Naunyn-Schmiedeberg's Archives of Pharmacology
https://doi.org/10.1007/s00210-022-02263-x

REVIEW

Drug repurposing—an emerging strategy in cancer therapeutics

Khadija Shahab Turabi[1] · Ankita Deshmukh[1] · Sayan Paul[2] · Dayanand Swami[1] · Shafina Siddiqui[1] · Urwashi Kumar[1] · Shreelekha Naikar[1] · Shine Devarajan[1] · Soumya Basu[3] · Manash K. Paul[4] · Jyotirmoi Aich[1]

Received: 15 May 2022 / Accepted: 3 June 2022

Abstract

Cancer is a complex disease affecting millions of people around the world. Despite advances in surgical and radiation therapy, chemotherapy continues to be an important therapeutic option for the treatment of cancer. The current treatment is expensive and has several side effects. Also, over time, cancer cells develop resistance to chemotherapy, due to which there is a demand for new drugs. Drug repurposing is a novel approach that focuses on finding new applications for the old clinically approved drugs. Current advances in the high-dimensional multiomics landscape, especially proteomics, genomics, and computational omics-data analysis, have facilitated drug repurposing. The drug repurposing approach provides cheaper, effective, and safe drugs with fewer side effects and fastens the process of drug development. The review further delineates each repurposed drug's original indication and mechanism of action in cancer. Along with this, the article also provides insight upon artificial intelligence and its application in drug repurposing. Clinical trials are vital for determining medication safety and effectiveness, and hence the clinical studies for each repurposed medicine in cancer, including their stages, status, and National Clinical Trial (NCT) identification, are reported in this review article. Various emerging evidences imply that repurposing drugs is critical for the faster and more affordable discovery of anti-cancerous drugs, and the advent of artificial intelligence-based computational tools can accelerate the translational cancer-targeting pipeline.

Keywords Cancer · Drug repurposing · Antibacterial drugs (antibiotics) · COX inhibitor (NSAIDs) · Metformin · HMG-CoA reductase inhibitors (statins) · Artificial Intelligence

Khadija Shahab Turabi and Ankita Deshmukh have equal contribution

Key points
1. Drug repurposing is a novel approach that can be implemented in oncology to find new applications for the old clinically approved drugs in cancer therapeutics.
2. Targeting critical mechanisms of cancer using repurposed drugs can be a prominent strategy in cancer treatment.
3. Advances in artificial intelligence and technology-based approaches may improve the discovery and use of repurposed drugs to target cancer.

✉ Manash K. Paul
manashp@ucla.edu

✉ Jyotirmoi Aich
jyoti.aich@gmail.com

[1] School of Biotechnology and Bioinformatics, DY Patil Deemed to Be University, CBD Belapur, Navi Mumbai, Maharashtra 400614, India

[2] Centre for Cardiovascular Biology and Disease, Institute for Stem Cell Science and Regenerative Medicine (inStem), Bangalore 560065, India

[3] Cancer and Translational Research Centre, Dr. D. Y. Patil Biotechnology & Bioinformatics Institute, Dr. D. Y. Patil Vidyapeeth, Pune, Maharashtra 411033, India

[4] Division of Pulmonary and Critical Care Medicine, David Geffen School of Medicine, University of California Los Angeles, Los Angeles, CA 90095, USA

Introduction

Cancer is a severe global health threat escalating in incidence and fatality. Cancer risk factors frequency and distribution are many and multifaceted, including aging, environmental pollution, and tobacco consumption and are closely linked to socioeconomic developmental status (Sawant and Shegokar 2014). In 2018, around 18 million

Published online: 13 June 2022

new cases of cancer were reported worldwide, with around 9.6 million cancer-related mortality. The World Health Organization (WHO) has estimated that these figures will nearly double by 2040 (Bray et al. 2018). As per the WHO statistics, the cancer condition led to nearly 10 million deaths in 2020. These alarming statistics suggest that we need to have more effective cancer management strategies, with special attention to cancer diagnosis and treatment.

In recent years, various therapies such as surgery, chemotherapy, radiation therapy, targeted therapy, and immunotherapy emerged to treat cancer. Surgery is the primary treatment for all solid cancers. To destroy tumor cells, high-frequency radiation such as X-rays, gamma radiation, and charged particles are administered in radiation therapy (Wang et al. 2018). The main drawback of surgery and radiation therapy is that they can only treat the tumor confined to a particular site. With the advancement in modern therapy, chemotherapy and targeted therapy are used to kill the metastatic tumor cells that migrated to distant sites in the body. However, cancer treatment has faced significant challenges in recent years due to acquired resistance and toxic side effects (Barzaman et al. 2020). Although many drugs are available for cancer treatment, the cancer cells evolve resistance to these drugs, resulting in treatment failure and cancer recurrence (Mansoori et al. 2017). Apart from drug resistance, drugs used for chemotherapy have several adverse side effects in patients. As the incidence of cancer is increasing, there is a need to develop new drugs with an improved safety profile. However, the development of new anti-cancer drugs has slowed down, as there are a relatively lesser number of drugs that are able to pass through the clinical trials compared to the non-cancer drugs (Pantziarka et al. 2014). The time taken for trials, safety evaluation, subsequent review, and approval is humongous for new drugs and further adds to the poor global cancer management.

Traditionally, drug development occurs in three stages: discovery, preclinical trials, and clinical trials (Hobbs et al. 2019). The first step usually involves the identification and validation of cancer target, followed by lead compound screening and optimization. The preclinical trial involves both in vitro and in vivo studies and provides information about the drug's efficacy, toxicity, pharmacokinetics, and pharmacodynamics properties. Finally, during the clinical trial stage, the medication is put to the test on individuals in a sequence of trials to see how it affects them (Sleire et al. 2017). Traditional drug development is time-consuming, as it would take 10–15 years for the new drug to come into the market (Parvathaneni et al. 2019). Also, the cost of developing a new drug can be as high as US$2.6 billion (DiMasi et al. 2016). Given the high cost and that only less than 25% of pharmaceuticals under research make it to market, it is financially problematic. Therefore, we require an alternative for a faster drug approval process to improve cancer management.

Drug repurposing (DR), also known as Drug Repositioning, is one of the most widely used methods that identify new applications for existing drugs (Corsello et al. 2017). This strategy aims to considerably reduce the cost and research time (Sleire et al. 2017). Compared to traditional drug discovery and development, DR is efficient, cost-effective, and less risky (Xue et al. 2018). Using the repurposed drugs that have already been tested on humans gives a preexisting cognizance of the pharmacokinetics, pharmacodynamics, dose, metabolic profiles, molecular pathways of the drugs, the mode of actions of the drug, different target interactions, etc. Thus, less research will be required to examine drug pharmacokinetic characteristics and toxicity profiles. Some of the most prominent examples of DR include sildenafil, aspirin, minoxidil, valproic acid, etc. Sildenafil, commonly known as Viagra, was initially developed as a hypertensive to treat hypertension and angina pectoris. However, during the phase II clinical trials, it was found that sildenafil caused penile erections. Hence, it was repurposed to treat erectile dysfunction (Shim and Liu 2014). In the present era, development in drugs, diseases, and bioinformatics knowledge is presenting innovative ways to design a novel DR approach through a comprehensive understanding of drug information (Katsila et al. 2016).

The primary objective of this article is to identify drugs that are currently being administered for purposes apart from cancer treatment. We aim to evaluate their underlying mechanisms of action and properties, which may make them suitable to be repurposed as cancer therapeutics (Fig. 1). This review article also includes the clinical trial status of repurposed drugs, which are currently being focused upon for the treatment of various cancer types (Table 1). We believe that this review article will enable a broader comprehension of repurposed drugs for cancer, based on their mechanism of action and effect on cancer.

Drugs targeting tumor invasion and metastasis

According to Hanahan and Weinberg, cancer metastasis is one of the dominant features of cancer (Hanahan and Weinberg 2011). Cancer is defined by uncontrolled cellular growth and the ability to spread to other body parts (Gandalovičová et al. 2017). Therefore, it is important to identify drugs that prevent the cancer cells from penetrating the extracellular matrix (ECM) and forming secondary metastatic tumors, which should be used in conjunction with cancer treatment (Balkwill and Mantovani 2001).

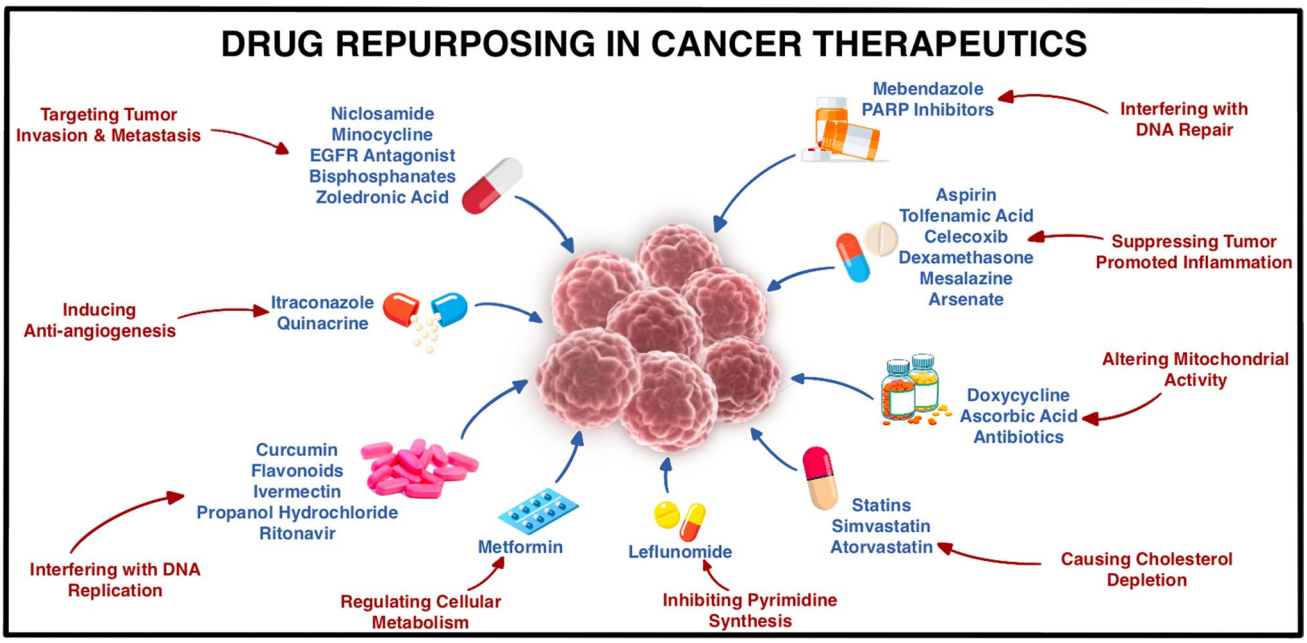

Fig. 1 Summary of the various mechanisms of action targeted by non-oncology drugs in cancer cells making them potential drug candidates in cancer therapeutics

