



15. Drug Repositioning

François Noël, July 2020

Although it has been widely discussed during these times of COVID-19, drug repositioning is a relatively new topic, since the first article addressing this concept was published in 2004 by Ashburn and Thor, and the number of articles on the subject only increased after 2010 (Langedijk et al., 2015).

As there is neither a legal definition nor a consensual definition in the academic literature for the term “**drug repositioning**”, we could adopt the definition proposed by IUPAC (Buckle et al., 2013): “*Strategy that seeks to discover new applications for an existing drug that were not previously referenced and not currently prescribed or investigated*”. It is noteworthy that IUPAC considers the terms drug repurposing, drug repositioning and drug reprofiling to be synonyms, as they all appear to be used interchangeably. Potential candidate drugs for repositioning can be divided into three categories (Cha et al., 2018):

1. Approved drugs that are no longer protected by patents;
2. Drugs that have gone through some stage of clinical development but are currently not on the market;
3. Patented drugs, approved or in advanced stages of clinical development.

Drug repositioning is highly attractive because it reduces the high costs and risks associated with the time and money spent in the traditional [drug discovery and development process](#). It is estimated that this strategy can considerably reduce the failure rate associated with safety or toxicity issues (estimated at 45%), in addition to saving up to 5 to 7 years in the average time required for drug development (Ashburn and Thor, 2004). Financially, the costs for drug repositioning have been estimated at an average of US \$300 million, compared with around US \$2-3 billion for a new chemical entity (Nosengo, 2016).

Many success stories illustrate the sound rationale behind this repositioning strategy (Pushpakom et al., 2019). In some cases, repositioning resulted from unexpected findings, such as sildenafil (VIAGRA®) for erectile dysfunction, which was based on retrospective clinical experience during clinical trials for angina; and thalidomide, whose redirection toward erythema nodosum leprosum and multiple myeloma was purely accidental (Pushpakom et al., 2019). In other cases, repositioning resulted from research efforts focused on the molecular mechanism of action of the drug or on screening compound libraries, as in the case of zidovudine (AZT), the first drug approved for AIDS treatment, whose original indication was cancer (Cha et al., 2018; Pushpakom et al., 2019). In fact, several companies have adopted a systematic, high-throughput and rational strategy to identify new therapeutic uses for marketed drugs or those still in development. In certain



cases, drug repositioning becomes a strategy to salvage drug candidates that failed for the initially proposed target diseases.

There are some incentives to encourage pharmaceutical companies to invest in repositioning programs for drugs with expired patents, such as market exclusivity (3 years in the USA and 10 years in Europe, provided new intellectual property is generated) or accelerated registration pathways (Cha et al., 2018). However, in practice, difficulties arise in obtaining patents for a new indication, since it is often already described in the academic literature or in clinical practice through off-label use (Pushpakom et al., 2019).

To conclude, we mention two areas in which drug repositioning may play a particularly relevant role:

1. **Academic and governmental projects:** Drug repositioning can increase the ability of non-industrial entities, such as universities and governments, to bring new and affordable treatment options, which may be especially relevant for [rare and neglected diseases](#) with little appeal for major pharmaceutical companies (O'Connor and Roth, 2005).
2. **Pandemics:** In pandemics such as COVID-19, where there is urgency in discovering active drugs, drug repositioning is the first option because it shortens several steps and therefore the time required for drug approval, which explains the race observed in the current search for repositioning of various drugs (Rameshrad et al., 2020).

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