Current Status and Future Perspectives on Old Drug Repurposing for Cancer Treatment

New, effective anticancer drugs are urgently needed. The development of new anticancer drugs is a time- and cash-consuming procedure, mainly due to the systemic toxicity leading to the high failure rate in clinical trials. In comparison, safety and pharmacokinetic profiles of clinically used old, existing drugs are well established [1]. Therefore, repositioning old, existing drugs for new indications, such as cancer treatment, has become an attractive strategy for drug development.

This special issue of Recent Patents on Anti-Cancer Drug Discovery, entitled “Current status and future perspectives on old drug repurposing for cancer treatment: Most updated reviews on patents and literatures”, has collected 5 comprehensive review articles, all of which are timely, novel, and written by authors who are experts in mentioned research fields. Each article has reviewed the history, literature and patents of indicated old drugs, summarized their known mechanisms of action, cellular targets and previous preclinical and clinical results, and offered strategies for using them as repurposed anticancer agents.

Fong, Christensen and Chan extensively reviewed literature and patents of several indicated repurposed drugs targeting Cancer Stem Cells (CSCs) [2]. The highlighted drugs acting against CSCs include those approved for the treatment of diabetes (metformin & thiazolidinediones), parasitic diseases (chloroquine, niclosamide, mebendazole & pyrvinium), psychotic disorders (thioridazine, clomipramine & phenothiazines), alcoholism (disulfiram), lipid disorder (statins), inflammatory diseases (triamter, auranofin, acetaminophen & celecoxib), antibiotics (azithromycin), and other disorders. Current research findings advocate the existence of beneficial effects by a combination of these repurposed drugs or through their complementary use with conventional cancer therapies. The authors believe that repurposing FDA-approved medications towards cancer care, by targeting the resistant CSCs, will allow for a quicker, cheaper development and approval process, and a larger drug library available to physicians will allow for increased efficacy during both first-line and recurrent cancer treatments.

Yadav and Safari discussed the recent patent-based perspective of drug repositioning on diagnostic and therapeutic interventions in Malignant Mesothelioma (MM) [3]. By searching the databases, the authors found 72 active patents related to diagnosis and therapy in the field of MM, which can be classified into eight broad categories. Of these, maximum 17 patents were attributed to immunotherapy and 13 attributed to “Drug Repositioning” and “Biological / synthetic” based candidates. A relatively low number of patents accounts for gene signature (7), epigenetics (3) and microRNA (2) based diagnosis and therapy. The remaining 17 patents were distributed amongst virotherapy and various miscellaneous categories. Clinical trial-based investigation revealed the futuristic impact of listed patents in MM patient management. Interestingly, immunotherapy and “drug repositioning” based therapy are the front-runners in the race to provide relief. This review article has provided an overview of patient-based advancement in the field of MM, which might become apex in the clinical settings in the future.

The next comprehensive review by Fong and To focuses on the molecular mechanisms, clinical evaluation and recent patents of Chloroquine (CQ) analogs in cancer therapy [4]. CQ analogs have been reported to elicit their anticancer effects by modulating autophagy, inducing apoptosis, eliminating cancer stem cells, normalizing tumor vasculature and modulating anti-tumor immunity. As documented by recent patents and clinical trials, CQ analogs have been repurposed as an adjuvant therapy and combined with other anticancer agents for synergistic enhancement of treatment efficacy. However, most clinical trials on CQ only demonstrated modest improvement in anticancer efficacy. Given that CQ loses its anticancer activity in acidic and hypoxic environment within a tumor, novel CQ analogs and/or their formulations are under active investigation to improve their physicochemical properties and biological activity. On the other hand, identification of new biomarkers for better patient selection has been advocated in future trials in order to realize the repurposing of CQ analogs for cancer treatment in a personalized manner.

Huang and Huang’s review article discussed repositioning the fungicide Ciclopirox (CPX) for cancer treatment [5]. Pharmacological and toxicological profiles from preclinical and clinical studies support that systemic administration of CPX and its derivatives is feasible and safe for cancer treatment. CPX exerts its anticancer activity by inhibiting cell proliferation, inducing apoptosis, suppressing cell migration and invasion, and inhibiting angiogenesis and lymphangiogenesis. Mechanistically, CPX impacts the expression or activities of multiple signaling molecules or pathways, such as ribonucleotide reductase, Myc, DJ-1, Wnt/β-catenin, DOHH/elF5A/PEAK1, VEGFR-3/ERK1/2, ATR/Chkl/Cdc25A, and AMPK/TSC/mTORC1. Most of these effects are attributed to iron chelation by CPX. Five CPX-related patents have been retrieved: four of them on the development of CPX produgs to improve the water solubility and bioavailability of CPX, and one patent on the methods of bladder cancer treatment with CPX, CPX-0, or a CPX prodruk. The authors suggest that CPX has a great potential to be repositioned for cancer therapy.

Finally, Dou, Ahmed and colleagues reviewed metformin literature and patents and its potential repurposing for cancer therapy [6]. Metformin acts as an antitumor agent, displaying a wide variety of anticancer properties. These properties appear to synergize with existing chemotherapeutics, allowing for a reduction in dosage without losing potency and minimizing adverse effects. Selected metformin-related patents claim various combination therapies, delivery methods, and uses for cancer therapy, displaying an increasing interest in metformin’s anticancer properties. The authors pointed out that, preclinical research, along
with early phase clinical trials, has demonstrated anticancer effects of metformin on a variety of cancers, offering great promise for improving patient prognosis. However, there is a significant lack of late phase clinical trials, specifically, those regarding nondiabetic cancer patients, and further research in this area is required.

Compared to typical drug discovery and development, old drug repurposing has both advantages and disadvantages [7]. The advantages of drug repositioning include previously well-known pharmacokinetics and pharmacodynamics in patients; fast drug development cycle; economical, efficient translation from bench to bedside; and easy to get clinical approval. The limitations of drug reposition include low target specificity and off-target effects. Further well-designed preclinical and clinical studies are warranted in the future.

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