Niclosamide

Niclosamide belongs to the anti-helminthic family of medicines, and this compound is utilized to treat tapeworm infections. However, studies have stated that niclosamide has clinical applications in colorectal cancer (CRC) (Chen et al. 2018). The anti-cancer activity of this drug is exhibited in CRC cells by inhibiting the pathways associated with multiplication, motility, and invasion, such as the Wnt/β-catenin pathway (Burock et al. 2018). Niclosamide degrades the components of the Wnt/β-catenin signaling via autophagy, thereby inhibiting this pathway. Phase II clinical trial is being conducted to test the anti-cancer functions of niclosamide (Newton 2019). Apart from CRC, the anti-neoplastic activity of niclosamide has also been reported in prostate cancer. Usually, it blocks continuously expressed androgen receptor variants (AR-Vs) and/or inhibits drug resistance pathways (Wnt signaling) (Fleming et al. 2013). Unlike other drugs, it contains multiple targets like the NF-κB, Wnt/β-catenin, Notch, and mTORC1, which enhances cancer development and progression.

Minocycline

Minocycline, a broad-spectrum, non-synthetic tetracycline (antibacterial drug) derivative, was used for treating prostate cancer. Its properties, other than toxicity to several microorganisms, were applied against disorders like Dermatitis, Periodontitis, Autoimmune diseases, and various cancer types like breast, prostate, myeloma, colorectal, and pancreatic, to name a few (Turanli et al. 2018; Madsen and Bugge 2015). It slows down cancer metastases by suppressing the action of extracellular-matrix degrading enzymes, specifically matrix metalloproteinases (MMPs), and the synthesis of proinflammatory cytokines (Turanli et al. 2018; Madsen and Bugge 2015). Several studies have highlighted the therapeutic role of MMPs in cancer invasion and metastases, as it degrades the already existing extracellular matrix of normal cells and replaces it with the matrix of the cancer cells needed for their growth and proliferation (Turanli et al. 2018; Madsen and Bugge 2015).

EGFR antagonist

Receptor-specific compounds, for example, an EGFR antagonist, have shown promising antitumor effects on several cancers. Cetuximab, being one of the class and approved drugs for head, neck cancer, and CRC, has been investigated in pancreatic cancer studies as well. Cetuximab acts by attaching to the extracellular domain of EGFR and preventing the binding of ligands which enables the activation of tyrosine kinase (Ciardiello and Tortora 2008). Therefore, it can successfully prevent autophosphorylation, which in turn initiates rapid cell proliferation and inhibition of apoptosis, which inevitably results in tumor invasion and metastasis (Ciardiello and Tortora 2008).

Table 1 Repurposed drugs currently being tested to treat different types of cancers and their clinical trial status

Drug	Original indication	Cancer type	Mechanism of action	NCT identifier	Phase	Status	Ref
Metformin	Type 2 diabetes mellitus	Lung	Pleiotropic effects on glucose metabolism (AMPK, mTOR, PI3K inhibitor)	NCT01578551 NCT01717482 NCT02186847 NCT03071705 NCT02115464 NCT03086733	II II II II II II	Completed Active Active Recruiting Recruiting Recruiting	Fatehi Hassanabad (2019)
		Breast	Insulin sensitizer	NCT01650506	I	Completed	Bayraktar et al. (2012)
		Colorectal	AMPK pathway is activated, and the mTOR pathway is suppressed	NCT01941953	II	Completed	Gong et al. (2014)
		Pancreatic	Inhibits IGF and mTOR signaling along with disturbing mitochondrial respiration	NCT01167738	II	Terminated (concern of detrimental effect)	Gong et al. (2014); Tomic et al. (2011); Elwood et al. (2009)
		Gastric	Prevents development via inhibition of the HIF1α/PKM2 signaling pathway	NCT04214990	III	Recruiting	Zhou et al. (2017)
		Skin	Inhibition of mTOR and NF-κB signaling pathway Caspase 3 activation Activation of p53 tumor suppressor protein and AMPK pathway	NCT01988831	II	Suspended (due to financial reasons)	Tomic et al. (2011); Elwood et al. (2009)
Itraconazole	Anti-fungal agent	Lung	Lanosterol 14α-demethylase inhibitor	NCT02357836	I	Completed	Tseng et al. (2013)
		Prostate	Inhibits hedgehog pathway and prevents angiogenesis	NCT00887458	II	Completed	Turanli et al. (2018); Pounds et al. (2017); Armando et al. (2020)
		Ovarian	Inhibits lanosterol 14-α-demethylase	NCT03081702	I/II	Completed	Tsubamoto et al. (2017)
		Skin	Inhibition of Hedgehog, PI3K/mTOR, and Wnt signaling pathways	NCT02735356	II	Completed	Tsubamoto et al. (2014)
Simvastatin	Cardiovascular risk reduction and Lipid-lowering medication	Lung	HMG-CoA reductase inhibitor	NCT03891615	I	Recruiting	Pedersen and Tobert (2004)
		Colorectal	Enhanced cellular oxidative stress and endoplasmic reticulum stress. Altered apoptosis and proliferative signaling. Inhibition of autophagy	NCT01238094	III	Unknown	Lochhead and Chan (2013); Lim et al. (2015)
		Ovarian	Inhibits HMG-CoA reductase	NCT04457089	I (early)	Recruiting	Li and Zhou (2018)

Table 1 (continued)

Drug	Original indication	Cancer type	Mechanism of action	NCT identifier	Phase	Status	Ref
Aspirin	Cox inhibitor analgesic (NSAID)	Colorectal	Inhibits COX-2 and suppresses PI3K signaling pathway	NCT00565708	III	Recruiting	Ali et al. (2011); Nowak-Sliwinska et al. (2019)
		Prostate	Inhibits pathways involving/not involving COX	NCT00316927	III	Completed	Joshi et al. (2021)
		Gastric	Lowers the production of prostaglandins	NCT04214990	III	Recruiting	Li et al. (2020); Niikura et al. (2020)
		Skin	Inhibition of COX enzymes	NCT01988831	II	Suspended (due to financial reasons)	Goodman and Grossman (2014)
Celecoxib	Antipyretic, analgesic, and cardiovascular risk reduction	Lung	Inhibition of COX-2	NCT00020878 NCT00030407 NCT00055978	II II II	Completed Completed Completed	Arora et al. (2018)
		Breast	Inhibition of COX-2	NCT02429427	III	Completed	Harris et al. (2006)
		Gastric	Alters E-cadherin, VEGF, and COX-2 expression	NCT04033107	II	Recruiting	Jin et al. (2016)
		Skin	Inhibition of COX-2	NCT00023621	II	Completed	Elmets et al. (2014); Kismet et al. (2004); Tang et al. (2010)
Atorvastatin	Coronary heart disease	Breast	Inhibits HMG CoA reductase	NCT02958852	II	Recruiting	Nielsen et al. (2012)
Leflunomide	Arthritis	Breast	Inhibits dihydroorotase dehydrogenase	NCT03709446	I/II	Recruiting	Van Roon et al. (2004)
Zoledronic acid	Osteoporosis	Breast	Inhibits tumor invasion and metastasis	NCT00171314	III	Completed	Ottewell et al. (2008)
Doxycycline	Respiratory, urinary tract, ophthalmic infection	Breast	Inhibits mitochondrial biogenesis	NCT01847976	II	Completed	Scatena et al. (2018; Lin et al. (2018)
Mebendazole	Parasitic infection	Breast	Inhibits tubulin polymerization	NCT03774472	I/II	Recruiting	Wang et al. (2016a, b)
		Colorectal	Tubulin disruption and VEGFR-2-mediated anti-angiogenesis	NCT03925662	III	Recruiting	Guerini et al. (2019)
Ritonavir	Anti-retroviral	Breast	Triggers cell cycle arrest at G1 phase	NCT01009437	I	Completed	Kumar et al. (2009)
Niclosamide	Anti- helminthic agent	Colorectal	Targets Wnt/β-catenin and other intracellular signaling pathways	NCT02519582	II	Unknown	Newton (2019)
		Prostate	Blocks ARVs and/or suppresses Wnt signaling pathway	NCT02532114 NCT03123978	I I	Completed Recruiting	(Fleming et al. (2013)

Table 1 (continued)

