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Review Article

Unlocking therapeutic potential: integration of drug repurposing and immunotherapy for various disease targeting

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Abstract: Drug repurposing, also known as drug repositioning, entails the application of pre-approved or formerly assessed drugs having potentially functional therapeutic amalgams for curing various disorders or disease conditions distinctive from their original remedial indication. It has surfaced as a substitute for the development of drugs for treating cancer, cardiovascular diseases, neurodegenerative disorders, and various infectious diseases like Covid-19. Although the earlier lines of findings in this area were serendipitous, recent advancements are based on patient centered approaches following systematic, translational, drug targeting practices that explore pathophysiological ailment mechanisms. The presence of definite information and numerous records with respect to beneficial properties, harmfulness, and pharmacologic characteristics of repurposed drugs increase the chances of approval in the clinical trial stages. The last few years have showcased the successful emergence of repurposed drug immunotherapy in treating various diseases. In this light, the present review emphasises on incorporation of drug repositioning with Immunotherapy targeted for several disorders.

Keywords: Cancer, infectious disease, Covid-19, cardiovascular diseases, drug discovery, drug repurposing, immunotherapy

Introduction

In highly competitive therapeutic and pharmaceutical industrial settings, drug repurposing immunotherapies are favored over the "de novo" approaches of drug discovery [1]. Drug repurposing is an approach which involves finding new indications for pre-existing, FDA approved, endorsed, vastly characterized medications used in different medical, experimental, or clinical backdrops [2]. These drugs could also be known to be failures in original indications but could hold a potential in curing various atypical and multifaceted terminal diseases depending on their structural as well as functional characteristics (**Figure 1**). The advancement of novel or new drugs is estimated to take approximately 15-20 years costing a valuation of USD ~3-5 billion to create and launch a drug into the market [3]. On the other hand, repurposed drugs are preapproved in terms of certified formulations, safety and preclinical examinations, with known pharmacokinetic reports from the primary stages of clinical tests. As a result, it is a more practical and efficient option with a reduced risk of failure [4].

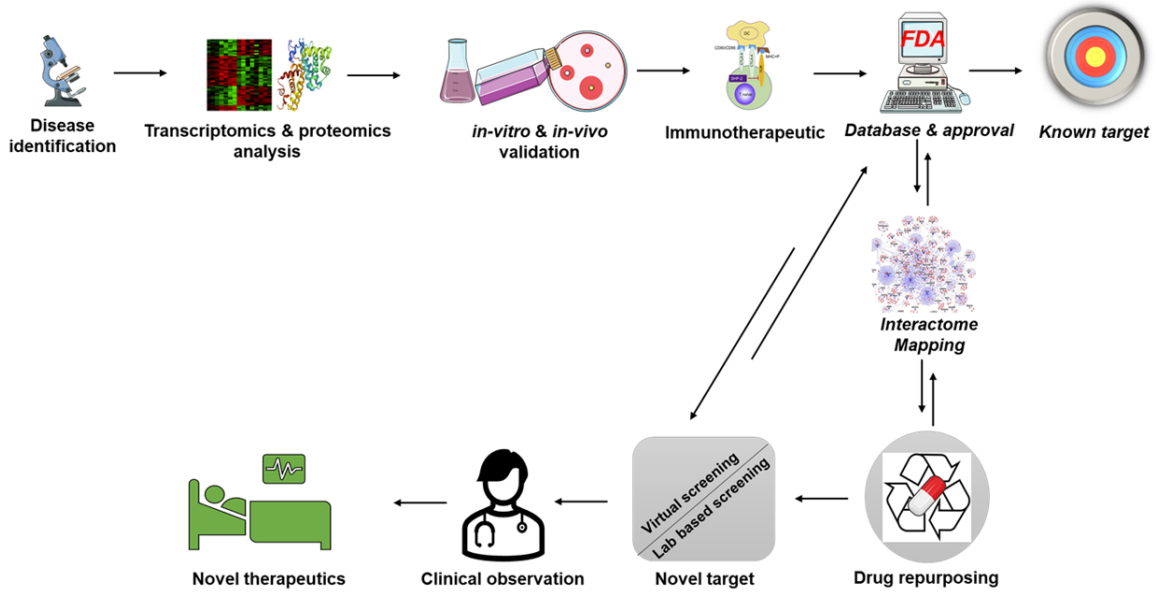

Figure 1. Drug repurposing strategy. This figure was created using the Servier Medical Art Commons Attribution 3.0 Unported Licence (http://smart.servier.com).

Many repurposed drugs were identified by a cause of unanticipated and serendipitous encounters. One of the well-known candidates is OnabotulinumtoxinA (BOTOX®; Allergan) which has eight distinctive sanctioned indications [5]. An unsuccessful chemotherapy drug, known as azidothymidine, worked well in curing human immunodeficiency virus [6]. With each passing year, a search for swifter, cost-effective and novel techniques is rising in the drug discovery and development sector. It demands advances in large data depositories and allied investigative techniques. This has gained attention in developing orderly approaches to drug repositioning. Diverse pioneering translational bioinformatics-based methods are empowering systematic repurposing screenings [7]. A research team has invented a progressive, commanding, and state-of-the-art artificial intelligence (AI) and network medicine technology that can accelerate remedial expansion [8]. The present review describes some of the main methodologies in drug repurposing immunotherapy, the means of successful applications of existing compounds to new symptoms, and their-benefits to the society as well as the pharmaceutical industry.

