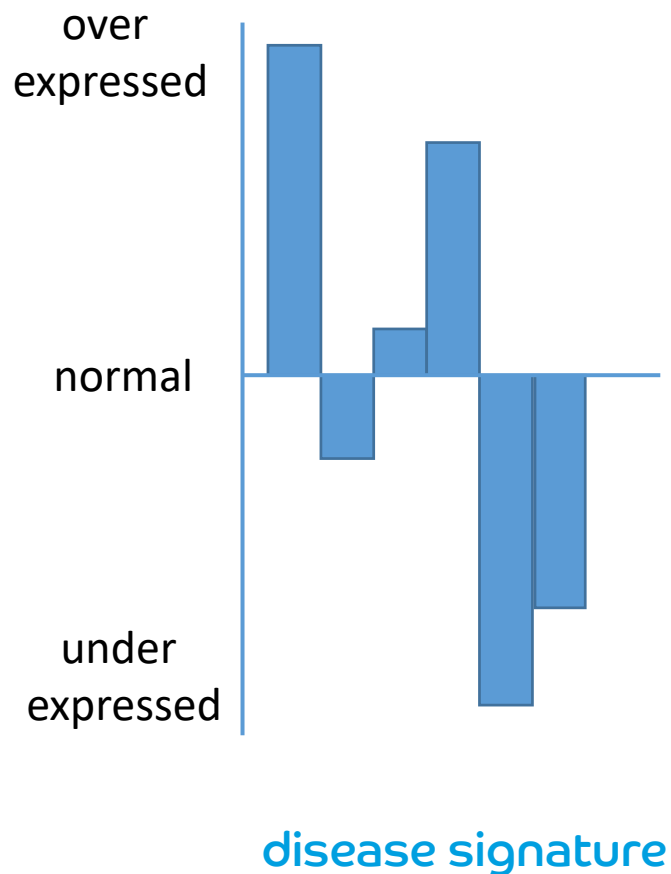


Expression levels
of different genes
in a disease
affected cell



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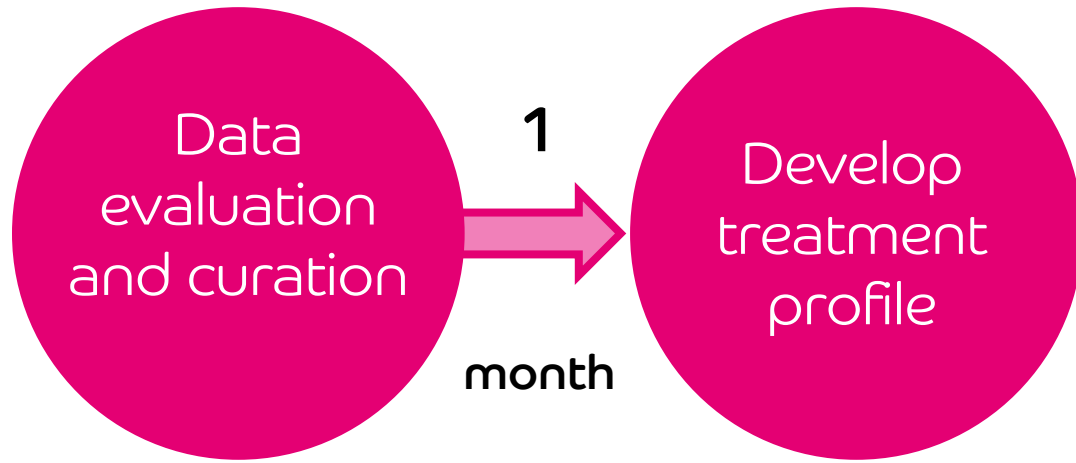