Drug	Original indication	Cancer type	Mechanism of action	NCT identifier	Phase	Status	Ref
Mesalazine	Ulcerative colitis and Crohn's disease	Colorectal	Wnt/β-catenin pathway inhibition and EGFR is suppressed	NCT02077777	II	Completed	Nowak-Sliwinska et al. (2019); Parenti et al. (2010)
Artesunate	Treating malarial infection	Colorectal	Suppression of NF-κB and Wnt/β-catenin mechanisms	NCT03093129	II	Recruiting	Augustin et al. (2020)
Curcumin C3 tablet	Powerful anti-inflammatory	Colorectal	Blocks NF-κB activates the caspase of PARP cleavage and suppresses COX-2	NCT01333917	I	Completed	Park and Conteas (2010); Chen et al. (2015)
Dexamethasone	Glucocorticoid	Prostate	Inhibits ERG pathway	NCT00316927	III	Completed	Adamo and Ladomery (2016)
Minocycline	Antibacterial (antibiotic)	Prostate	Reduces action of MMPs and cytokines	NCT02928692	III	Recruiting	Turanli et al. (2018); Madsen and Bugge (2015)
Quinacrine	Anti-malarial agent	Prostate	DNA intercalation, autophagy induction, prevention of angiogenesis, cell cycle arrest	NCT00417274	II	Completed	Zhang et al. (2020); Bryant et al. (2019); Oien et al. (2021)
Olaparib	Inhibitor of PARP	Pancreatic	Prevents tumor cells from repairing damaged DNA	NCT02677038	III	Active, Not recruiting	Singh et al. (2021); Gupta et al. (2019)
Rucaparib	Inhibitor of PARP	Pancreatic	Prevents tumor cells from repairing damaged DNA	NCT03140670	II	Active, Not recruiting	Singh et al. (2021); Gupta et al. (2019)
Niraparib	Inhibitor of PARP	Pancreatic	Prevents tumor cells from repairing damaged DNA	NCT03553004	II	Recruiting	Singh et al. (2021); Gupta et al. (2019)
Propranolol + Etodolac	Anti-hypertensive agent (propranolol), analgesic (etodolac)	Pancreatic	Block stress and inflammatory pathways	NCT01167738	II	Terminated	Bustamante et al. (2019; Wrobel and Le Gal (2015)
Propranolol Hydrochloride	High blood pressure	Skin	Enhanced TP53 signaling pathway Decreased VEGF production	NCT01988831	II	Suspended (due to financial reasons)	Bustamante et al. (2019); Wrobel and Le Gal (2015)
Tolfenamic acid	Analgesic	Pancreatic	Prevents the transcription of oncogene receptors	NCT02159248	I	Withdrawn	Rebelo et al. (2021); Sankpal et al. (2017)
Cetuximab	EGFR antagonist	Pancreatic	Inhibits EGFR	NCT00075686	III	Completed	Ciardiello and Tortora (2008)
Ivermectin	Anti-parasitic	Ovarian	Suppress cell proliferation and block cell cycle progression	NCT02366884	II	Recruiting	Li and Zhan (2020) , Liu et al. (2020)
Ascorbic acid	Treat and prevent scurvy	Skin	Increased expression of caspase-3 and caspase-9	NCT04279535	I	Completed	Chen et al. (2019)

Bisphosphonates

Bisphosphonates are medications used to control and cure osteoporosis in postmenopausal females. Bisphosphonates reduce osteoclast activity and thus act as inhibitors of osteoporosis (Zhang et al. 2018; Hirata et al. 2006). Bisphosphonates block the activity of farnesyl pyrophosphate synthase, which is involved in the synthesis of farnesol and geranylgeraniol. These compounds are important for maintaining osteoclast function, and hence, there is a reduction in osteoclast activity. Thus, bisphosphonates are expected to exhibit anti-cancer properties against different types of cancer. Bisphosphonates have been demonstrated to decrease the development of ovarian cancer, by suppressing tumorigenesis (Kobayashi et al. 2019).

Zoledronic acid

Zoledronic acid is bisphosphonate having a nitrogen and suppresses osteoclastic bone breakdown by blocking the activity of farnesyl-diphosphate synthase within the mevalonate pathway and protein lipidation (Aft et al. 2010). Although the main target of nitrogen-containing bisphosphonates is the osteoclast, recent studies have suggested the direct antitumor effects of bisphosphonate in the in vitro models, such as preventing tumor growth and stimulating cancer cell death, inhibiting cancer cell adhesion and invasion, and anti-angiogenesis (Ottewell et al. 2008). Similarly, anti-cancer effects of zoledronic acid are suggested for in vivo models of different types of cancers such as multiple myeloma, osteosarcoma, breast, prostate, leukemia, and lymphoma (Croucher et al. 2003; Michigami et al. 2002).

Drugs targeting tumor-promoted inflammation

Chronic inflammation is associated with cancer and is known to induce cellular proliferation, angiogenesis, and metastasis (Balkwill and Mantovani 2001). Tumor and inflammatory cells exhibit phenotypic resemblance in their early stages because they produce cytokines, chemokines, and their receptors (Zappavigna et al. 2020). These mediators then lead to mutations in cells due to their constant secretion, which causes tissue and DNA damage (Zappavigna et al. 2020). Furthermore, this creates an inflammatory microenvironment, contributing to cancer development (Zappavigna et al. 2020). Thus, anti-inflammatory drugs like COX inhibitors or non-steroidal anti-inflammatory drugs (NSAIDs) identified through DR may be utilized to inhibit tumor progression and effectively treat cancer.

Nonsteroidal anti-inflammatory drugs (COX inhibitors)

Due to their antipyretic, analgesic, and anti-inflammatory effects, COX inhibitors (NSAIDs) are recommended to treat fever, pain, and inflammation (Thun et al. 2002). These drugs exhibit anti-inflammatory properties, and they are known to inhibit prostaglandin synthesis by blocking the enzyme cyclooxygenase (COX) (Abou-Issa and Alshafie 2004). Several clinical trials and epidemiologic studies have reported the potent chemo-preventive activity exerted by COX inhibitor (NSAIDs) (Kim et al. 2017; PubChem Apricoxib (n.d.)). COX inhibitors (NSAIDs), specifically the cyclooxygenase (COX)-2 inhibitors, have shown potential as anti-cancer drugs in various experimental, epidemiologic, and clinical trials. Apart from their anti-inflammatory responses, the NSAIDs are also known to trigger apoptosis, antagonize the angiogenesis process, and induce cellular immune responses (Xu et al. 2016).

Recent preclinical studies have suggested that non-aspirin COX inhibitors (NSAIDs) have more potent anti-cancer activity than aspirin in ovarian cancer (Xin et al. 2007; Nagaraj et al. 2018). Aspirin acts against cancer by inhibiting COX1 and COX2, whereas non-aspirin COX inhibitors (NSAIDs) inhibit COX-2 and suppress inflammation. COX-2 expression is observed to be increased in malignant tumors and considered to be a reason for poor outcome and resistance to anti-cancer therapy (Verdoodt et al. 2018). COX inhibitor (NSAIDs) also suppresses estrogen biosynthesis and thus can serve as an ovarian anti-cancer agent because evidence shows that estrogen plays a role in ovarian carcinogenesis (Gharwan et al. 2015; Mørch et al. 2012). As a precautionary note, various COX inhibitor (NSAID)-based studies also indicate an increased risk of specific cancers, especially at old age, and suffer from potential side effects.

Aspirin

Aspirin (acetylsalicylic acid) is a COX inhibitor (NSAIDs) prescribed to reduce fever, pain, or inflammation. People at high risk of further heart attacks, blood clots, and ischemic strokes may prevent further complications by long-term aspirin use (Awtry and Loscalzo 2000). The studies indicate that aspirin at a low dose decreases the risk of various cancers, including colorectal, gastric, ovarian, lung, and skin cancer (Ye et al. 2019; Guo et al. 2021). The mechanism of action exhibited by aspirin in CRC is by inhibiting COX-2, which downregulates the signaling activity of phosphatidylinositol 3-kinase (PI3K), which is seen to participate in cancer development. A study reported that the inhibition of metastasis and survival rate could be improved by inhibiting the platelet-derived signals that are important for the c-Myc upregulation when aspirin was administered at antiplatelet

doses. Therefore, the CRC-related deaths are lowered by using aspirin, and also clinical trials are being conducted for a deeper understanding of aspirin's role in CRC (Ali et al. 2011; Nowak-Sliwinska et al. 2019).

Aspirin is known to reduce gastric cancer development as well as induce apoptosis due to its anti-inflammatory, antipyretic, and antiplatelet properties and inhibits angiogenesis. The inhibition of angiogenesis and tumor apoptosis induced by activated NF-κB significantly reduced its incidence (Li et al. 2020; Niikura et al. 2020). A recent study has revealed the anti-cancer effect of aspirin in melanoma. In melanoma, prostaglandins have a crucial role in metastasis, angiogenesis, proliferation, migration, and invasion, and therefore, its production is decreased by inhibiting the COX enzymes. In the domain of the enzymatic active site, the N-terminal serine residue is acetylated, and therefore, COX activity is irreversibly inhibited by aspirin (Goodman and Grossman 2014). Caution may be practiced while taking aspirin as high frequency, and doses are associated with other cancers like prostate and lung (Wang et al. 2021).

Tolfenamic acid

Tolfenamic acid has been studied extensively for prophylaxis in preclinical pancreatic cancer models (Rebelo et al. 2021; Sankpal et al. 2017). It prevents the disease by destroying a transcription factor, specificity protein 1 (Sp1), and suppressing the expression of cMet, VEGF, and Survivin (Rebelo et al. 2021; Sankpal et al. 2017).