Repurposing immunotherapy in cancer

One of the most advanced treatments in the cancer field is immunotherapy which aids the immune system to fight the disease [9]. The immune system which is composed of white blood cells and tissues of the lymphatic system identify and fight against cancer [10]. However, a dynamic microenvironment of malignant cells makes them unrecognizable and hides them from immune cells [11, 12]. The M2 vs M1 macrophage recruitment paradigm executes a crucial function in tumor succession [13, 14]. Conventional immunotherapy involved the use of remedies that either improved the cell's defense mechanism against cancer or inhibited the tumor's efficacy to disguise the antigens in the system [15]. In 1972, the very first case of drug repurposing was reported for treating leukemia with the help of a hypertoxic Arsenic trioxide which was used in traditional chinese medicine [16, 17]. A drug previously used for morning sickness, the Thalidomide along with its analogues like thalidomide, lenalidomide and pomalidomide are repurposed for treating multiple myeloma [18, 19]. Many clinical trials involving engineered T cells, natural killer (NK) cells, Adoptive cell therapy etc. have exhibited promising outcomes in a variety of malignant conditions [20-22]. However, the restrictions involved in these approaches open the room for improvement in terms of efficiency, cost effectiveness and time consumption. These limitations could be resolved by combining the repurposing of drugs with immunotherapy. It would not only decrease the expense and

necessity of trial or testing but would also reduce the time that accompanies novel drug research [23]. Lately, numerous in silico advances and high-performance assessment techniques have been established to assist drug repurposing practice [24, 25]. Based on the structure-activity relationship (SAR), various drugs have been evaluated to explore analogous clinical indications using electronic tools like Protein Data Bank and DrugPredict etc. [26-29]. Databases like the Library of Integrated Ntework-based Cellular Signatures are efficient in classifying drugs amongst similar transcriptional signatures for drug repositioning [30]. Human transcriptome and interactome data were combined in a recent study that took a network medicine strategy to screening diagnostic and prognostic biomarkers and exploring medication repurposing in human cancer [31]. One report presented a wide-ranging graphic analytics tool, ClinOmicsTrailbc, which examines epigenomics and transcriptomics datasets to distinguish as well as assess the tumor mutational burden, and biomarkers etc. [32]. The user-friendly databases like repoDB and repurposeDB combine data about clinical consequences of drug repurposing [33-35].

The immune checkpoint inhibitors (ICIs) are monoclonal antibodies that block receptors like TIM-3, cytotoxic T-lymphocyte-associated protein 4 (CTLA-4), LAG-3, programmed cell death-1 receptor (PD-1R) or anti-PD-L1 [36]. This augment T-cell activity, stemming an expansion in antineoplastic immunity which leads to demolition and eradication of tumor cells [37]. However, eventually, these immunotherapeutic means failed to control the disease due to the acquired resistance in cancer patients. When repositioned drugs were combined with ICIs, a remarkable improvement was observed with respect to antitumor immunity. For example, Metformin, a type 2 diabetes drug was reported to escalate CTL levels by destabilizing and misbalancing membrane localization of PD-L1 by triggring AMP-activated protein kinase (AMPK) and thereby inducing ER-associated protein degradation (ERAD) via S195 phosphorylation of PD-L1 [38]. Li et al. (2020) executed calcium flux blockade by Amlodipine which activate PD-L1 degradation and stimulated antitumor immunity. Cytokines, the ~30 KDa glycoprotein or polypeptide signaling molecules are paracrine facilitators [39]. Their pro-apoptotic and cytotoxic properties have been explored in cancer research as prospective drugs in combination with advanced immunotherapies to revitalize the immune system against cancer succession [40]. Mansurov et al., inactivated the immunotoxic properties of IL-12 by modifying its conformation using tumor-protease-cleavable linker [41]. Lately, studies have categorized novel T cell adapting remedies by phenotypical assessment of chemical libraries [42, 43]. Marro et al., reported ingenol mebutate, a compound identified from a chemical library created on ReFRAME drug-repurposing collection, that expanded the endurance of wearied CD8+ T cells and provided immunity against LCMV infection and suppressed tumor progression inside the B16 sarcoma model [44]. These repurposed drugs possess the capacity to exhibit synergy with existing checkpoint-blockade immunotherapies.

In the tumor microenvironment (TME), the tumor puts the immune cells under metabolic stress by modulating the metabolic networks for its progression. Therefore, reprogramming the TME by means of drug repurposing may increase the efficiency of cancer immunotherapy [45]. Numerous examples of efficacious drug repurposing for Cancer immunotherapy are summarized in **Table 1**.

The Warburg effect postulates that cancer cells gain energy more efficiently via glycolysis than oxidative phosphorylation. This rises lactic acid levels and makes the pH of TME acidic and heightens immunosuppressive properties of TME by preventing the propagation of CTLs [13, 46]. Lactate dehydrogenase (LDH), an enzyme involved in the glycolytic conversion of pyruvate to lactate, can be inhibited to slow tumor growth. Although, galloflavin was shown to disable LDH, it was also found to decrease interferon gamma (IFN-γ) levels by T-cells. In a glioma model, diclofenac an non-steroidal anti-inflammatory drug (NSAID) was reported to decrease the acidic levels of TME and obstruct cancer proliferation [47]. Inhibiting the PI3-KeAKTemTOR network was found to downregulate the glycolysis. Amino acid metabolism stimulates the tumor's growth as well as endurance with the help of building block synthesis, a decline in oxidative stress, and immune circum-