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CDKL5



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



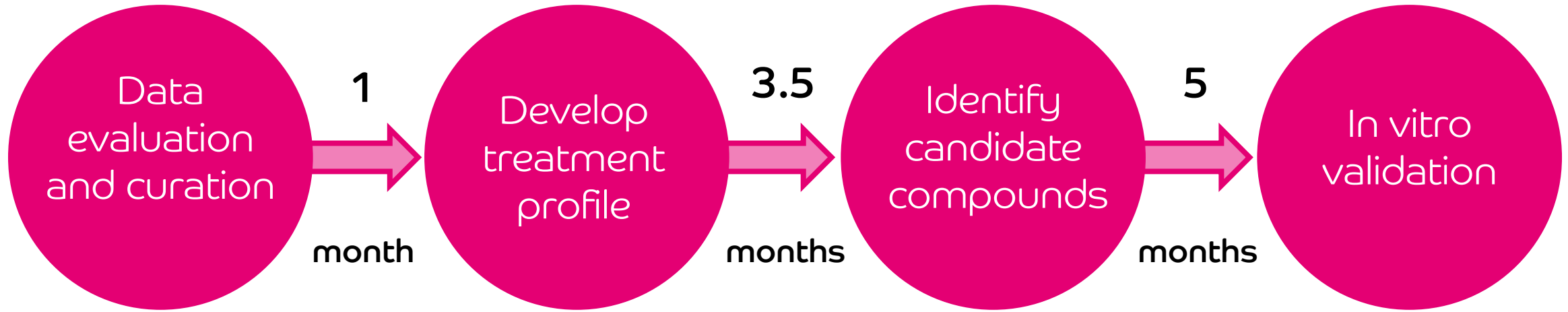
CDKL5



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Identified a generic antidepressant that could benefit patients

CDKL5



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Identified a generic antidepressant that could benefit patients

Showed that the drug counter-acted gene silencing on neurotransmitter receptors

A note on data driven approaches

These 'omic and literature based approaches clearly have huge potential to identify new repurposing opportunities but they should be seen as tools that need careful application:

- Results are only as good as the available data.
- Most approaches require careful sense checking by human experts.
- They can produce an overwhelming level of ideas and information, but that in itself does not get a treatment to a patient – if using these approaches you need a clear plan:
 - What do I want to get out?
 - How will I use the output?
 - How will we test the resulting repurposing ideas to take the best forward to the clinic?

How do we deliver a
repurposed drug to
patients?



Considering the context

In any repurposing project the context of the candidate, and your route to deliver the drug to the patient makes a huge impact on your strategy.

Under patent – a drug that is under patent, or still benefiting from marketing exclusivity from another source (e.g. ODD) cannot be produced or marketed by another company.

Generic – a generic drug is no-longer affected by a patent, and can be produced by multiple companies.

On-label – a drug that is prescribed for a condition for which it has marketing approval.

Off-label – a drug that is prescribed for a condition for which it does not have marketing approval.

The status of your candidate

	Pros	Cons
Under patent	<p>Have an obvious route to approach an industry partner to develop a drug for your condition.</p> <p>A clear business benefit to repurpose for the patent holder.</p>	<p>Have to convince the patent owner to either allow you to work on the drug, or to develop it themselves – clinical evidence likely to be key here.</p> <p>Limited understanding of safety in a wider range of patients.</p>
Generic	<p>Lots of data on human use.</p> <p>Low cost of drug, and can be readily produced.</p> <p>Accessible for off-label use.</p> <p>Ideal for an academic-led clinical trial.</p>	<p>Less options to defend IP.</p> <p>Less obvious business models for industry partners.</p> <p>Current formulation or delivery method may not be patient appropriate.</p> <p>Could be taken by patients outside of clinical studies.</p>

Your aim for patient delivery

	Pros	Cons
On-label	<p>Marketing authorisation gives a route to reimbursement and uniform patient access in each country.</p> <p>Securing marketing authorisation suggests robust evidence of efficacy and good monitoring of safety.</p>	<p>Requires a much higher level of evidence, which could be even higher to secure reimbursement.</p> <p>Longer and more costly clinical trials, and increased level of industry expertise is required.</p>
Off-label	<p>Clinical trials should aim to provide enough evidence of efficacy to convince clinicians to prescribe off-label.</p> <p>Low cost, shorter studies, needing less industry input or guidance.</p> <p>Chance to secure low-cost generic drug price.</p>	<p>Lower evidence of efficacy, and no monitoring of safety without MA.</p> <p>Access likely to be patchy – the more clinicians who serve your population the truer this becomes.</p> <p>Could be subject to predatory price hikes.</p>