Celecoxib

Celecoxib, a powerful anti-inflammatory, and specific COX-2 inhibitor, was licensed to treat conditions such as osteoarthritis and rheumatoid arthritis. The medication was easily accepted and showed no signs of digestive or kidney damage when taken orally. Multiple second-stage clinical trials suggested that inhibiting COX-2 with celecoxib will improve susceptibility to cytotoxic chemotherapy and radiotherapy by interfering with proliferation and angiogenesis, boosting cell death, and immunological monitoring, or by other mechanisms (Arora et al. 2018). In lung cancer and numerous tumors depending on COX-2-related processes for development and sustainability, celecoxib has demonstrated promising antitumor activity (Arora et al. 2018).

Several preclinical studies suggest that celecoxib can be used as a chemo-preventive agent in breast cancer. Animal model studies of breast cancer suggest reducing incidence, proliferation, and tumor volume when treated with celecoxib. In addition, it also prevents metastasis in the brain and lung (Jin et al. 2016).

Similarly, in gastric cancer, it suppresses the invasion by altering the expression of elements like E-cadherin, vascular endothelial growth factor (VEGF), and COX-2, which promotes changes in several pathways like nuclear factor-κB (NF-κB) signaling (Jin et al. 2016). However, the mode of action of celecoxib is unclear and requires further study.

Various studies have indicated that COX-2 expression is upregulated in skin cancer cells, and for its treatment and prevention, COX-2 might be the target (Elmets et al. 2014). Further report has also demonstrated the topical use of celecoxib to prevent skin cancer. Therefore, celecoxib has an anti-cancer effect on skin cancer, and a clinical trial has been conducted to prevent basal cell carcinoma (BCC) by celecoxib (Kismet et al. 2004; Tang et al. 2010).

Dexamethasone

Dexamethasone, which has been initially used to treat allergic, inflammatory, or respiratory disorders, has been tested on prostate tumors, which mediates its effect by blocking ERG (ETS Related Gene) activity. ERG is one of the most overexpressed genes in prostate cancer and plays an essential role in cancer progression from localized to metastatic (Adamo and Ladomery 2016). Besides, dexamethasone is a well-known analgesic and anti-inflammatory agent for fever, cold, headache, or other pain-related issues. It works by inhibiting both COX-dependent and independent pathways to suppress the synthesis of metabolites, thereby reducing pain and inflammation (Turanli et al. 2018; Joshi et al. 2021).

Mesalazine

Mesalazine, also known as mesalamine, belongs to the amino salicylate class of drugs. This medication is used to treat ulcerative colitis, and it also helps reduce the swelling in the colon (Adamo and Ladomery 2016). Several studies reported that mesalamine had reduced the survival and growth of CRC cells, and further, it is stated that cell growth of CRC can also be inhibited via COX-2-dependent and independent mechanisms. One of the major targets of mesalazine in CRC cells is the Wnt/β-catenin pathway that is overexpressed. The repurposed drug inhibits this pathway and relies on elevated phosphate group addition to the N-terminal of β-catenin. Another important target for the drug is the epidermal growth factor receptor (EGFR). Its activation causes different intracellular events that eventually stimulate the growth and survival of CRC. Reports suggest that the phosphorylation/activation of EGFR in CRC cells is effectively suppressed by mesalazine (Nowak-Sliwinska et al. 2019; Parenti et al. 2010). The clinical trial has been effectively conducted for the use of mesalazine in CRC.

Artesunate

Artesunate is the artemisinin derivative, and it is used to treat malarial infections. Artesunate is used as a repurposed drug against various cancer cell lines as it has exhibited a robust cytotoxic effect (Krishna et al. 2015). Activating the mitochondrial apoptosis by suppressing reactions such as NF-κB activation and fatty acid biosynthetics leads to the inhibition of cell proliferation in CRC by artesunate. NF-κB has an essential role in the transcription of DNA, cell survival, cytokine production, and inflammation. A study also reported that the Wnt/β-catenin pathway is inhibited by artesunate in CRC, therefore decreasing cancer cell growth. Proliferation and apoptosis of CRC cells were effectively suppressed by artesunate in a dose-dependent manner (Augustin et al. 2020). Phase II clinical trial is currently ongoing to study effects of artesunate in overall survival in stage II/III CRC (Krishna et al. 2015).

Drugs causing cholesterol depletion in cancer cells

Various studies have found that increased cholesterol synthesis (Clendening and Penn 2012; Ginestier et al. 2012; Mo and Elson 2004) and the accumulation of cholesterol are related to cancer progression (Esau et al. 2016; Yue et al. 2014). Therefore, one method that can be utilized to treat cancer can be by using drugs known to cause cholesterol depletion to destroy cancer cells and prevent their rapid proliferation.

Statin-HMG-CoA reductase inhibitors

The FDA approved statins in the late 1980s, since then they are being used as one of the most important drugs for the clinical management of cholesterol. Several studies have shown that individuals prescribed statins had a lower cancer-specific death rate. HMG-CoA reductase inhibitors (Statins) mainly inhibit the mevalonate pathway, which is involved in the de novo synthesis of cholesterol and nonsterol isoprenoid. They suppress 3-hydroxy-3-methylglutaryl-coenzyme A reductase (HMGCR), an essential enzyme in the mevalonate pathway. Statins trigger tumor-specific apoptosis by inhibiting mevalonate or geranylgeranyl pyrophosphate (GGPP) biosynthesis, which stimulates mitochondrial apoptotic signaling mechanisms (Wang et al. 2016a; Lam et al. 2017). In recent, past several studies have highlighted the potential anti-cancer effect of HMG-CoA reductase inhibitors (statins). In lung cancer cell lines, statins were found to induce apoptosis (Zeybek et al. 2011), reduce metastasis (Aftab et al. 2011), and inhibit angiogenesis and tumor growth (Aftab et al. 2011; Wong 2019). These findings suggest that HMG-CoA reductase inhibitors (statins) can be administered alone or in conjunction with chemotherapy and TKIs for treating lung cancer.

Rosuvastatin may have lipid-lowering and anticancer properties. It binds to and blocks hepatic HMG-CoA reductase, which facilitates the conversion of HMG-CoA to mevalonate, a cholesterol progenitor. The enzymatic inhibition resulted in a decrease in hepatic cholesterol and higher LDL cholesterol absorption. In addition, rosuvastatin, like other HMG-CoA reductase inhibitors (statins), promotes apoptosis and differentiation and prevents growth in a variety of tumors (Kata et al. 2016).

Similarly, in ovarian cancer, statins were reported to block the HMG-CoA reductase to inhibit the proliferation of cancer cells and delay malignant tumor formation and progression. Statins also decrease cell migration in vitro, suppressing ovarian cancer metastasis (Kobayashi et al. 2015; Greenaway et al. 2016).

Simvastatin

Simvastatin is an inhibitor of HMG-CoA reductase and lowers lipid levels; it also belongs to a group of medicines called statins. In the blood, simvastatin reduces low-density lipoprotein (LDL) cholesterol, commonly known as bad cholesterol, and raises high-density lipoprotein (HDL) cholesterol, generally known as good cholesterol. Therefore, its use prevents angina strokes, heart attacks, and heart disease (Pedersen and Tobert 2004). Various experimental studies have determined simvastatin's role as an anti-cancer agent in CRC. In CRC cell lines, it manifests proapoptotic and growth-inhibitory effects. The molecular mechanisms of simvastatin in CRC indicated from different studies include enhancement of cellular oxidative stress and endoplasmic reticulum stress, apoptotic pathway expression is altered, inhibition of autophagy, proliferative signaling molecule is altered, and bone morphogenic protein signaling pathway is modulated (Lochhead and Chan 2013). The clinical trial was conducted to confer a clinical benefit to CRC patients when simvastatin is added to XELIRI/FOLFIRI chemotherapy, and no significant clinical effects were observed. Therefore, clinical trials must be implemented in the future to investigate the effects of simvastatin in CRC (Lim et al. 2015).

Atorvastatin

Atorvastatin suppresses the enzyme 3-hydroxy-3-methylglutaryl-coenzyme A (HMG-CoA) reductase. Atorvastatin is used to decrease lipid levels and minimize cardiovascular risk (Nielsen et al. 2012). Atorvastatin reduces cholesterol production in the liver by preventing HMG-CoA conversion to mevalonate. Furthermore, atorvastatin maximizes the quantity of LDL receptors on hepatic cells' membrane.

(Ma et al. 2019). Atorvastatin inhibits tumor proliferation in breast, pancreatic, liver cancer, and prostate (Sierra et al. 2015; Braeuning et al. 2014). It has an antiproliferative effect on breast cancer cells, modifies the cell cycle, and induces apoptosis in malignant cells (Ma et al. 2019).

Drugs interfering with DNA replication

Inhibition of apoptosis and senescence and accelerated replication in tumor cells is what essentially leads to cancer progression (Schmitt 2003). Cell-cycle checkpoints in normal cells regulate the process of replication (Schmitt 2003). However, this is not seen in tumor cells that exhibit hyperproliferation. Hence, drugs that may disrupt the DNA replication process in the tumor cells may pose a potential treatment strategy for cancer.

Curcumin

Curcumin, (1,7-bis(4-hydroxy-3-methoxyphenyl)-1,6-heptadiene-3,5-dione), is a bioactive natural polyphenol found in the rhizome of Curcuma longa and is also called as diferuloylmethane. It is a traditional remedy used for thousands of years. Curcumin has anti-inflammatory properties and increases the level of antioxidants in the body; it is used to treat depression, anxiety, and osteoarthritis; boosts brain function; reduces acne, etc. Curcumin has been researched widely, and it exhibited a robust anti-cancer activity against a variety of cancer cell lines. Therefore, it has both properties, i.e., anti-carcinogenic and anti-inflammatory properties (Hewlings and Kalman 2017). NF-κB is a major target in anti-cancer therapy, and it was reported that curcumin blocks the signaling of NF-κB and therefore inhibits the activation of IKK activation in CRC. Bcl-2, cyclin D1, IL-6, MMP, and COX-2 are cell survival genes, and proliferation and curcumin suppress these genes. Curcumin triggers apoptosis by activating the breakdown of caspase of poly (ADP-ribose) polymerase (PARP). By downregulating COX-2 expression, which has a crucial role in tumor and cancer promotion, curcumin decreases the proliferation of CRC cells. Cumin suppressed the progression and promotion of CRC cells by decreasing the signaling pathway of β-catenin (Park and Conteas 2010).

