A Prospective Overview of Drug Repurposing in Drug Discovery and Development

The pursuit of approved drugs and unapproved drug candidates repurposing for novel clinical applications is an attractive strategy due to its speed and high efficiency. Most successful repurposing discoveries have been serendipitous. However, recent studies have shown that drug repurposing for the treatment of illnesses may not be cheaper and more efficient than developing new drugs. For this reason, it is important to broaden the search for established drugs with rational methods to repurpose for new indications.

The review is provided by Chen et al., focused on the recent advances in drug repurposing for Parkinson’s disease (PD) [1]. Availability of several established clinical drug libraries and advances in biology, genomics, and bioinformatics of the disease led to the successful clinical introduction of several repurposed drugs for the treatment of PD. The authors provided an interesting overview of activity-based drug repurposing of non-PD drugs that have shown efficacy in preclinical PD models and investigated in clinical studies. Many repurposed agents, which may help to accelerate the development of novel therapeutics for PD have been presented. Among them, c-Ab1 (ABL1; Abelson tyrosine kinase) inhibitors such as nilotinib, bafetinib and imatinib, the Nuclear receptor-related 1 protein (Nurr1) agonists (C-DIM 12, amodiaquine, chloroquine, glafenine), β2-adrenoreceptor (β2-2AR) agonists (salbutamol, salmeterol, propranolol), dipeptidyl peptidase IV (DPP-IV) inhibitors (sitagliptin, saxagliptin, vidagliptin, linagliptin), peroxisome proliferator-activated receptor-γ (PPARγ) agonists (pioglitazone, rosiglitazone, MSDC-0160, ibuprofen, fenoprofen, flufenamic acid, indomethacin), and nuclear factor erythroid 2-related factor 2 (Nrf2) activators (D3T, sulforaphane, s-allyl cysteine, DMF, CDDO-EA, CDDO-TFEA) were reported for the treatment or prevention of the PD. Mechanism of these drugs, potential advantages over other existing drugs, their well-established dose regimen with favorable pharmacokinetics, pharmacodynamics and side effects were explained. In addition, other drugs (isradipine, methylphenidate, doxycycline, raloxifene, astemizole, ketoconazole) holding repurposing promise for PD were reported and their mechanisms and potential therapeutic properties were discussed.

In the review by Konreddy et al., they emphasized the importance and difficulties of new antibiotic development and explained the key role of drug repurposing in the development of antibiotics during 2016-2017 years from various existing FDA-approved drugs that have potential antibacterial properties [2]. Besides the combination therapies with existing antibiotics, their potential for new implications of multidrug-resistant bacterial infections (MDRBIs) was discussed. Authors also aimed to provide essential data for the development of safe, effective, and novel antibiotics for current needs and showed the effective applications of inhibiting MDRBIs by repurposing existing drugs. Several classes of compounds were reported in this innovative drug repurposing process for their antibacterial properties. In this frame, anticancer drugs (gallium nitrate, mitomycine, tamoxifen, toremifene), antifungal drugs (clotrimazole, naftifile), antihyperlipidemic drugs (atorvastatin, fluvastatin, rosuvastatin, simvastatin), antiinflammatory drugs (aspirin, diclofenac sodium, diflussenil, ibuprofen, indomethacin, mefinamic acid), antimalarial drugs (artemisinin, artesunate), antiparasitic agents (auranofin, niclosamide, nitazoxamide, oxyclozanide), antimalarial drugs (ibavirin, zidovudine), genetic disorder drugs (deferripine, ivacaftor, zafirlukast), and immune modulator drugs (glatiramer acetate, granulysin) were demonstrated as potential antibacterial agents against Gram-positive and Gram-negative bacteria. It was also reported that combination therapies with these drugs overcame the crucial situation created by drug-resistant bacteria and provided safe and effective supplementary data for treating bacterial infection.

Karaman and Spill highlighted the importance and applications of computational strategies such as bioinformatics, cheminformatics mining tools and in silico chemical screening approaches to predict off-target interactions and identify novel therapeutic uses for known medications for drug repurposing [3]. The review focused on target-based and ligand-based computer-assisted data mining strategies and provided a critical review of the challenges and benefits of computational tools for drug repurposing. One such strategy is the use of off-label
commercially available drugs by comparing disease-gene-drug associations by comparing drug-gene expression profiles. The authors emphasized the importance of data integration to address the shortcomings to determine gene expression profiles with phenotypic drug screening data for the potential of drug repurposing studies. In this review, a combination of these efforts with the target- and ligand-based data mining was also discussed in multiple case studies that led to identifying potential repositioning candidates.

Olgen and Kotra summarized the recent drug repurposing studies of anticancer drugs, strategies for their development. Authors focused on the discovery of anticancer agents from non-oncological drugs and their new therapeutic applications in cancer treatment [4]. Sedative drugs (thalidomide and analogues), NSAIDs (various coxibs), anticonvulsant drugs (valproic acid and derivatives), antihyperlipidemic drugs (statins), antidiabetic drugs (biguanides), antimalarial drugs (artemisinin and derivatives, romidepsin, belinostat, panobinostat, niclosamide), antiviral drugs (acyclovir, zidovudine, DDI), antifungal drugs (itraconazole, thiabendazole, rapamycin) and drugs for osteoporosis (bisphosphonates, zoledronic acid) were reviewed by highlighting the effects of chemical scaffolds in new cancer therapeutic applications. Finally, the effects of genetic differences and personalized treatments on drug repurposing studies were highlighted.

In this issue, recent advances of drug-repurposing discoveries, various methods, including computational, chemical and biological approaches for efficient drug repurposing, research directions, advantages, disadvantages, and challenges associated within this field were summarized. This issue overall provides a good overview of the state of repurposing drugs that it has been reached up to today.

REFERENCES

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