Strategic decisions

Current status of repurposing candidate

		generic drug	drug under patent
		<p>Low market price</p> <p>Low IP potential</p> <p>Lesser pharma interest</p>	<p>High market price</p> <p>Potential to extent IP or exclusivity</p> <p>More pharma interest</p>
Delivery of repurposed drug to patients	off-label	<p>Unlikely to see any pharma involvement – no reformulation.</p> <p>Lower evidence, lesser uptake.</p> <p>Quick and inexpensive.</p> <p>Low price for drug.</p>	<p>Pharma can't work off-label – hard to access the drug for trial.</p> <p>Lower evidence, and need to reach clinicians.</p> <p>Drug price high.</p>
	on-label	<p>Could use pharma & look at reformulation.</p> <p>Strong evidence to secure MA.</p> <p>Longer process, higher costs.</p> <p>Drug price will be higher.</p>	<p>Pharma collaboration likely with good business model.</p> <p>Strong evidence, with delay of generic take over for company.</p> <p>Drug price current value.</p>

Case studies

Repositioning for rare diseases



Alkaptonuria

Black bone disease

Affects ≈ 1 in 1,000,000 people

Inherited genetic condition

AKU is a progressive disease, caused by an error in one of the body's enzymes. This causes a build up of homogentisic acid in the body. This acid attacks cartilage and bone throughout life, turning them black and damaging them.

Early in life there are few symptoms, but it leads to an early onset form of osteoarthritis, and multiple joint replacements are required.