Flavonoid

Interestingly, a flavonoid extracted from *Bidens pilosa* plant species, named as isoquercitrin (a derivative of quercitrin), was checked for its anti-cancer properties in several cancers, including pancreatic cancer. According to an in vitro study, it was stated that it inhibited tumor cell proliferation through MAPK signaling, leading to apoptosis and the G1 phase cell cycle arrest. Apart from being applied to oncological studies, it has been tested for its anti-allergic, anti-inflammatory, antioxidant, and anti-injury effects (Chen et al. 2015; Katayama et al. 2020).

Ivermectin

Ivermectin is an anti-parasitic medication. Ivermectin induces paralysis in insects and eventually leads to death by increasing the permeability of cell membranes to chloride ions by attaching to the glutamic acid–activated chloride ion channel in nerve and muscle cells (Kobayashi et al. 2019). Ivermectin has been demonstrated to inhibit tumorigenesis, halt cell cycle development, and increase cell death in ovarian cancer cells. Ivermectin has been shown to have anti-cancer properties in ovarian, breast, cervical, lung, gastric, colon, and skin cancer, among others (Li and Zhan 2020; Liu et al. 2020). In cancer, ivermectin impacts various molecules and mechanisms such as chloride channel, PAK1 protein, WNT-TCF pathway, Akt/mTOR pathway, NS3 DDX23 helicase, SIN3 domain, multi-drug resistance (MDR) protein, Nanog/Sox2/Oct4 genes, and P2X7/P2X7 receptors, KPNB1 (Li and Zhan 2020; Ferenc and Levin 2019; Dou et al. 2016).

Propanolol hydrochloride

The hydrochloride form of propranolol is the propranolol hydrochloride. To treat coronary insufficiency, propranolol has been used since 1964, and it is a non-cardioselective β1 and β2-AR blocker. It is also utilized for irregular heartbeats, high blood pressure, tremors, etc. (De Giorgi et al. 2020). To inhibit melanoma growth, β-blockers have recently appeared as a novel therapy. In melanoma, TP53 signaling is altered, leading to uncontrolled cell survival and proliferation, and this signal is also inhibited due to the overexpression of CDK4 and MDM2 genes. The studies reported that after propranolol treatment, TP53 expression is enhanced, and it also suppresses PiK3R5 and Akt3 genes through MDM2 that contribute to the TP53 pathway inhibition. ERK/MAPK1/3 is activated by β-AR 1, 2, and 3. Apoptosis is induced by propranolol in the melanoma cell line via non-selective β1 and β2-AR antagonism by inhibiting ERK/MAPK1/3 and releasing intracellular calcium by negatively blocking the ERK/MAPK pathway (Bustamante et al. 2019; Wrobel and Le Gal 2015). Propranolol decreases VEGF production, inhibits cell migration and proliferation, induces apoptosis, and halts cell cycle in the G1 phase in melanoma cells. Preclinical studies have been conducted, and it is revealed that through inhibition of the noradrenaline-dependent pathway, angiogenesis and migration of cancer cells are inhibited by propranolol (Rotjanapan et al. 2011).

Ritonavir

Ritonavir inhibits antiretroviral protease, which hinders with the reproductive cycle of HIV. It can be utilized in combination with other protease inhibitors to prevent and treat HIV infection. Ritonavir has shown antitumor activity against breast, ovarian, prostate cancer, and in Kaposi's sarcoma and glioma (Srirangam et al. 2011). Ritonavir prevents cell proliferation by enabling the cell cycle arrest at the G1 phase by regulating the activity of retinoblastoma protein-induced phosphorylation and cyclin-dependent kinase (CDK) inhibitors, thus preventing the tumor cells from entering the S-phase of the cell cycle (Kumar et al. 2009). Furthermore, it causes suppression of the proteasome, heat shock protein 90 (HSP90), cytochrome P450 3A4 (CYP3A4), and P-glycoprotein and enhances the immunity against the tumor (Sato 2015).

Drugs interfering with DNA repair

For cancer cells to rapidly proliferate and metastasize, DNA replication is a vital process that needs to occur. Often, in tumor cells, the DNA is damaged, and for it to successfully replicate and initiate the next cell cycle, it needs to undergo DNA damage response (DDR) (Zhu et al. 2020). A potential anti-cancer strategy that can be utilized is the prevention of proper DDR taking place in the tumor cells, which will prevent DNA repair, induce apoptosis, and inhibit the proliferation of cells.

Mebendazole

Mebendazole is a broad-spectrum anti-helminthic drug that is generally prescribed to treat parasitic worm infections such as tapeworms, roundworms, threadworms, nematodes, and trematode infections. The antiparasitic activity of Mebendazole is because it disrupts the microtubule, which prevents the polymerization of tubulin in the gut of Helminthes, which leads to their death (Pantziarka et al. 2014). The anti-cancer activity of mebendazole is due to tubulin depolymerization, angiogenesis inhibition, inhibition of signal transduction pathways involved in cancer progression, sensitization to chemotherapy and radiotherapy by regulating the DNA repair process, induction of apoptosis and cytotoxicity, inhibition of kinases, and induction of antitumor immune response (Guerini et al. 2019).

Apart from breast cancer, the anti-cancer effect of mebendazole (MBZ) has also been widely studied for the treatment of CRC. HCT-116, RKO, SW626, HT-8, and HT29 are the CRC cell lines in which MBZ has exhibited cytotoxic activity. The mechanism of action of MBZ in CRC is by disruption of tubulin and VEGFR-2-mediated anti-angiogenesis. Case studies of repurposing mebendazole for colorectal cancer have been described, and a clinical trial is in progress (Williamson et al. 2016).

PARP inhibitors

Poly- (ADP Ribose) polymerase (PARP) is a nuclear enzyme that repairs single-strand DNA breaks. Upon usage of an inhibitor of PARP (PARPi), it shows interference in cell's DNA repair, a strategy used for killing pancreatic ductal adenocarcinoma (PDAC) cells. Olaparib, rucaparib, and niraparib are some of the types of PARPi which went into the clinical pipeline (Singh et al. 2021; Gupta et al. 2019). Their mechanism of action can collectively be described as disturbing the catalytic process of the cells by trapping PARP-1 proteins at single-stranded DNA breaks, resulting in progression of the replication fork and ultimately forming double-strand breaks, thus preventing the cancer cells from repairing their DNA damage (Zhu et al. 2020).

Drugs regulating cellular metabolism

One of the many characteristics of cancer malignancies is the dysregulation of cellular metabolism in the tumor cells. This altered metabolism is seen due to various oncogenes and varied signal transduction pathways that are seen to take place in cancer cells (Kuo et al. 2010). Thus, utilizing drugs that can be repositioned into regulating tumor metabolism can be another method of treatment.

Metformin

Metformin is administered for type 2 diabetes mellitus patients. It acts by suppressing the gluconeogenesis pathway, decreasing intestinal glucose absorption, and increasing susceptibility to insulin. Metformin can be repurposed in various cancers as they are seen to be involved in various pathways linked to tumor formation. Metformin inhibits mTOR pathway, inactivates insulin-like growth factors, and regulates the PI3K/AKT pathway, all of which can reduce tumorigenesis. Metformin also induces apoptosis by triggering the enzyme 5′ adenosine monophosphate-activated protein kinase (Fatehi Hassanabad 2019). The medicine can be used alone or in conjunction with other hypoglycemic agents such as sulfonylureas, thiazolidinediones, and incretin-based therapies. It opposes glucagon-mediated signaling in the liver and increases glucose uptake in skeletal muscles (Xia et al. 2019). Its main site of action is the mitochondrion. The major advantage of using metformin is that the drug shows an increased action against tumors in several animal models. It can prevent the proliferation and growth of tumors (Lin et al. 2016). Furthermore, studies have found that metformin prevents the development of lung, prostate,

and colon cancer (Saraei et al. 2019). Metformin is proposed to have anti-cancer potential through adenosine monophosphate kinase activation, modulation of adenosine A1 receptor (ADORA), decrease in insulin/insulin growth factors, and suppression of reactive oxygen species (ROS) (Ugwueze et al. 2020). Metformin has been shown in preclinical investigations to work in conjunction with platinum-based drugs (DNA-binding alkylating agents) and taxane (mitotic inhibitors), to boost the anticancer activity of tyrosine kinase inhibitors (TKIs), and act as a radiosensitizer (Lohinai et al. 2016).

Studies have also investigated the efficacy of metformin to reduce chances of breast cancer in diabetics (Libby et al. 2009; Dougan et al. 2005). STK11 mutations or suppression are reported to be linked to a variety of human malignancies, including lung, breast, and cervical cancers (Dougan et al. 2005; Bodmer et al. 2010).

According to the previous literature, metformin administration has better results in CRC patients with decreased incidence and prolonged survival rates. The antitumor effect exhibited by metformin in CRC cells includes the AMPK pathway activation and reducing circulating insulin levels. Another effect of metformin is through downregulation of the mTOR pathway, which results in a reduction in cell proliferation. Modest antitumor activity was displayed in a phase II trial when metformin was combined with fluorouracil in CRC patients. Therefore, additional clinical trials must be conducted for a deeper understanding of metformin as an anti-cancer agent in CRC (Nowak-Sliwinska et al. 2019; Miranda et al. 2016).