Table 1. Drug repurposing cases for treating malignant systems

Sr No.	Original indication	Name of the Drug	Repurposing immunotherapy used for treating type of cancer	Mode of action	Reference
1	Bone remodeling	Denosumab	Melanoma	M1 macrophage activation T-cell activation Production of nuclear factor kappa B Dendritic cell survival and function	[23, 157]
2	Antibiotic	Doxycycline	Breast cancer	Suppression of stem cell marker Inhibition of Autophagy	[158, 159]
		Tigecycline	Ovarian cancer/Myeloid leukemia	Inhibition of mitochondrial translation Suppression of MYC, HIFs, PI3K/AKT or AMPK-mediated mTOR, cytoplasmic p21 CIP1/Waf1, and Wnt/β-catenin signaling	[160]
3	Viral Infection	Ritonavir	Ovarian cancer/Melanoma	AKT signaling Suppression Apoptosis	[161]
4	Antiretroviral Drug-HIV-1 integrase (IN) inhibitor	L-870810	Cancer	Cytotoxicity Blocking oncogenic kinases	[162, 163]
5	Anti-neurodegenerative agent	Benserazide	Colon cancer Melanoma	Suppression of M2 splice isoform of pyruvate kinase (PKM2)	[164, 165]
		Riluzole	Pancreatic Cancer	Suppressing the Wnt-β-catenin pathway	[166]
6	Anti-bacterial agent	Ciprofloxacin	Colon cancer	Reversal of MDR	[17, 167]
7	Fungal infection	Enilconazole	Colorectal cancer	Suppression of PI3K/AKT pathways	[168]
8	Malaria	Chloroquine	Glioblastoma	Autophagy inhibition Reduction of tumor hypoxia	[169]
9	Antipsychotic drugs	Chlorpromazine	Glioblastoma	Inhibition of cytochrome c oxidase	[170]
		Risperidone	Colorectal Cancer	Apoptosis Anti-proliferative activity	[171]
10	Antidepressants	All-trans retinoic acid (ATRA)	Acute myeloid leukemia	Suppression of PKCβ, MEK/ERK and Akt activity	[172]
11	Cardiovascular Prevention/ antihypertensive drug	Losartan	Ovarian cancer	Apoptosis Decrease in fibroblast infiltration Lower expression of collagen (Col)-I (Col)-III Lower expression of alpha smooth muscle actin (Acta2)	[173]
		Enalapril	Colorectal cancer	Activation of nuclear factor-κB (NF-κB) signaling proteins Upregulation of vascular endothelial growth factor (VEGF) expression Anti-proliferative activity Apoptosis	[174]
		Valsartan	Gastric cancer	Regulation of PI3K/AKT Pathways	[175, 176]
		Telmisartan	Lung cancer/Gastric cancer	Induction of apoptosis Inhibition of cadherin-mediated activation FGFR signaling Inhibition of the PI3K/AKT pathway	[177]

	Irbesartan	Prostate cancer	Renin-angiotensin blockade	[176]
	Benazepril	Esophageal carcinoma	Inhibition of Ki-67 nuclear protein Inhibition of angiogenesis	[178]
	Digoxin	Prostate cancer	Inhibition of VEGF Inhibition of angiogenesis	[179]
	Fluvastatin	Breast cancer Renal cancer endometrial cancer (EC) Lung adenocarcinoma	Expression of Sirtuin 6 (SIRT6) Activation of mTOR pathway Endoplasmic reticulum (ER) stress leading to aggresome formation Anti-proliferative activity Apoptosis	[180, 181]
	Propranolol	Malignant Melanoma	Suppression of ERK/Cyclin D1/Rb/Cyclin E pathway Stimulation of G0/G1/S phase arrest	[182]
Anti-inflammatory drugs	Ibuprofen	Gastric cancer	Apoptosis Inhibition of cell proliferation Inhibition of cyclooxygenase	[183, 184]

Abbreviations: MYC, MYC Proto-Oncogene; HIF, Hypoxia-inducible factor; PI3K, phosphoinositide 3-kinases; AMPK, AMP-activated protein kinase; mTOR, Mammalian target of rapamycin; p21 CIP1/Waf1, cyclin-dependent kinase inhibitor p21; Wnt, Wingless-Type; Akt, Ak strain transforming; PK, pyruvate kinase; MDR, Multidrug resistance; PKCβ, Protein kinase C-β; ERK, Extracellular signal-regulated kinase; MEK, Mitogen-activated protein kinase kinase MEK; Col, collagen; Acta, alpha smooth muscle actin; NF-κB, nuclear factor-κB; VEGF, vascular endothelial growth factor; FGFR, fibroblast growth factor receptor; SIRT6, Sirtuin 6; ER, Endoplasmic reticulum.