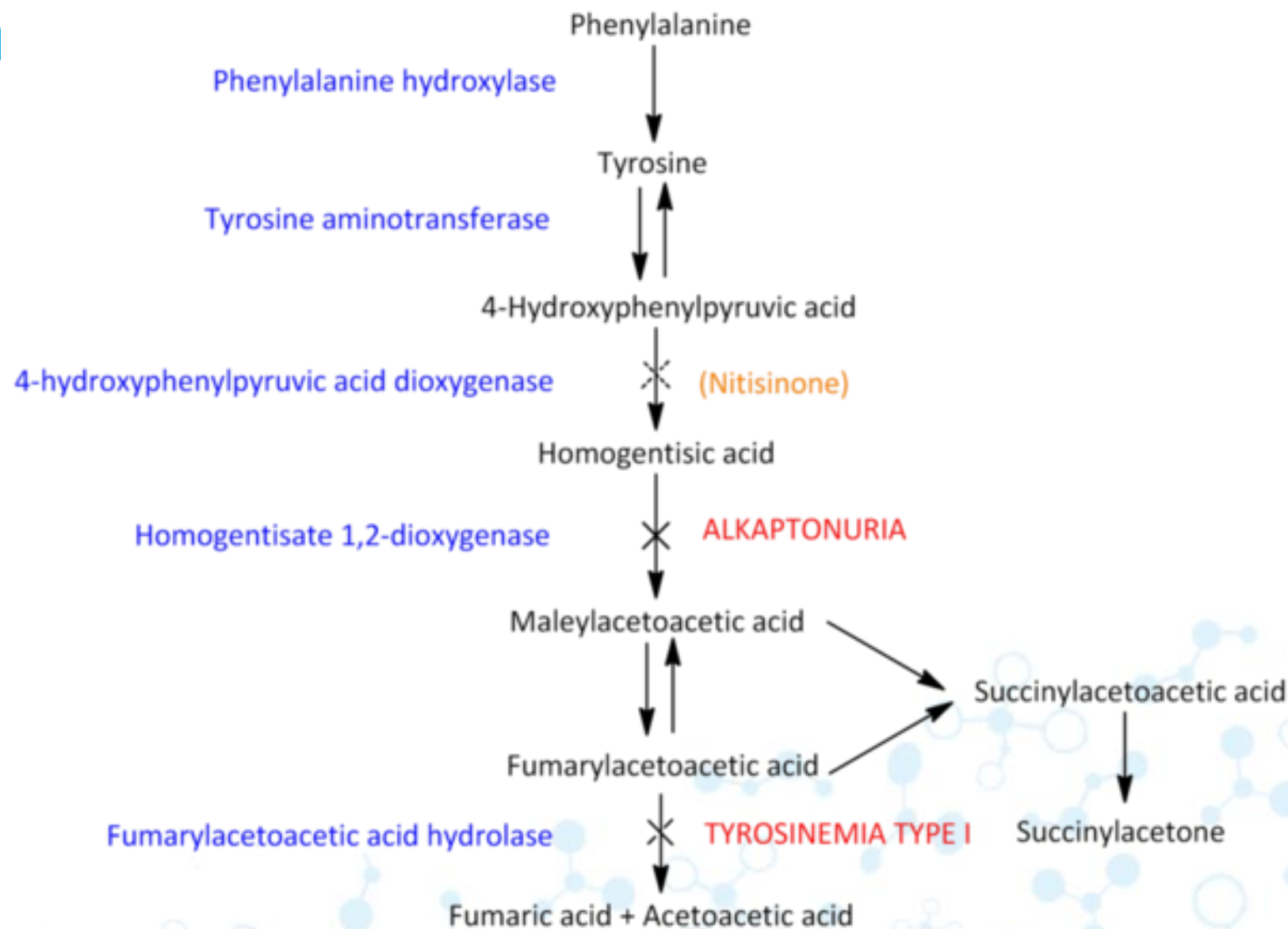


Alkaptonuria

Nitisinone is a drug approved for the treatment of tyrosinemia type 1.

It works on the pathway that produces HGA, and can effectively block HGA production.

This should prevent the condition.



Nitisinone and the AKU society



DevelopAKUre



- Failed trial in the US – due to poor end point selection
- Conducted first human autopsy in AKU to better understand condition
- Developed AKU mouse model
- Developed an AKU severity score to better assess disease progress and for use as a trial endpoint
- Secured a specialist centre for AKU in the UK – prescribing nitisinone off- label
- Built an international consortium for a clinical trial including the patent holding pharma company and a CRO.
- Secured FP7 EU funding to run a phase II and phase III clinical trial to assess the efficacy of nitisinone in alkaptonuria.
- EMA advice suggests a biomarker change could be sufficient for approval, but patient relevant endpoint included.
- Over 140 patients recruited for phase III study, mostly excludes English patients.
- Trial nearing completion with positive mid-point data.
- Ultimately the MA will be held by pharmaceutical partner.

Everolimus for tuberous sclerosis

- Began with academic 'fundamental' research identifying an underlying mechanism.
- Suggested the use of mTOR pathway inhibitors.
- Basic science led to interest in running a human trial, but funding for a full academic trial on a generic was rejected by MRC.
- Charity and governmental funding helped an open label phase II trial in kidney tumours – evidence of efficacy convinced Novartis to fund a large international phase III study of their existing drug Everolimus, which was under patent.
- Novartis got involved in developing the drug for TSC to access benefits of the ODD – this extended market exclusivity for the drug to 2021 – patent expired in 2013.
- Drug now approved for a number of different TSC tumours as an on-label medicine. Cost is estimated at around £36,000 per patient per year.