Like lung, breast, and CRC, metformin has also been repurposed in other cancers like pancreatic cancer. It is stated to lower its incidence in pancreatic cancer patients suffering from type II diabetes mellitus. Inhibiting IGF (insulin-like growth factor) and mTOR (mammalian target of rapamycin) signaling along with disturbing mitochondrial respiration is the mechanism of action of metformin (Miranda et al. 2016).

A recent study has demonstrated that metformin lowered skin cancer risk. A previous study has revealed that the proliferation of melanoma cells is inhibited by metformin in vitro, and in in vivo, the tumor growth is reduced, and these effects were due to the cell cycle arrest. Metformin prevented metastasis development by activating the AMPK pathway and p53 tumor suppressor protein (Tomic et al. 2011). In skin cancer, the therapeutic effects of metformin must be explored, and therefore clinical trials are in the process (Tomic et al. 2011; Elwood et al. 2009).

Drugs inducing anti-angiogenesis

Angiogenesis is a hallmark of carcinogenesis and a significant driver of tumor proliferation, metastasis, and recurrence. The process involves sprouting or branching new blood vessels from existing blood vasculature to provide essential nutrients, oxygen, waste product removal, and creating a favorable tumor microenvironment. Various studies have found that anti-angiogenesis activity or inhibition of angiogenesis can be utilized as a methodology to effectively treat cancer (Ferrara and Kerbel 2005). Because of its significance, angiogenesis is closely managed by stimulants and inhibitors and is critical in normal health and an array of diseases. Therefore, the use of repurposed drugs exhibiting anti-angiogenesis activity is a bright idea to treat cancer.

Itraconazole

Itraconazole is an antifungal drug widely used against systemic fungal infections. Itraconazole reduces tumor formation in lung cancer by blocking the Hedgehog signaling system and angiogenesis. Itraconazole has been proven to promote autophagy, which inhibits glioblastoma growth by downregulating sterol carrier protein 2 (SCP2) activity and displacement of intracellular cholesterol, according to recent research (Tseng et al. 2013). According to one study, itraconazole improved cell chemosensitivity to platinum and taxanes (Endo et al. 2014). In relevant preclinical angiogenesis and lung cancer systems, itraconazole shows anti-cancer properties. In response to angiogenic stimulation mediated by both vascular endothelial growth factor (VEGF) and basic fibroblast growth factor (bFGF), itraconazole inhibited endothelial cell multiplication, metastasis, and tube formation in a powerful, selective, and dose-dependent manner (Giardiello et al. 1995).

Like lung cancer, the effect of itraconazole has been widely studied in prostate cancers. The drug is considered to be an excellent compound to overcome the dilemma of chemoresistance. In addition to this, it has been advantageous in research as it has shown the least possible adverse effect on the body (Turanli et al. 2018; Pounds et al. 2017; Armando et al. 2020). Several clinical studies also suggest using itraconazole for therapeutic purposes in breast, ovarian, NSCLC, prostate, and pancreatic cancers (Shuch et al. 2012; Rudin et al. 2013; Tsubamoto et al. 2017, 2015, 2014). Besides lung, prostate, and ovarian cancers, the antifungal drug itraconazole has been repurposed for skin cancer treatment. It suppresses the growth of the most prevalent kind of melanoma, i.e., BCC. Oral itraconazole was also reported to reduce BCC tumor area and cell proliferation. Itraconazole also exhibited its effects by suppressing other signaling pathways such as PI3K/mTOR and Wnt.

Quinacrine

Quinacrine is a well-known anti-malarial drug used to treat and prevent Giardiasis (infection of the small intestine) and reduce the inflammation in systemic lupus erythematosus

and rheumatoid arthritis. Quinacrine, commonly known as mepacrine, is a sclerosing drug used to treat malignant pleural effusions and avoid pneumothorax in patients at high risk. Sclerosing agent activates inflammation and limits fluid from reaccumulating in the pleural space, a problem often associated with high-grade cancer. It has been stated that the repurposed drug shows promising anticancer activity in colon, breast, lung, kidney, and prostate cancer by common yet diversified pathways, proving to be toxic to the cancer cells through DNA intercalation, autophagy induction, prevention of angiogenesis, and cell cycle arrest (Zhang et al. 2020; Bryant et al. 2019; Oien et al. 2021). Recent studies suggest that quinacrine affects its anticancer potential by inhibiting NFB repression of p53 and interacts with the DNA damage repair process.

Drugs altering mitochondrial activity

Mitochondria are a vital part of the cell, which enable the cell cycle and the proper functioning and survival of the cell. Mitochondrial dysfunction, aberrant energy metabolism, and resistance to apoptosis are linked to several malignancies. mtDNA mutations are common and have a role in cancer pathogenesis. Thus, targeting the energy metabolism and mitochondria proteins may be an efficient way to overcome apoptotic resistance (Paul and Mukhopadhyay 2007). Many variations between normal and cancer mitochondria allow targeting cancer cell mitochondrial bioenergetics, biogenesis, and function in cancer cells. The cancer stage, type of cancer, and the tumor microenvironment are a few factors that affect mitochondrial functionality (Vyas et al. 2016). Hence, identifying and utilizing repurposed non-oncology drugs to alter mitochondrial activity and biogenesis in tumor cells and prevent further tumorigenesis can be a potential anti-cancer treatment strategy.

Doxycycline

Doxycycline is a tetracycline derivative and a wide-spectrum anti-bacterial drug (antibiotic). The bacteriostatic effect of doxycycline is due to the inhibition of protein formation by preventing the attachment of activated aminoacyl-tRNAs on the A-site of the 30S subunit of bacterial ribosomes (Zhang et al. 2017). Doxycycline can cause inhibition of mitochondrial biogenesis and can also target breast cancer stem cells (BCSCs). It inhibits the self-renewal capacity of stem cells and may be a potential drug for treating breast cancer by acting on cancer stem cells (CSCs) (Scatena et al. 2018; Lin et al. 2018). The drug has also been repurposed in skin cancer treatment. Cell growth of melanoma was inhibited by doxycycline, and its antitumor effects were exhibited through caspase-8 activation, the release of cytochrome C, decreased antiapoptotic protein expression, and NF-κB pathway inhibition. By impairing the homeostasis of the cells and lowering intracellular levels of reduced thiols, proliferation and the survivability of the melanoma cell line were diminished by doxycycline. Apoptosis is induced by inhibiting the MMP-2 and MMP-9 metalloproteinase activity and activating the apoptosis signal-regulated kinase 1, caspases, c-Jun, and N-terminal kinases. However, the clinical trial that has been completed revealed no significant effects in melanoma patients when ipilimumab, temozolomide, and doxycycline are administered as a combination (Cortés et al. 2020). Doxycycline also decreased the cell proliferation, metastasis, and invasion of the human small cell lung cancer line (NCI-H446) and inhibited tumor growth in NCI-H446 and A549 lung cancer xenografts (Qin et al. 2015; Wang et al. 2016b). The antitumor mechanism of doxycycline is not clear. Damaged mitochondria release reactive oxygen species (ROS), which triggers the production of NLRP3 inflammasome. Doxycycline affects NLRP3 regulation, inhibits tumor inflammation, and induces early death in cancer cells in prostate cancer (PC3) and lung cancer (A549) cells (Alsaadi et al. 2021). These findings warrant more investigation into the long-term consequences of antibacterial drug (antibiotic)-mediated modulation of inflammation and carcinogenesis.

Ascorbic acid

Vitamin C, commonly known as ascorbic acid, is found in various foods, and is also sold as a dietary supplement. It is used in patients with the condition known as scurvy which results from a decrease in the vitamin C levels in the body (Levine and Downing 1992). Various reports have demonstrated the anti-cancer properties exhibited by the ascorbic acid in melanoma, squamous cell carcinoma (SCC), and BCC of the skin. Vitamin C promoted apoptosis and cell growth arrest in the human melanoma (A375) cell line by releasing cytochrome c and reducing the mitochondrial membrane potential. It was found that the mitochondrial-dependent pathway triggered apoptosis after vitamin C treatment, which resulted in a substantial upregulation of caspase-3 and caspase-9 expression (Chen et al. 2019). When BCC was treated with a high dose of ascorbic acid, hydrogen peroxide was generated, and thus, cancer cell death occurred. A clinical trial has been conducted for the treatment of BCC with vitamin C, and more clinical trials are underway for a deeper understanding of the role of ascorbic acid in skin cancer (Pernice et al. 2021).

Antibiotics–antibacterial drugs

The antimicrobial agent tigecycline (TIG) is a member of glycylcycline bacteriostatic agents. The drug is known to

treat complicated intra-abdominal and skin-structure infections due to its activity against gram-positive and gram-negative bacteria. Several studies in the recent past have highlighted the antitumor potential of TIG. The anti-cancer effects of TIG depend on targeting key signaling pathways, including PI3K/AKT and Wnt/β-catenin and mitochondrial function in cancer cells (Xu et al. 2016). TIG exerts and acts synergistically with preexisting chemotherapy drugs, contributing to tumor cell death. Compared to conventional treatments such as chemotherapy, TIG may result in reduced side effects, which may be attributed to its selectivity and non-invasiveness (Rebelo et al. 2021).

Drugs inhibiting pyrimidine synthesis

Nucleotide synthesis plays an important role in the uncontrolled cellular proliferation associated with cancer. The tumor cells depend on pyrimidine synthesis in order to provide them with deoxyribonucleoside triphosphates (dNTPs), required for cell proliferation and the survival of the cancer cells (Siddiqui and Ceppi 2020). In order to prevent tumor proliferation in cancer patients, drugs are known to inhibit the de novo synthesis of pyrimidines and can be repurposed as a strategy to prevent cancer development.

