Drug Repurposing : an opportunity for rare diseases

Christine Fetro, Roseline Favresse, Nicolas Pineau, Anne-Sophie Miossec, Nadège Penhaleux
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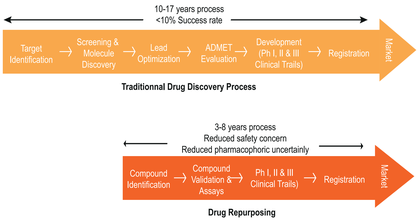
Background

Pharmaceutical industries are facing the biggest challenge since the 90s: how to develop new medicines faster, cheaper and with higher probability of success?
Developing a new molecular entity (NME) takes an average of 10 to 15 years and costs a pharmaceutical company more than $1 billion.
For approximately every 5,000 to 10,000 compounds that enter preclinical testing, only one is approved for human use.

Drug Repurposing (DR) : an alternative strategy in drug development and an opportunity for rare diseases

DR versus traditional de novo approach

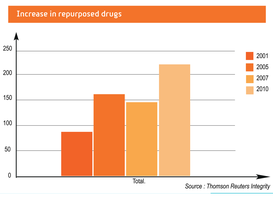
DR – also referred to as drug repositioning- is the process of finding new indications for existing drugs.
Finding a new use for an existing drug can be favorable for many reasons : bioavailability, pharmacology, toxicity and manufacturing routes are known.
Compared to traditional approach clinical development of a repurposed drug can be on average 5 years shorter, cheaper and with a higher probability of success.
In comparison to the number of approvals for de novo drugs, repurposed drugs are more frequently approved (30% versus 11%).



Dramatic increase of DR in recent years

DR is not new but it has dramatically increased in recent years.
Repurposed drugs have grown from around 80 in 2001 to 222 by 2010, a 300% increase in almost 10 years.

It is now estimated that around 30% of new drugs approved by the FDA are repurposed drugs.



Success stories of DR

The most well-known example is **Sildenafil**, a repurposed drug with a new indication.
Originally developed for the treatment of hypertension and angina pectoris, it failed in phase II clinical trials and was successfully redirected to the treatment of erectile dysfunctions.
Marked induction of penile erections was serendipitously found as side effects during the phase I clinical trials

Drugs that have been successfully repositioned[1]

DRUG	ORIGINAL INDICATION	NEW INDICATION
Amphotericin B	Fungal infections	Leishmaniasis
Aspirin	Inflammation, pain	Antiplatelet
Bromocriptine	Parkinson's disease	Diabetes mellitus
Finasteride	Prostate hyperplasia	Hair loss
Gemcitabine	Viral infections	Cancer
Methotrexate	Cancer	Psoriasis, rheumatoid arthritis
Minoxidil	Hypertension	Hair loss
Raloxifene	Cancer	Osteoporosis
Thalidomide	Morning sickness	Leprosy, multiple myeloma
Sildenafil	Angina	Erectile dysfunction, pulmonary hypertension

[1]Thomson Reuters

Minoxidil is another example of a repurposed drug with a new indication and a new formulation.
It was used as an oral antihypertensive drug but in early studies, hirsutism was noted as significant side effect.
Topical solutions were then approved to treat androgenic alopecia.

DR : an opportunity for rare diseases

The need for developing therapeutics for rare diseases is huge.
There are approximately 7,000 rare diseases and only 5% of them have a treatment.
Due to the small patient market of a rare disease population, there are limited drug discovery initiatives funded by pharmaceutical companies.

Some key initiatives have been undertaken to foster DR in rare diseases.

- The FDA has established a Rare Disease Repurposing Database (RDRD) to facilitate drug repurposing and speed the delivery of new therapies.
  Over 2010-12, half of the 46 FDA approvals in orphan indications were repositioned drugs.
- The International Rare Disease Research Consortium (IRDiRC) has the objective of developing 200 new treatments for rare diseases by 2020. DR has become a key priority of the IRDiRC, which has a working group on it.
- The French Foundation for rare diseases (FFRD), a non-profit, private structure dedicated to the coordination and acceleration of research on all rare diseases works alongside research teams in order to detect and support projects demonstrating therapeutic potential of drug candidates in rare diseases.
  Since its creation in 2012, the FFRD has identified 125 drug candidate projects.
  50% of these projects are DR projects.

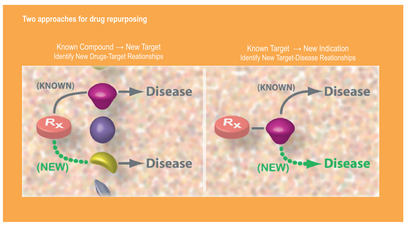
Drug Repurposing strategic considerations

2 main approaches

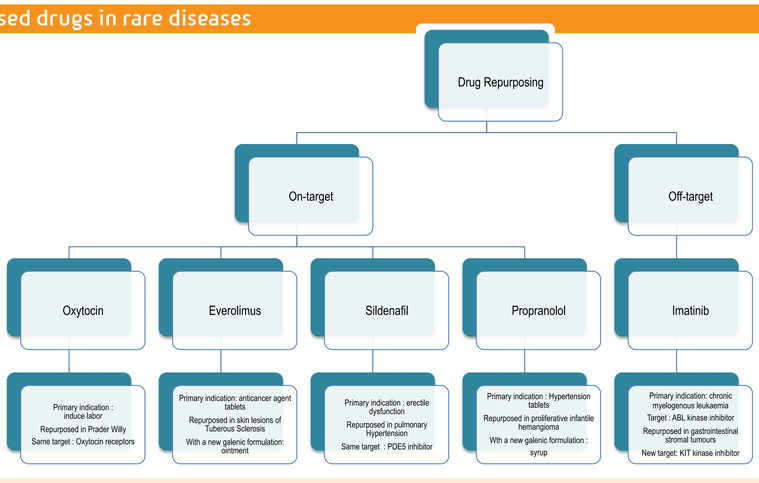
1. On-target approach: finding new uses of a drug acting through the originally known target
2. Off-target approach: finding new uses of a drug acting through a novel or unanticipated target

Regulatory and intellectual property considerations

A new indication with the same formulation may have a high risk of off-label use and a weak patent protection while a new indication with a high level of innovation may be synonym of strong intellectual property protection, accelerated market approval and gold route to private funding.
A new galenic formulation is also a well-established practice to extend the protection for a drug.
Moreover DR in rare diseases benefits from incentives associated with orphan drugs development including fee reductions and market exclusivity(10 years in the EU).



Examples of repurposed drugs in rare diseases



Conclusion

An alternative strategy in drug development, Drug Repurposing can be an opportunity for rare diseases.
It represents a viable, risk-managed strategy for pharmaceutical companies developing orphan drugs.
It also offers new opportunities for patients with rare diseases and for which there remain high-unmet medical needs.

Retrouvez nous
christine.fetro@fondation-maladiesrares.com
http://foundation-rarediseases.org