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Drug-repositioning opportunities for cancer therapy: novel molecular targets for known compounds

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Teaser: Effective therapies against cancer require novel strategies to ensure a sustainable pipeline of drug development; thus, the repositioning of old, safe drugs as anticancer agents represents an evolving pharmacological approach.

Drug repositioning is gaining increasing attention in drug discovery because it represents a smart way to exploit new molecular targets of a known drug or target promiscuity among diverse diseases, for medical uses different from the one originally considered. In this review, we focus on known non-oncological drugs with new therapeutic applications in oncology, explaining the rationale behind this approach and providing practical evidence. Moving from incompleteness of the knowledge of drug–target interactions, particularly for older molecules, we highlight opportunities for repurposing compounds as cancer therapeutics, underling the biologically and clinically relevant affinities for new targets. Ideal candidates for repositioning can contribute to the therapeutically unmet need for more-efficient anticancer agents, including drugs that selectively target cancer stem cells.

Introduction

Drug repurposing is the identification of new therapeutic indications for already approved drugs; that is, a known molecule in common use, or a drug under development for treating specific diseases but showing potential efficacy for a different pathological condition, is reinvestigated for that purpose. This process is also referred to as 'drug repositioning', to indicate specifically the different use of a safe but 'shelved' compound from its original development (here, drug repurposing and repositioning are used interchangeably). Repositioning is gaining increasing interest compared with the traditional *de novo* drug discovery pipeline, which is more time consuming and expensive: repurposed drugs, for which preclinical and safety studies in humans for the original indication have already been performed, enable a faster, cheaper, and more efficient translation from bench to bedside [1]. In recent years, the number of new drugs (new chemical entities; NCEs) developed by pharmaceutical companies and entering preclinical testing, clinical trials, or clinics has gradually declined, despite consistent investments in drug development and biomedical research. Moreover, drug repurposing overcomes the possibility of postmarketing and clinical applicability risks for companies. In addition, patients will benefit from repurposing that might reduce safety risks and speed up successful access to treatment. Current biotechnology advances enable the rapid screening of drugs for their potential repositioning for unmet medical needs, such as cancer, central nervous system disorders, and rare diseases, boosting the interest of researchers and becoming a strategic approach to drug development.

However, drug repurposing is not completely risk-free because it still represents a drug development phase and, thus, biological activity, pharmacological parameters, and clinical observations need to be analyzed fully, to limit failure in late-stage clinical trials or after marketing. The novel medical use will likely involve: (i) new patient groups with different physiopathological conditions and potentially different or unexpected adverse effects; (ii) new drug formulations with diverse bioavailability and pharmacokinetics; and (iii) new dosing and scheduling, especially if used at higher therapeutic concentrations than in the original registration, and unforeseen toxicities. These concerns will need to be addressed to meet stringent safety requirements before they can be used as reposition therapy.

Re-investigation of old drugs is often performed as 'on-target repositioning', if a different clinical application is assigned to the known pharmacological activity of a molecule or, more rarely, as 'off-target repositioning', when a new mechanism of action identified for a known drug leads to novel clinical indications. A good example of the first approach is finasteride: its known target (blockade of testosterone activity via type II 5α-reductase inhibition) was exploited originally to treat benign prostatic hyperplasia and subsequently switched to male-pattern baldness. A typical example of 'off-target repositioning' is thalidomide, initially marketed as a sedative, but whose molecular