Leflunomide

Leflunomide is a synthetic isoxazole derivative representing the novel class of disease-modifying antirheumatic drugs (DMARDs) (Osiri et al. 2002). Leflunomide is an oral prodrug hydrolyzed to an active metabolite called A771726 during the first-pass metabolism in the gut and liver. A771726 inhibits pyrimidine synthesis through the inhibition of dihydroorotase dehydrogenase. Since lymphocytes rely on the de novo synthesis of pyrimidines for cell division, this restricts their proliferation (Van Roon et al. 2004). In cancer, leflunomide plays a role in cell division, death, and the MAPK and p53 signaling mechanisms. To overcome medication resistance in malignancies like melanoma and breast cancer, leflunomide would be most successful when combined with cytotoxic medicines (Zhang and Chu 2018).

Challenges in drug repurposing

Even though DR appears to be a promising cancer therapeutic strategy, a few challenges may affect the extent of its practical utilization in cancer care. Firstly, introducing a new use to an established drug still necessitates a significant amount of high-risk expenditure (Breckenridge and Jacob 2019). Secondly, in clinical studies, the repurposed medicine could fail to exhibit a profitable benefit-risk assessment that would justify regulatory clearance for the new use (Breckenridge and Jacob 2019). Lastly, new legal and regulatory implications may arise with repurposed drugs. It may be difficult to patent and incentivize an existing drug for alternate use. Additionally, substantial information about repurposed drugs already exists in the public domain, reducing their novelty and chances of being awarded a patent (Talevi and Bellera 2020; Micklus and Muntner 2018).

Artificial intelligence and drug repurposing for targeting cancer

Though several lacunae and caveats exist, the advent of advanced translational bioinformatic technology solutions has raised the hopes for better cancer management. Advances in artificial intelligence (AI) and technology-based approaches may improve the discovery and efficacious use of repurposed drugs for clinical translation to target cancer. Another important aspect is the rise of large-scale multi-omics datasets that present enormous prospects for computationally modeling novel interactions of repurposed drugs using drug repurposing methodologies. AI and machine learning (ML) methods possess great potential in the field of drug repurposing. Modeling biological systems to identify novel drug targets and understand the interaction of drugs with disease receptors is already being done by utilizing in silico–based tools. Further advancement of these techniques can be done with the help of AI. Particularly, two of the most prominent and widely used AI technologies currently are ML and deep learning.

These ML algorithms are programmed to predict trends and correlations from data generated by users, eliminating the need for programmers to encode information explicitly. The algorithms extrapolate the response of the drugs to the cancer targets either as stand-alone drugs or in combination with other drugs to improve their efficacy (Koromina et al. 2019). One such ML algorithm is the drug-induced genomic residual effect (DIGRE) computational model, which analyzes the information of varied gene expression in cancer cells due to drugs to predict the mechanism of action of the drugs when used in combination (Koromina et al. 2019). ML algorithms can be further divided into three learning categories, supervised techniques, unsupervised, and reinforcement learning techniques. An example of a supervised technique is when the algorithms evaluate the dataset to determine whether the response of the cancer cells upon administering the drugs is favorable (Fersini et al. 2014), or to analyze the extent of sensitivity of the tumor cells to the drug in question (Neto et al. 2013). K-means clustering is a widely used example of an unsupervised ML learning algorithm that divides the genomic training dataset into clusters and

recognizes drugs that show effects against particular clusters (Hoadley et al. 2014).

Accurate protein-drug interaction prediction may be achieved using support vector machines and random forest classifiers. Geometric deep learning may quicken and facilitate the prediction and generation of molecular surface contact fingerprinting to better understand repurposed drug-protein interactions (understanding interaction fingerprints from protein molecular surfaces using geometric deep learning) (Gainza et al. 2020; Chatterjee et al. 2022). It is now possible to create models that can learn and analyze data patterns and draw conclusions from a vast amount of test data using AI. Data mining using computational intelligence in the field of drug chemo- or pharmaco-informatics can provide relevant information regarding target and off-target effects of repurposed drugs. AI-empowered computation models to decipher in silico repurposed drug-novel-target interaction can also be used to design patient-centric drug repurposing. AI-based algorithms can link drugs and diseases based on shared molecular mechanisms and target pathways (Hernández-Lemus and Martínez-García 2020).

Another computational tool that is rapidly being used for integrating systems biology and disease gene networks is called network medicine. An approach integrating AI and network medicine can be very potent. The Predictive Database for Drug Repurposing (PAD) and NeDRex are valuable resources for identifying and rating drug candidates that might be repurposed for cancer therapy, as well as finding novel therapeutic benefits of current treatments (Sadegh et al. 2021; Cheng et al. 2021). These algorithms provide a broad range of research capabilities, facilitating the discovery of biomolecules whose suppression or augmentation could increase the efficacy of cancer treatments. Though in its infancy, the role of AI in drug repurposing for targeting cancer and also for personalized therapies is going to be tremendous in the coming years.

Conclusion

Traditional drug development is a costly and time-consuming process, and DR provides the possibility to reduce the time and investment needed to introduce a drug to a specific therapeutic purpose. The need for additional studies is reduced because the profiles such as pharmacokinetics, toxicology, and pharmacodynamics are already well established, and this is one of the major advantages of DR. In this approach, to select a suitable compound for repurposing detailed search is required through multiple dataset analyses as well as through structure-based virtual screening. Before undertaking clinical trials, extensive in vitro and in vivo characterizations are necessary. Patient survival can be extended, and relapse risk can be reduced by using the repurposed drugs, which may target different signaling pathways and enhance their anti-cancer effect. Finally, when compared to generating new anti-cancer medications, repurposing current drugs minimizes the cost of development.

Acknowledgements The authors wish to thank the School of Biotechnology and Bioinformatics, D Y Patil Deemed to be University for providing the necessary facilities. M.K.P. acknowledges S. Dubinett, B. Gomperts, and V. Hartenstein for providing the constant support and mentoring.

Author contribution MP and JA: conceptualization, resources, original draft preparation, reviewing, and editing. KT and SP: writing, editing, and reviewing. AD, DS, SS, UK, SN: original draft preparation. SD and SB: editing, reviewing, and supervision.

Data availability Data sharing does not apply to this article as no datasets were generated or analyzed during the current study.

Declarations

Competing interests The authors declare no competing interests.

References

Abou-Issa H, Alshafie G (2004) Celecoxib: a novel treatment for lung cancer. Expert Rev Anticancer Ther 4:725–734. https://doi.org/10.1586/14737140.4.5.725

Adamo P, Ladomery MR (2016) The oncogene ERG: a key factor in prostate cancer. Oncogene 35:403–414. https://doi.org/10.1038/onc.2015.109

Aft R, Naughton M, Trinkaus K et al (2010) Effect of zoledronic acid on disseminated tumour cells in women with locally advanced breast cancer: an open label, randomised, phase 2 trial. Lancet Oncol 11:421–428. https://doi.org/10.1016/S1470-2045(10)70054-1

Aftab BT, Dobromilskaya I, Liu JO, Rudin CM (2011) Itraconazole inhibits angiogenesis and tumor growth in non-small cell lung cancer. Cancer Res 71:6764–6772. https://doi.org/10.1158/0008-5472.CAN-11-0691

Ali R, Toh H-C, Chia W-K, Trial Investigators ASCOLT (2011) The utility of aspirin in dukes C and high risk dukes B colorectal cancer–the ASCOLT study: study protocol for a randomized controlled trial. Trials 12:261. https://doi.org/10.1186/1745-6215-12-261

Alsaadi M, Tezcan G, Garanina EE et al (2021) Doxycycline attenuates cancer cell growth by suppressing NLRP3-mediated inflammation. Pharmaceuticals (Basel) 14:852. https://doi.org/10.3390/ph14090852

Armando RG, Mengual Gómez DL, Gomez DE (2020) New drugs are not enough-drug repositioning in oncology: an update. Int J Oncol 56:651–684. https://doi.org/10.3892/ijo.2020.4966

Arora R, Jain S, Rahimi H (2018) Evaluating the efficacy of tigecycline to target multiple cancer-types: a review. STEM Fellowsh J 4:5–11. https://doi.org/10.17975/sfj-2018-002

Augustin Y, Staines HM, Krishna S (2020) Artemisinins as a novel anti-cancer therapy: targeting a global cancer pandemic through drug repurposing. Pharmacol Ther 216:107706. https://doi.org/10.1016/j.pharmthera.2020.107706

Awtry EH, Loscalzo J (2000) Aspirin. Circulation 101:1206–1218. https://doi.org/10.1161/01.cir.101.10.1206

Balkwill F, Mantovani A (2001) Inflammation and cancer: back to Virchow? Lancet 357:539–545. https://doi.org/10.1016/S0140-6736(00)04046-0

Barzaman K, Karami J, Zarei Z et al (2020) Breast cancer: biology, biomarkers, and treatments. Int Immunopharmacol 84:106535. https://doi.org/10.1016/j.intimp.2020.106535

Bayraktar S, Hernadez-Aya LF, Lei X et al (2012) Effect of metformin on survival outcomes in diabetic patients with triple receptor-negative breast cancer. Cancer 118:1202–1211. https://doi.org/10.1002/cncr.26439

Bodmer M, Meier C, Krähenbühl S et al (2010) Long-term metformin use is associated with decreased risk of breast cancer. Diabetes Care 33:1304–1308. https://doi.org/10.2337/dc09-1791