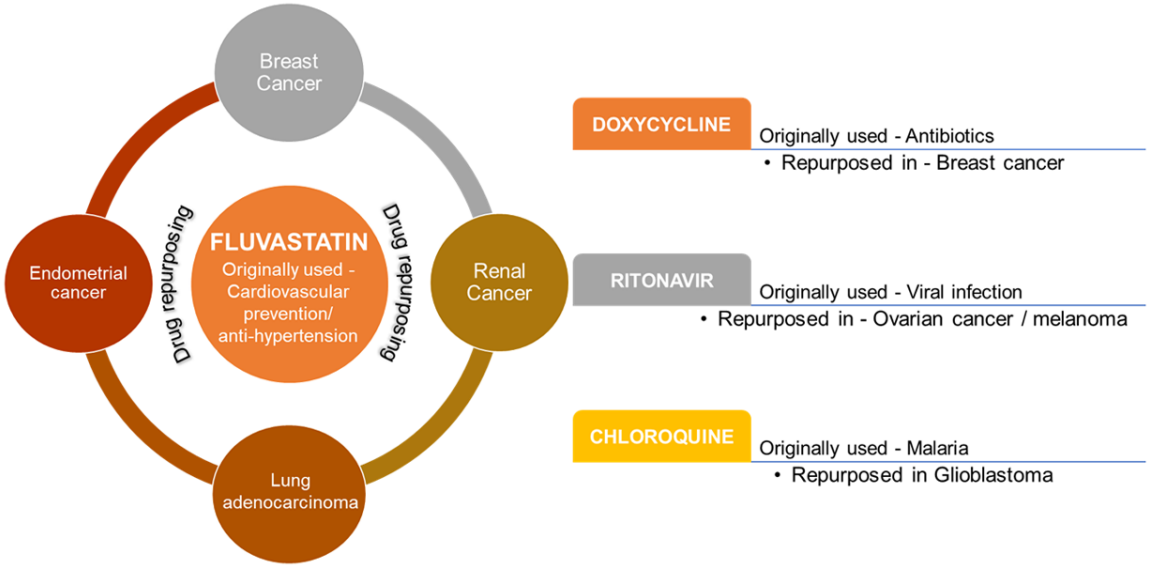

Figure 2. Schematic illustration of drugs that have been used to treat various malignancies.

vention provokment [48]. Therefore, inhibition of indoleamine 2,3-dioxygenase (IDO), an enzyme responsible for the breakdown of tryptophan was found to be effective in augmenting antitumor immunity of the subjects in liver cancer [49, 50]. In this regard, Imatinib was also reported to enhance antitumor immunity by activation of effector T cells. Leone et al., reported expansion of antitumor activity of T cells upon using glutamine antagonist 6-diazo-5-oxo-L-norleucin (DON) or its prodrug JHU-083 as a treatment for cancer therapy which supported tumor suppression [51]. Byun et al., also reported a synergic effect of Glutamine inhibition with ICI in supporting immunity against cancer [52]. Many studies have that adoptive T cell therapies are proven to be efficient in cancer treatment involving anti-CD19 chimeric antigen receptor (CAR) T cells and TILs. Many reviews have provided excellent information on these powerful treatment alternatives [53-55].

Oncolytic viruses were shown to work as an antigen-agnostic vaccine for various cancer conditions within the TME by activating innate immunity involving macrophages, dendritic cells, and NK cells [56]. As a response, OV-infected tumor cells get demolished. The expansion and accumulation of activated T cells within the TME results in elimination of cancer cells. Vijayakumar et al., showed the efficient synergy of Newcastle disease (ND) virus expressing anti-CTLA4 single chain variable fragment (scFv) with radiotherapy for boosting immune cell activity against murine melanoma [57]. Shekarian et al., provided a preclinical validation in support of intramural-attenuated rotavirus to prevent resistance towards immune checkpoint immunotherapies in pediatric cancers by expressing double-stranded RNA receptor retinoic acid-induced gene-I (RIG-I) [58]. In this regard, many advanced approaches are being explored to treat numerous cancer conditions [56, 59-61]. Nanoparticle (NP)-centered drug transport schemes are being explored intensively for attaining targeted delivery of several antineoplastic mediators, counting small molecule drugs, monoclonal antibodies, DNAs, and siRNAs to the cancer sites [23]. Kadiyala et al., showed efficacy of a synthetic high-density lipoprotein nanodiscs for chemo-immunotherapy for treating glioblastoma [62]. Feng et al., evalutaed the efficiency of a prodrug nanoparticle in shunting the cancer proliferation and blocking metastasis in murine models of the breast as well as 4 colorectal cancer [63]. **Figure 2** exhibits a schematic illustration of a few drugs that have been used to treat various malignancies.

Repurposing immunotherapy in cardiovascular diseases

Despite the development of novel therapeutics and medical innovations, cardiovascular dis-

eases (CVD) continue to rank higher as a major contributor to the mortality index of the world. Drug repurposing can play a pivotal role to improve the treatment regime for the selection of the best drugs without or with minimum side effects. While the success rate of generating a new molecular entity is only 2.01%, the field of drug repurposing is gaining popularity [64], and the number of approved drugs has declined in the past three decades. In the pharmaceutical sector, drug repurposing accounts for roughly one-third of approvals over the past decade. It is considered as a direct application of polypharmacology where one drug molecules target multiple genes/proteins or disease pathway.

Initially, atherosclerosis was considered as an accumulation of lipoprotein in the arterial wall. With the advancement in decoding the disease pathophysiology, the role of inflammation was also recognized equally in cardiovascular diseases [65, 66]. Inflammation is mediated by pro-inflammatory cytokines, chemokines, lipids, and adhesion molecules [67-69]. Fernandez-Gutierrez et al., highlighted the relevance between CVD and inflammation and suggested that the occurrences of inflammatory diseases like systemic lupus erythematous, arthritis, and psoriasis increase the risk of CVD [70]. Thus, a treatment involving the blockade of the inflammatory cytokines could hold a potential of health improvements in CVD patients, clinically [71] and the immunomodulatory effects of ketogenic diet reduces inflammation in various immune disorders including CVDs [72]. Pro-inflammatory cytokines include IL-1, IL-6, IL-18, and tumour necrosis factor (TNF), while IL-1R antagonists, IL-10, IL-19, and IL-33 antagonize inflammation [73]. Inflammation and disturbed immune system evokes occurrences of CVD and others. The increased level of inflammation is a challenge to clinicians as it predisposes an individual towards developing end organ comorbidities. Activated lymphocytes and monocytes run towards the endothelium, which penetrates the arterial wall and thus induce atherogesesis [74]. The healing of injury induced by the above cytokines favours the formation of atherosclerotic plaques which further increase the risk of plaque rupturing and may result in thromboembolic events [75]. Moreover, the availability of monoclonal antibody-based immunotherapies targeting pro-atherogenic cytokines paves a path to address the role of immunotherapy in CVD [76].

