Editorial

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Drug Discovery: Computational Chemistry-Based Drug Repurposing

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Abstract

Despite increasing investments and an improved understanding of disease, the pharmaceutical industry has failed to translate these into credible therapeutic outputs. This has resulted in a need for innovative approaches like drug repurposing to treat both common and rare diseases. Some of the earliest examples of repurposing relied on serendipity and retrospective clinical experience, leading to the successful repurposing of previously failed drugs such as thalidomide and sildenafil in multiple disease conditions. However, modern repurposing approaches tap into an ever-increasing wealth of drug- and disease-related data, computationally driven hypothesis generation and high throughput screening methods for the identification of newer uses for existing drugs. This book discusses some of the most widely used approaches in drug repurposing and the major stakeholders involved; it also highlights various challenges and suggests innovative solutions to take forward. Because of the high risk, substantial cost and slow pace of new drug discovery and development, drug repurposing is becoming an attractive and economically viable strategy for identifying new indications for approved or investigational drugs. Great successes have been witnessed in recent years. Particularly, some existing drugs have shown promise for treating SARS-CoV-2 infection and are currently undergoing clinical investigation. For example, remdesivir, a drug candidate for the treatment of Ebola developed by Gilead Sciences, is currently being assessed for treating SARS-CoV-2 infection and has also received approval for emergency use in some regions of the world. Additionally, various computational methods have been used in drug repositioning, promoting the efficiency and success rates of this approach.

Introduction

This book on drug repurposing will be published whilst the global community is suffering from the impact of a once-in-a-century pandemic and there has never been a more pertinent time to shine a light on this innovative approach as we scramble for quick therapeutic solutions to treat COVID-19 and fast-track their development. It is therefore worth highlighting that several compounds predicted in silico for potential therapeutic effect in COVID-19 are already being repurposed to treat critically ill COVID-19 patients. Examples include dexamethasone which was supported by the RECOVERY trial1 and hydrocortisone which has also demonstrated efficacy in critically ill patients [1].

Repurposing Drugs as Anti-Infective Therapies

One approach to identify and provide novel treatment options rapidly is to repurpose existing drugs as agents against various epidemic viral infectious diseases. Namasivayam et al. outline antiviral drug candidates identified using drug repurposing, with their potential mechanism of action and antiviral potency. Martinez MA discussed whether drug repurposing is the best option for finding effective therapies to eradicate SARS-CoV-2 and other viral human infections. Kumar et al. discuss drug repurposing against SARS-CoV-2 using computational approaches. Among the hits identified by computational methods, 35 candidates were suggested for further development, among which ten drugs are in clinical trials for treating SARS-CoV-2 infection [2].

Ngan et al. identified preferred drug candidates from their in-house database of approved drugs found via anti-SARS-CoV-2 activity screen and the analysis of the inhibitory profiles

of the human ether-à-go-go-related gene, phospholipidosis and many cytotoxicity screens. In addition, the hERG liability of anti-SARS-CoV-2 drugs currently enrolled in clinical trials was also highlighted.

With several US FDA-approved drugs and high barriers to resistance, nucleoside analogues remain the cornerstone of antiviral therapies. Thus, Roy V. et al. summarize recently reported ribonucleoside-based inhibitors of the viral RNA-dependent RNA polymerase, which would be suitable for further development as new antiviral nucleosides.

The polymerases from HIV and HBV, sharing common architecture at their active sites, are the most common drug target for viral inhibition. Emtricitabine and lamivudine are widely used L-nucleoside drugs, targeting HIV reverse transcriptase and HBV polymerase [3]. Ruiz et al. discuss the structural details of their binding to RT (Pol)/nucleic acid and L-dNTPs. Opportunities for drug development and repurposing of L-nucleoside drugs were also reviewed.

Cyclophilin A acts as a proviral component in HCV (hepatitis C virus), coronavirus and HIV (human immunodeficiency virus), thus, its inhibitors were considered to be potential treatments for diverse viral infections. Han et al. discuss the feasibility of repurposing of cyclophilin A inhibitors as broad-spectrum antiviral agents in the context of the virus lifecycle.