Generic estimated as low as £250 pppa

Case studies

Repurposing generics for rare diseases



MCDS-Therapy



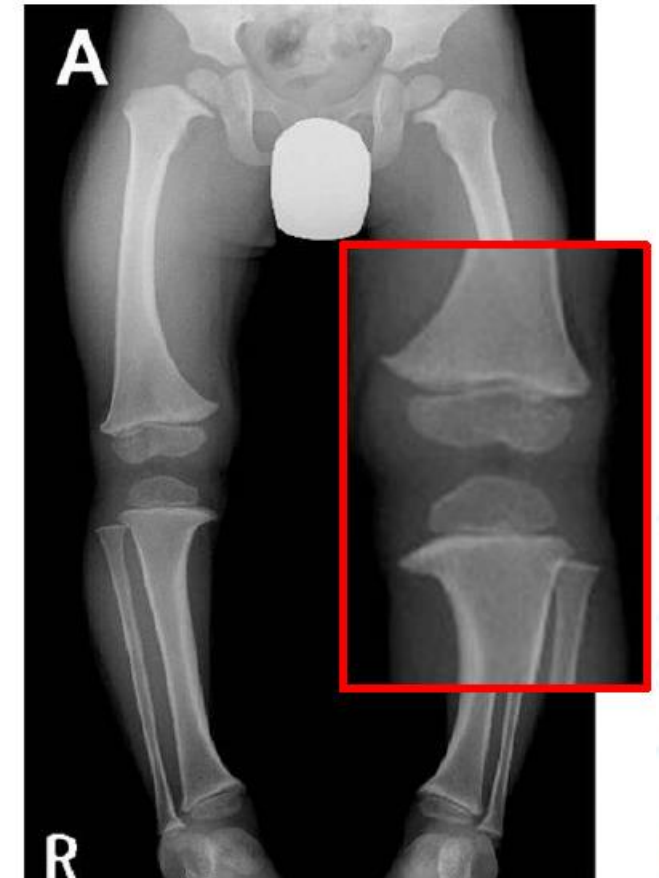
MCDS-Therapy Project has received funding from the European Union's Horizon 2020 research and innovation programme under grant agreement No 754825.

MCDS = Metaphyseal Chondrodysplasia Type Schmid

MCDS is a rare condition that leads to short stature, disproportionately short limbs, and bowed legs. Patients often suffer from joint pain and can have an unusual gait, both of which limit quality of life.

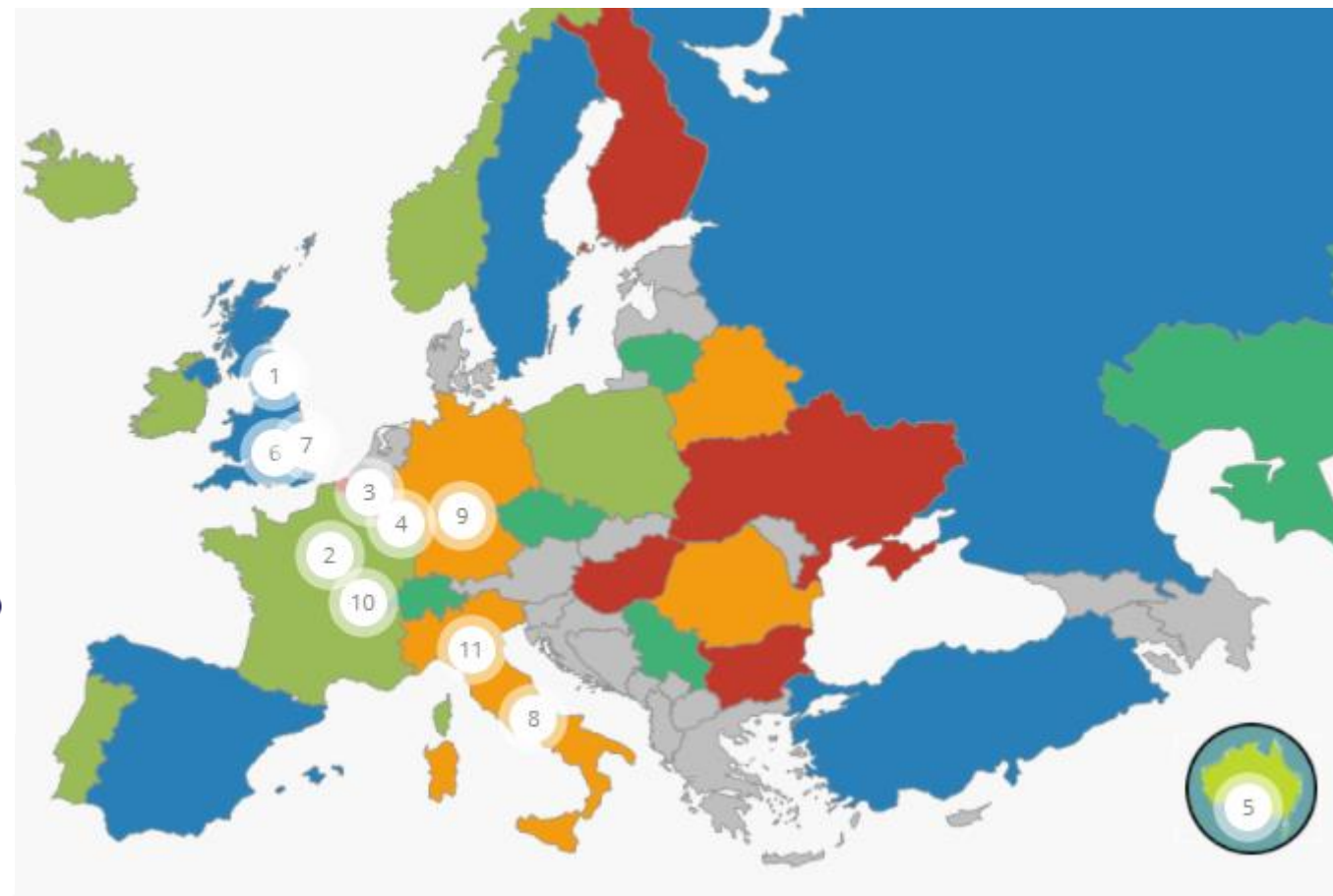
MCDS is caused by a mutation in collagen X.