Interestingly, cancer and heart failure interact with each other in a bidirectional way [77, 78]. It has been studied by Armenian et al., that 89% of lung cancer patients possess high risk of developing atherosclerosis [79]. In fact, the low grade inflammation is associated with the release of TNF-α, interlukin (IL)-1β, IL-6 and IFN-γ which increase the risk of heart disease. Anti-TNF-α therapy (Infliximab, Adalimumab, Certolizumab etc.) was associated with a reduced risk of all cardiovascular events [80]. Canakinumab (anti-IL-1), and Toclizumab (anti-IL-6) are the candidate of choice as immunotherapeutic agents to manage the inflammatory status. Canakinumab Anti-Inflmmatory Thrombosis Outcome Study (CANTOS) trial is one of the largest trials in the series of anti-cytokine immunotherapy which hints the roles of inflammation in triggering both CVD and cancer. The mature B lymphocytes are involved in the mobilization of inflammatory monocytes in the heart which leads to the declined heart function [81]. Rituximab was the first monoclonal antibody approved for cancer patients. It was developed in the form of anti-CD20 molecules [82] that caused depletion in normal and malignant B cells. Many studies are supporting CAR-T cell therapy as an interesting therapeutic option for treating several malignancies with respect to its anti-imflammatory effects on various functions of the heart [83]. Tocilizumab, a monoclonal antibody targeting IL-6 receptors used for the treatment in RA was found equally effective in myocardial injury [84]. Another monoclonal anti-IL-17 antibody, secukinumab, has been approved to treat arthritis and psoriasis, and it has been shown to improve myocardial function parameters like the global longitudinal strain rate during early diastole and left ventricular twisting, as well as the coronary flow reserve and pulse wave velocity.

The above facts strongly highlighted the key role of inflammation in the onset and progression of CVDs. However, the knowledge about the side effects of anti-inflammatory drugs limits the possibility to see their potential role in the cardiovascular field. With the support of various medical evidence, drug repurposing could be considered as a powerful strategy that offers a great hope in the treatment regime of

the cardiac ailments within a clinically attainable safety range.

Repurposing immunotherapy in infectious disease

Infectious diseases continuously pose a significant burden to human health with a high rate of morbidity and mortality and are considered globally in the top 10 in mortality rate [85]. Globally, it is estimated that every third death results from an infectious disease and is predicted to acquire the highest contributor of mortality by the year 2050. The outspread of infectious diseases was majorly caused by viruses, bacteria, fungi, and protozoans which augmented weaker immunity. The WHO's annual data estimated 300-500 million people infected with malaria, over 330 million with sexually transmitted diseases, 33 million cases of HIV/AIDS, and 14 million with tuberculosis. A recent survey carried out by the national sample survey organization (NSSO) estimated that over 30% of people in India are suffering from infectious diseases [86]. The prevalence of acute and chronic infectious diseases has been further challenging to mitigate after rapidly evolving resistance against frontline clinical therapies and most of the conventional treatments seem to be ineffective to work. The most recent, Covid-19 pandemic infection outbreak with higher morbidity and mortality rate throughout the different continents of the world, and no standalone therapy is available even today [87]. It is a serious concern to search for various strategies to resist such ailments. Much attention has been drawn to repurposing the existing therapies and drugs. Collectively, immunotherapies can be defined as the collection of treatments which able to boost the human immune system in such a precise way to promptly fight against infectious diseases. It is well-stated that infectious pathogens are not able to clear up, and remain present in the host when immunity gets weakened. Immunotherapy treatment can potentiate immune responses that will help to eradicate pathogens and fight against threats. Mechanistically, immunotherapy can either be passive which synthesizes ex-vivo and injected in the host for protection. In contrast, active immunotherapy induces immunological memories in the host using active effectors or virulence factors. Over a period, different immunotherapies have been investigated and tested to mitigate several infectious diseases. Immunomodulatory molecules, cell therapies, Monoclonal antibodies, and vaccines are such prominent examples of immunotherapy that have been successfully employed against infectious diseases. For a long time, vaccines symbolize the foremost immunotherapy used to protect hosts against different diseases. The success of the vaccine lies in an immunization program of vaccine run over a decade which has successfully eradicated polio and smallpox, as devastating diseases from India. Henceforth the research on vaccines has been shifted last few decades to find out their new activities (repurposed) against different infectious diseases. Some of the prominent examples of vaccines have been repurposed for the protection of infectious diseases. The promising BCG vaccine is a formulation of live attenuated Mycobacterium bovis. It is a standalone vaccine for the treatment of tuberculosis over the last 100 years. The efficacy of BCG was also repurposed for the treatment of non-muscular bladder cancer and melanoma. However, BCG has emerged as an adjuvant to cancer treatment without any successful completion of clinical trials.