In contrast with the number of newly-launched anti-infectives on the market, the rapid development of cross- or multidrug-resistant strains and the rapidly-increasing prevalence of so-called 'superbugs' are stark. Thus, Jampilek summarized the causes of antimicrobial resistance, discussed drug repurposing strategy in seeking novel anti-infective drugs.

Rising incidences and mortalities have drawn attention to Clostridioides difficile infections in recent years, which has generated a critical need for new treatments. Here, Chen et al. present a refined focus on 16 FDA-approved drugs that will be exploited for the discovery of potential anti-C difficile drugs.

Repositioning existing drugs to treat fungal diseases has gained significant attention in recent years; however, such proposed drug-repurposing compounds frequently suffer from unsatisfactory efficacy and pharmacokinetics [4]. Against this background, Donlin et al. illustrate the current antifungal drug pipeline and recent strategies to improve existing drugs into novel agents with an original mechanism of action.

Recent research reported that auranofin, an approved gold metallic drug, has robust antibacterial potency against multiple Gram-positive bacteria via inhibition of thioredoxin reductase, and has inspired further development of other gold complexes as antibacterial agents. Thus, Liu et al. discuss recent progress in the exploitation of gold complexes as antibacterial agents.

Drug Repositioning Trends in Others Diseases

Ontology-based analysis of clinical trial data revealed that drug repositioning occurs actively in rare and intractable diseases. In this respect, Sakate et al. review the current trends of ontology in rare and intractable diseases, the situation in drug development and an efficient approach to drug repositioning based on drug target gene information.

Autophagy has opposing, context-dependent roles in cancer, and interventions to both stimulate and inhibit autophagy have been proposed as cancer therapies. Bu et al. describe the application of diverse drug-repurposing methodologies in autophagy for the treatment of cancer and focus on autophagy-targeting drug repurposing to treat malignant neoplasms.

Drug repurposing has been attracting mounting attention in the hunt for potential therapeutic agents for neurodegenerative diseases, including Alzheimer's disease, Parkinson's disease, amyotrophic lateral sclerosis and Huntington disease. In this issue, Liu et al. focus on summarizing a list of repurposed drugs capable of inhibiting or eliminating toxic protein aggregates and further reviews their intricate mechanisms of action to optimize the current treatment of neurodegenerative diseases.

Stroke remains a significant cause of mortality and morbidity worldwide and drug repurposing may represent a shortcut to useful novel therapies. Ghosh et al. present an overview of approved drugs that could

be repurposed based on their efficacy and safety profiles. Their mechanisms of action were briefly discussed and many repurposed drugs under trials for ischemic stroke therapy were highlighted.

Paradoxically, the repurposing of antidepressants might represent a promising strategy for cancer treatment. Notably, three approved antidepressants have advanced into clinical trials for cancer therapy. Song et al. briefly review the anticancer molecular mechanisms of antidepressants and also discuss future directions and the challenges of repurposing antidepressants for anticancer drug discovery.

Computational Chemistry-Based Drug Repurposing

Recently, deep learning has attracted much attention for its potential in drug repositioning and target prediction. In this special issue Yu et al. focus on the basic principles of commonly used deep learning architectures and their applications in drug repositioning and target prediction and discuss possible approaches in dealing with current challenges, to promote drug repositioning [5].

Arul Murugan et al. provide an overview of various deep-learning and machine-learning-based scoring functions for solving classification and ranking problems in drug discovery. They focus on studies in which deep-learning and machine-learning models were successfully deployed to find lead compounds for which the experimental verification are available from biology assays.

Structure-based drug repurposing is a popular computational repurposing strategy. Choudhury et al. review traditional and modern AI-based in silicon methods and tools used at various steps for structure-based drug discovery pipelines. In addition, the role of generative models in generating compounds with scaffolds from repurposable chemical space was highlighted.

Drug Discovery by Repositioning Natural Products

Last but by no means has least, repurposing natural products also shown promise for novel therapeutics. Thus, Huang et al. analyze the drug repositioning of six prototypical natural products and their derivatives to expose additional drug-disease associations. Besides, challenges and opportunities in future application of natural product-based drug repositioning were also highlighted.

In recent years, with the continuous development of biochem informatics, drug repurposing has gradually developed into a data-driven innovative drug development strategy. We envision that, with the guidance of biochem informatics, more progress will be made in exploration of the chemical space of existing drugs for additional bioactivities with translational potential.

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