A generic drug, Carbamazepine, has been shown to restore bone growth and form in MCDS mice. The collaboration will trial this drug in humans for the first time.



MCDS partners

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Findacure's role in MCDS-Therapy

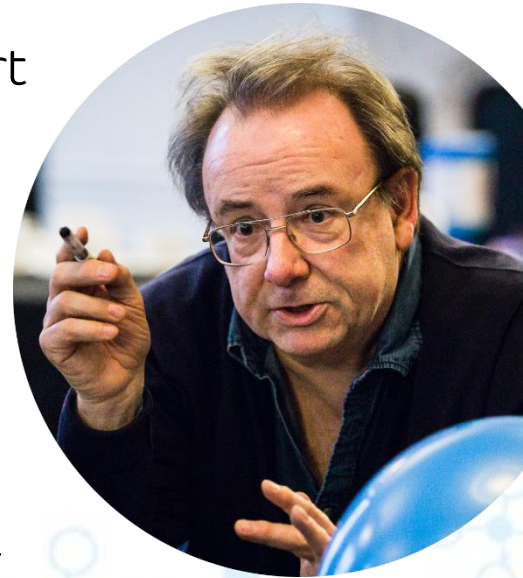
To **disseminate information** about the project, its aims, and its progress to the patients, rare disease community, and general public.

To help to **build the MCDS patient community** so that they are able to support the trial and provide their insights to enable us to deliver the best possible project for the patients.

Project aim

We are trying to **pioneer** an academic drug repurposing pathway, delivering a transformative treatment for a rare patient population from **bench to bedside**, independent of the pharmaceutical industry.

The end strategy is plastic, both patents and Orphan Drug designation have been secured by Newcastle University. EMA advice has also been sought for the clinical trial protocol, with the ultimate aim of securing European marketing authorisation for the drug.



ALPS and sirolimus



Autoimmune Lymphoproliferative syndrome patients suffer from enlarged lymph nodes and spleen, increased infections and anemia. ALPS patients may spend as many as **5-10 days** in the hospital each month and may not survive beyond their teens.

Cures Within Reach funded a **single researcher** to run a study of repurposed drugs in a mouse model of ALPS, which demonstrated potential efficacy for the condition.

The charity provided further support for a **pilot clinical study in six patients** – five of the six were in **complete remission** after 90 days.