The long-term phase-3 trial of the BCG vaccine was carried out on colon cancer patients and showed a promising result in overall survival when it was injected as an adjuvant after surgery [88, 89]. Linezolid, marketed under the brand name Zyvox, is an antibiotic from the first generation. It works by blocking the production of proteins in bacteria. When bound to bacterial ribosomes, it prevents the production of functional 70S ribosomes and slows down the translation process [90, 91]. In the past, linezolid was only used to treat infections caused by gram-positive bacteria like *Staphylococcus aureus*. Despite showing excellent antibacterial capabilities, linezolid's usage against drug-resistant tuberculosis (DR-TB) is time-limited due to its neurological adverse effects [90]. Both Moxifloxacin and Gatifloxacin are fourth-generation antibiotics derived from fluroquinolone class of medicines. The major purpose of these medicines is to limit the enzymatic activity of DNA gyrases and topoisomerase-IV, therefore preventing the replication of DNA in bacteria and other microorganisms [92, 93]. It was first approved for use against skin and stomach germs, but its encouraging effect led experts to conclude that it was also a safe candidate for treating tuberculosis [94]. While

clofazimine's approval [95] is limited to treating leprosy, the antibiotic's antibacterial anti-inflammatory characteristics have been found to be highly effective in combating multidrug-resistant and extensively drug-resistant tuberculosis [96]. Similar to how the antibacterial drugs sanfetrinem cilexetil, spectinamide, meropenem, and faropenem were initially developed to treat various bacterial infections, they were later found to have a novel role against tuberculosis [97-99].

The Diptheria vaccine contains inactivated toxins that potentially protect the host from *Corynebacterium diphtheriae* infections. Different trials of the diphtheria vaccine combined with the tetanus vaccine (Td) have been found to induce immunogenic responses against the brain, prostate, pancreas, liver, breast, or lung cancer. Similarly, the influenza vaccine was reported to show antitumor activity if administered without adding any adjuvant against tumors on intratumoral administration. However, the Human Papillomavirus vaccine is formulated by viral-like particles (VLPs) of major capsid protein (L-1) effectively preventing Human Papillomavirus (HPV) infection and providing protection from cervical cancer [100]. The clinical trials of the HPV vaccine administered with sintilimab (anti-PD-1) showed promising results to prevent pre-cancerous anal or vulvar lesions. The 17D-204 strain of the yellow fever virus is transfected into a chicken embryo for preparation of yellow fever vaccine, used for the protection of travellers from this virus that transmits through a mosquito bite. The yellow fever vaccine also suppresses tumor progression in human and mouse cell lines via T-cell-mediated cell immunity [88]. In a recent study, the cancer approved drug Bruton's tyrosine kinase (BTK) [101] inhibitor known as ibrutinib has been repurposed for the treatment of COVID-19 infection that promisingly reduces inflammation in the lungs. The use of ibrutinib is approved for clinical trials after receiving promising results against Covid-19 infections [102].

Repurposing immunotherapy in COVID-19 for targeting inflammatory pathway in disease progression

SARS-CoV-2, the new beta coronavirus responsible for the recent global public health disaster known as COVID-19, causes severe illness and millions of people have lost their lives due to COVID-19 infection. Acute respiratory distress syndrome (ARDS) is the most notable clinical symptom of COVID-19 infection among severely infected patients. Many of the extrapulmonary symptoms of COVID-19 are believed to have their origins in rapid virus replication and severe inflammatory response in the lung. Numerous tissues and nearly all bodily fluids have yielded SARS-Co-2 RNA [103]. Extrapulmonary involvement and systemic inflammatory symptoms are hallmarks of COVID-19, which can ultimately cause multiorgan failure and death [104, 105]. Intriguingly, hospitalized patients with spiked inflammatory cytokines and persistent lung injury even after SARS-CoV-2 is under control or eradicated [105].

Immunotherapy refers to the use of medications comprised of immune cells or antibodies to modulate the immune system to treat SARS-CoV-2 infection and it is a relatively novel strategy to treat various cancers and infectious diseases [106, 107]. Though, the toxicity outline of these treatment strategy, such as constrain in using CAR-T cells, despite the fact that immunotherapy has shown outstanding responses in patients with malignancies [108]. Cytokine storm, also known as cytokine release syndrome, is a potentially fatal consequence of immunotherapy that manifests with fever, hypotension, and respiratory failure alongside increased cytokine and inflammatory markers [109]. In the years following immunotherapy, many medications have proven effective in treating cytokine release syndrome, and numerous serologic markers are now accessible for both diagnosis and therapy response monitoring. It is possible that the pathophysiologic mechanisms underlying systemic symptoms of COVID-19 and toxicity after immunotherapy are identical. Therefore, immunotherapy may have an important role in COVID-19 treatment. Here in **Table 2**, we have summerized available immunotherapeutic targets for COVID-19.

SARS-CoV-2 causes acute lung inflammation

SARS-CoV-2 detects ACE2 on respiratory epithelial cells. Spike protein mediates viral adherence and ACE2 recognition [110]. Most COVID-19 patients hospitalized had pneumonia or ARDS, viral replication in the respiratory tract might migrate to the lower respiratory tract and produce pneumonia [111]. Fewer, low oxygen saturation, shortness of breathing and dry cough are early SARS-CoV-2 lung symptoms,

Table 2. Overview of available immunotherapeutic targets for COVID-19

Sr No.	Target	Immunotherapeutic role	Available drugs	Intervention	Role of COVID-19	Recommendation	Overall Conclusion	Reference
1	IL-6	Elevated in cytokine restoration syndrome during CAR-T treatment	Tocilizumab Sarilumab Otilimab	anti-IL-6	Elevated with severity of diseases	Recommended for sever respiratory disease in combination of Dexamethasone	Beneficial	[185-187]
2	JAK/STAT	Steroid refractory GVHD	Baricitinib Ruxolitinib Tofacitinib Imatinib	Jak kinase activate after interleukin stimulation	Interleukin receptor activation	Recommended for progressive ARDS in combination of Remdesivir	Partial beneficial	[188-190]
3	IL-1R	IL-1R inhibition to reduce inflammation and slower tissue damage	Anakinra Canakinumab	anti-IL-1	IL-1b elevated during COVID-19	Radiologically and PCR confirm sever hospitalize patients	Beneficial	[191-193]
4	IFN-γ	IFN blocker in familiar hemophagocytic lymphohistiocytosis	Emapalumab	anti-IFN-γ	Reduced inflammation	Radiologically and PCR confirm sever hospitalize patients	Partial beneficial	[194-196]
5	TNF-α	Inflammation suppression in autoimmune diseases	Infliximab Adalimumab	anti-TNF-α	Hyperactive immune status	Radiologically and PCR confirm sever hospitalize patients	Partial beneficial	[197, 198]
6	Complement C5a	Hyperactivated during transplant associated thrombotic microangiopathy	Vilobelimab	anti-C5a	Anti-inflammatory effect and improved PaO_2/FiO_2	Radiologically and PCR confirm sever hospitalize patients	No significant effect	[199-201]
7	Spike protein of SARS-CoV-2	---	Bamlanivimab Casirivimab	anti-spike protein mAb	Change is log viral load	Patients with mild to moderate severity	Beneficial	[202, 203]

Abbreviations: IL, Interleukin; CAR-T, Chimeric antigen receptor; JAK/STAT, Janus kinase/signal transducers and activators of transcription; ARDS, Acute respiratory distress syndrome; GVHD, Graft-versus-host disease; IFN-γ, Interferon gamma; TNF-α, Tumor necrosis factor alpha; SARS-CoV-2, Severe acute respiratory syndrome coronavirus 2; mAb, monoclonal antibody.

also 20% to 33% of patients need ICU hospitalization [112-114]. The most common histologic finding is diffuse alveolar injury, which damages the blood-air contact and causes inflammation and mucosal thickening during acute infection. Patients receiving mABs aiming TME by fetching PD-1 and CTLA4 receptors called checkpoint inhibitors (CPIs), to reverse cancer-induced T-cell anergy have similar pathophysiology (30546008). CPI, notably nivolumab, can cause severe inflammatory interstitial pneumonitis that resembles COVID-19 lung involvement [115]. PD-1-positive T cells may regulate pulmonary dendritic cells and macrophages in CPI-related pneumonitis [116]. CPI-related pneumonitis and COVID-19 pulmonary symptoms shares PD-1 and toll-like receptors (TLRs) mechanism. TLR stimulation on CD8+ T cells lowers PD-1 expression and SARS-Co-2 spike protein binds to TLR and stimulates inflammatory cytokines [117, 118].

Endothelial impairment and systemic inflammation in COVID-19 and immunotherapy

COVID-19 patients observed with activated complement cascade that causes microvascular damage, thrombosis in the circulatory system, and intravenous catheters causes morbidity and mortality in COVID-19 patients [119-121]. ACE2-expressing endothelial cells in arteries and veins throughout the body may explain SARS-tropism CoV-2's to renal, cardiac, and gastrointestinal organs outside the respiratory tract [122]. SARS-CoV-2 invades lung endothelial cells and is crucial to pneumonitis worsening and spreading to other organs. Endothelialitis can block fibrinolysis, stimulate the complement system, and cause microthrombi and microvascular dysfunction [123]. Thus, histopathology shows neutrophil extracellular traps, fibrin deposition, and/or microthrombi [124]. Many proinflammatory cytokines activate the coagulation system, making COVID-19 procoagulant. Acute inflammatory conditions were associated with high levels of tumor TNF-α, IL-6, and IL-1 and hypercoagulability, occasionally leading to diffuse intravascular coagulation [125, 126]. A prelimilinary investigation recommends that SARS-CoV-2 directly promotes platelet adhesion and aggregation [127, 128]. Thus, COVID-19 and post-CAT-T associated toxicity share endothelial involvement. Hay et al., showed that endothelial activation was associated with cytokine release syndrome and elevated levels of circulating endothelial-derived factors such as Von Willebrand and angiotensin-2 (28924019). SARS-CoV-2 may inhibit the host interferon response and downregulate major histocompatibility complex class I (MSC-I) molecules on many cells during early infection [129-131]. This prevents immune detection and slows viral clearance. COVID-19's induced lymphopenia may cause uncontrolled viral replication [132].