Results were published open access to promote **off-label use**, and monitoring of treatment is on-going in the literature.

Cures Within Reach estimate the use of sirolimus, a low cost generic, **saves \$50,000 per patient** per year, while hugely improving their health and quality of life.



Published in final edited form as:

Br J Haematol. 2009 April ; 145(1): 101. doi:10.1111/j.1365-2141.2009.07595.x.

Treatment with sirolimus results in complete responses in patients with autoimmune lymphoproliferative syndrome

David T. Teachey¹, Robert Greiner², Alix Seif¹, Edward Attiyeh¹, Jack Bleesing³, John Choi⁴, Catherine Manno¹, Eric Rappaport¹, Dirk Schwabe⁵, Cecilia Sheen¹, Kathleen E.

Summary – repurposing IS the future

- 📌 Traditional drug discovery routes cannot deliver for all rare diseases on their own.
- 📌 Repurposing offers a quicker, cheaper, and collaborative route to the development of effective treatments.
- 📌 Academic and patient led collaborations are proving successful, and more approaches are being developed right now.
- 📌 There are many ways into the field of repurposing – [understanding the available evidence](#) will allow you to identify the best repurposing opportunities for you, while [clarifying your charity's aims](#) will ensure that you select the best strategy to deliver the drug to the patients.



www.findacure.org.uk

Section 1 – What is needed from a new repurposed treatment for your condition?





- 📌 What are the major benefits your patient population would like to receive from a new treatment?
- 📌 What symptoms have the largest impact on the daily lives of your patients?
- 📌 Is there a difference in the patient perception of the condition in different patient cohorts?
- 📌 What are the major obstacles to patients taking a drug?
- 📌 What tolerance will patients have for risk and side effects?

Section 2 – What is your current position, and what avenues does this open up for research?

Patient organisation situation – These questions should help to understand how your organisation can influence research into your condition.

- What is your disease prevalence?
- How many patients is your organisation in direct contact with? Is there a patient registry?
- What kind of contact and involvement do you have with researchers, and clinicians in field?
- What financing routes are currently available to your organisation?
- Is the data about your disease available online? If so, who can access it and where is it stored?

Current treatment status – The questions assess the existing opportunities for treatment development. Do you want to supplement or improve on an existing treatment, or develop an existing idea? What infrastructure could be used to deliver a trial?

-  Are there any treatments currently available?
-  Are there dedicated treatment centres for the condition?
-  Are there existing repurposing candidates?
-  Are any pharmaceutical companies currently interested in your condition?



Current research status – These questions should help to understand the starting point for research – who is involved, what evidence can any new treatment ideas be based on, and how can they be effectively assessed?

- Who is currently researching the condition?
- What types of research are being conducted? (fundamental, applied, gene expression)
- Is the underlying cause of the condition (disease mechanism) understood?
- Is there 'omic data available?
- What model systems are available? In vitro, cell models, animal models, human derived cell models?
- Are there good, validated measures of disease progress or severity?

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Current status of repurposing candidate

		generic drug	drug under patent
		<p>Low market price</p> <p>Low IP potential</p> <p>Lesser pharma interest</p>	<p>High market price</p> <p>Potential to extent IP or exclusivity</p> <p>More pharma interest</p>
Delivery of repurposed drug to patients	off-label	<p>Unlikely to see any pharma involvement – no reformulation.</p> <p>Lower evidence, lesser uptake.</p> <p>Quick and inexpensive.</p> <p>Low price for drug.</p>	<p>Pharma can't work off-label – hard to access the drug for trial.</p> <p>Lower evidence, and need to reach clinicians.</p> <p>Drug price high.</p>
	on-label	<p>Could use pharma & look at reformulation.</p> <p>Strong evidence to secure MA.</p> <p>Longer process, higher costs.</p> <p>Drug price will be higher.</p>	<p>Pharma collaboration likely with good business model.</p> <p>Strong evidence, with delay of generic take over for company.</p> <p>Drug price current value.</p>

[illegible][illegible]

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