IL-6, IL-1b, and TNF-α were considerably raised in severe COVID-19 patients and caused cytokine release syndrome, according to recent meta-analyses [133]. IL-6 has a key function in autoimmune disorders and is considered as a major proinflammatory cytokine, it affects IL-6R expressing cells like T cells, B cells, monocytes, and hepatocytes [134, 135]. Multiple viral infections require IL-6, although the main source of IL-6 during COVID-19 remians unclear, upon IL-6R binding on the surface of target cells, intercellular signal leads to the activation of JAC/STAT3 axis [136]. Post-CAR-T therapy cytokine release syndrome has extremely elevated serum IL-6 levels [137]. In CAR-T-associated cytokine syndrome, release of IL-1 tends to precede that of IL-6; consequently, targeting IL-1 might attenuate or prevent cytokine release syndrome [138]. mABs (rituximab) and the bispecific antibody blinatumomab also produced IL-6 in B cell malignancies [139, 140]. IL-6 concentrations correlated with pulmonary disease severity in 69 hospitalized SARS-CoV-2 patients, while IL-2 and IL-4 did not [141]. In conclusion, SARS-CoV-2 shares the rise of IL-6 with cytokines release syndrome due to CAR-T infusion and has an inflammatory profile more similar to other related cytokine release syndrome than other systemic inflammation.

Potential immunotherapeutic repurposing for COVID-19

Immunotherapy has the potential to treat COVID-19 by either eliminating the infected cells themselves or modulating the inflammatory responses that result in cytokines response syndrome. Treatment using SARS-CoV-2 specific T cells has not been documented in any investigations so far. T cell clones from recovering patients were used to prevent or treat SARS-CoV-2 infection in immunocompro-

mised after bone marrow transplantation [142]. T cells with engineered tumor-recognizing T cell receptors can steer the immune system to target antigen (TCR). TCR-rngineered T cells have shown promise in acute myeloid leukemia, melanoma esophageal cancer, synovial sarcoma, and Wilms tumor [143]. Most clinical trials tolerated ex vivo expanded TCR-modified cell infusion. TCR-engineered T cells against SARS-CoV-2 antigen have been studied and may have similar downsides as CAR-T cells.

NK cells, part of the innate immune system are crucial to immunological surveillance and can be employed as adoptive immunotherapy [144]. Engineered CAR-NK cells may treat cancer, allogeneic NK cells from cord blood can be safely delivered without comprehensive human leukocyte antigen matching or CAR product customization [145]. Few in-vitro studies show, CAR-NK cells target anti-SARS-CoV-2 infected cells and show high efficacy in to abolishing them [146-148]. Mesenchymal stromal cells (MSCs) are a heterogeneous population of stromal cells that migrate to specific tissue in the setting of remodelling and regeneration. In some haematological malignancies, they immunomodulate the TME and increase local tumor aggressiveness [149, 150]. Engineered MSCs to hyperexpress IFN-γ and injected tumor tissue [151, 152]. MSC cell treatment is intriguing for targeting many inflammatory patterns. Many COVID-19 clinical trials use MSC from autologous or allogenic adipose tissue, dental pulp, bone marrow, or cord blood Wharton's jelly.

Neutralizing antibodies can target SARS-CoV-2 spike protein to prevent virus-cell interaction and restrict SARS-CoV-2 from circulation. Several stabilized SARS-CoV-2 spike protein vaccines have shown potential efficacy in eliciting a protein-specific antibody response with an acceptable rate of anomalies [153, 154]. In a recent randomized experiment, volunteered pooled plasma from recovered SARS-CoV-2 patients are proved to be helpful if administered within 72 hours of symptom start [155, 156]. This approach is restricted by donor availability, allergic reaction safety, and blood-derived products. Conversely, B cell-produced non-neutralizing antibodies may accelerate SARS-CoV-2 infection through antibody-dependent augmentation and worsening organ damage.

Inflammation is the hallmark of COVID-19, a disease brought on by a virus. Global vaccination against SARS-CoV-2 is the best hope for the pandemic. Vaccines for both high- and low-risk populations are becoming increasingly accessible thanks to their recent approval in several nations. Treatment of individuals with COVID-19 may benefit from immunotherapeutic techniques that control the immune system, since these may help to reduce viral replication and stop the cascade of inflammatory processes triggered by SARS-CoV-2. Few immune-modulating effective against COVID-19 so far. The FDA-approved REGN-COV2 mAb combination is for newly infected COVID-19 and ARDS patients with limited symptoms and a high risk of deteriorating. Hospitalized patients are recommended for baricitinib, an anti-JAK medication, along with remdesivir. Tocilizumab and dexamethasone are now recommended for fast-progressing respiratory illness. Besides ruxolitinib and anakinra, other anti-IL6 drugs like sarilumab have shown promising outcomes, many clinical trials are testing cell therapy and inhibition of such defibrotide and eculizumab. If patients are classified by cytokines implicated in the COVID-19 inflammatory process, we may be able to learn more about the efficacy of the above drugs in specific subgroups.

Future perspective and conclusion

The ever increasing burden of the diseases in the present scenario warranted the need for the development of the quick and effective therapies to control the human diseases. The role of the immune response in the diverse diseases have been well established which makes the targeting of the immune system as an alternative tool for targeting the disease. Drug repurposing using immunotherapy could provide a quick and effective therapy against the diseases. In the recent years, several drugs have been repurposed either alone or in combination and have been found to be effective. Rigorous efforts in the drug repurposing may lead to the emergence of successful therapies against different diseases. Despite the development of the artificial intelligence and machine learning based drug designing, there are still road blocks which hinders and delays the human use. For this reason, drug repurposing provides the advantage over the AI designed drugs. In the near future, drug repurposing

could develop into a cost effective and quick method for the diverse diseases. Further research is required to ensure the safety and efficacy of the patients with repurposed drugs. Overall, the future of the repurposing of the immunotherapy is promising.

Disclosure of conflict of interest

None.

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