Braeuning A, Bucher P, Hofmann U et al (2014) Chemically induced mouse liver tumors are resistant to treatment with atorvastatin. BMC Cancer 14:766. https://doi.org/10.1186/1471-2407-14-766

Bray F, Ferlay J, Soerjomataram I et al (2018) Global cancer statistics 2018: GLOBOCAN estimates of incidence and mortality worldwide for 36 cancers in 185 countries. CA Cancer J Clin 68:394–424. https://doi.org/10.3322/caac.21492

Breckenridge A, Jacob R (2019) Overcoming the legal and regulatory barriers to drug repurposing. Nat Rev Drug Discov 18:1–2. https://doi.org/10.1038/nrd.2018.92

Bryant J, Batis N, Franke AC et al (2019) Repurposed quinacrine synergizes with cisplatin, reducing the effective dose required for treatment of head and neck squamous cell carcinoma. Oncotarget 10:5229–5244. https://doi.org/10.18632/oncotarget.27156

Burock S, Daum S, Keilholz U et al (2018) Phase II trial to investigate the safety and efficacy of orally applied niclosamide in patients with metachronous or sychronous metastases of a colorectal cancer progressing after therapy: the NIKOLO trial. BMC Cancer 18:297. https://doi.org/10.1186/s12885-018-4197-9

Bustamante P, Miyamoto D, Goyeneche A et al (2019) Beta-blockers exert potent anti-tumor effects in cutaneous and uveal melanoma. Cancer Med 8:7265–7277. https://doi.org/10.1002/cam4.2594

Chatterjee A, Paul S, Bisht B et al (2022) Advances in targeting the WNT/β-catenin signaling pathway in cancer. Drug Discov Today 27:82–101. https://doi.org/10.1016/j.drudis.2021.07.007

Chen Q, Li P, Li P et al (2015) Isoquercitrin inhibits the progression of pancreatic cancer in vivo and in vitro by regulating opioid receptors and the mitogen-activated protein kinase signalling pathway. Oncol Rep 33:840–848. https://doi.org/10.3892/or.2014.3626

Chen W, Mook RA Jr, Premont RT, Wang J (2018) Niclosamide: beyond an antihelminthic drug. Cell Signal 41:89–96. https://doi.org/10.1016/j.cellsig.2017.04.001

Chen X-Y, Chen Y, Qu C-J et al (2019) Vitamin C induces human melanoma A375 cell apoptosis via Bax- and Bcl-2-mediated mitochondrial pathways. Oncol Lett 18:3880–3886. https://doi.org/10.3892/ol.2019.10686

Cheng X, Zhao W, Zhu M et al (2021) Drug repurposing for cancer treatment through global propagation with a greedy algorithm in a multilayer network. Cancer Biol Med 18:0–0. https://doi.org/10.20892/j.issn.2095-3941.2020.0218

Ciardiello F, Tortora G (2008) EGFR antagonists in cancer treatment. N Engl J Med 358:1160–1174. https://doi.org/10.1056/NEJMra0707704

Clendening JW, Penn LZ (2012) Targeting tumor cell metabolism with statins. Oncogene 31:4967–4978. https://doi.org/10.1038/onc.2012.6

Corsello SM, Bittker JA, Liu Z et al (2017) The Drug Repurposing Hub: a next-generation drug library and information resource. Nat Med 23:405–408. https://doi.org/10.1038/nm.4306

Cortés H, Reyes-Hernández OD, Alcalá-Alcalá S et al (2020) Repurposing of drug candidates for treatment of skin cancer. Front Oncol 10:605714. https://doi.org/10.3389/fonc.2020.605714

Croucher PI, De Hendrik R, Perry MJ et al (2003) Zoledronic acid treatment of 5T2MM-bearing mice inhibits the development of myeloma bone disease: evidence for decreased osteolysis, tumor burden and angiogenesis, and increased survival. J Bone Miner Res 18:482–492. https://doi.org/10.1359/jbmr.2003.18.3.482

De Giorgi V, Geppetti P, Lupi C, Benemei S (2020) The role of β-blockers in melanoma. J Neuroimmune Pharmacol 15:17–26. https://doi.org/10.1007/s11481-019-09876-9

DiMasi JA, Grabowski HG, Hansen RW (2016) Innovation in the pharmaceutical industry: New estimates of R&D costs. J Health Econ 47:20–33. https://doi.org/10.1016/j.jhealeco.2016.01.012

Dou Q, Chen H-N, Wang K et al (2016) Ivermectin induces cytostatic autophagy by blocking the PAK1/Akt axis in breast cancer. Cancer Res 76:4457–4469. https://doi.org/10.1158/0008-5472.CAN-15-2887

Dougan S, Gilbart VL, Sinka K, Evans BG (2005) HIV infections acquired through heterosexual intercourse in the United Kingdom: findings from national surveillance. BMJ 330:1303–1304. https://doi.org/10.1136/bmj.38393.572188.EB

Elmets CA, Ledet JJ, Athar M (2014) Cyclooxygenases: mediators of UV-induced skin cancer and potential targets for prevention. J Invest Dermatol 134:2497–2502. https://doi.org/10.1038/jid.2014.192

Elwood PC, Gallagher AM, Duthie GG et al (2009) Aspirin, salicylates, and cancer. Lancet 373:1301–1309. https://doi.org/10.1016/S0140-6736(09)60243-9

Endo H, Yano M, Okumura Y, Kido H (2014) Ibuprofen enhances the anticancer activity of cisplatin in lung cancer cells by inhibiting the heat shock protein 70. Cell Death Dis 5:e1027. https://doi.org/10.1038/cddis.2013.550

Esau L, Sagar S, Bangarusamy D, Kaur M (2016) Identification of CETP as a molecular target for estrogen positive breast cancer cell death by cholesterol depleting agents. Genes Cancer 7:309–322. https://doi.org/10.18632/genesandcancer.122

Fatehi Hassanabad A (2019) Current perspectives on statins as potential anti-cancer therapeutics: clinical outcomes and underlying molecular mechanisms. Transl Lung Cancer Res 8:692–699. https://doi.org/10.21037/tlcr.2019.09.08

Ferenc NN, Levin M (2019) Effects of ivermectin exposure on regeneration of D. dorotocephala Planaria: exploiting human-approved ion channel drugs as morphoceuticals. Macromol Biosci 19:e1800237. https://doi.org/10.1002/mabi.201800237

Ferrara N, Kerbel RS (2005) Angiogenesis as a therapeutic target. Nature 438:967–974. https://doi.org/10.1038/nature04483

Fersini E, Messina E, Archetti F (2014) A p-Median approach for predicting drug response in tumour cells. BMC Bioinformatics 15:353. https://doi.org/10.1186/s12859-014-0353-7

Fleming MT, Rathkopf DE, Gibbons J et al (2013) Enzalutamide in combination with docetaxel in men with prostate cancer (PC): preliminary results from a phase I study. J Clin Oncol 31:63–63. https://doi.org/10.1200/jco.2013.31.6_suppl.63

Gainza P, Sverrisson F, Monti F et al (2020) Deciphering interaction fingerprints from protein molecular surfaces using geometric deep learning. Nat Methods 17:184–192. https://doi.org/10.1038/s41592-019-0666-6

Gandalovičová A, Rosel D, Fernandes M et al (2017) Migrastatics-anti-metastatic and anti-invasion drugs: promises and challenges. Trends Cancer 3:391–406. https://doi.org/10.1016/j.trecan.2017.04.008

Gharwan H, Bunch KP, Annunziata CM (2015) The role of reproductive hormones in epithelial ovarian carcinogenesis. Endocr Relat Cancer 22:R339–R363. https://doi.org/10.1530/ERC-14-0550

Giardiello FM, Offerhaus GJ, DuBois RN (1995) The role of nonsteroidal anti-inflammatory drugs in colorectal cancer prevention. Eur

J Cancer 31A:1071–1076. https://doi.org/10.1016/0959-8049(95)00137-8

Ginestier C, Monville F, Wicinski J et al (2012) Mevalonate metabolism regulates Basal breast cancer stem cells and is a potential therapeutic target. Stem Cells 30:1327–1337. https://doi.org/10.1002/stem.1122

Gong J, Robbins LA, Lugea A et al (2014) Diabetes, pancreatic cancer, and metformin therapy. Front Physiol 5:426. https://doi.org/10.3389/fphys.2014.00426

Goodman JR, Grossman D (2014) Aspirin and other NSAIDs as chemoprevention agents in melanoma. Cancer Prev Res (phila) 7:557–564. https://doi.org/10.1158/1940-6207.CAPR-14-0018

Greenaway JB, Virtanen C, Osz K et al (2016) Ovarian tumour growth is characterized by mevalonate pathway gene signature in an orthotopic, syngeneic model of epithelial ovarian cancer. Oncotarget 7:47343–47365. https://doi.org/10.18632/oncotarget.10121

Guerini AE, Triggiani L, Maddalo M et al (2019) Mebendazole as a candidate for drug repurposing in oncology: an extensive review of current literature. Cancers (Basel) 11:1284. https://doi.org/10.3390/cancers11091284

Guo C-G, Ma W, Drew DA et al (2021) Aspirin use and risk of colorectal cancer among older adults. JAMA Oncol 7:428–435. https://doi.org/10.1001/jamaoncol.2020.7338

Gupta M, Iyer R, Fountzilas C (2019) Poly(ADP-ribose) polymerase inhibitors in pancreatic cancer: A new treatment paradigms and future implications. Cancers (Basel) 11:1980. https://doi.org/10.3390/cancers11121980

Hanahan D, Weinberg RA (2011) Hallmarks of cancer: the next generation. Cell 144:646–674. https://doi.org/10.1016/j.cell.2011.02.013

Harris RE, Beebe-Donk J, Alshafie GA (2006) Reduction in the risk of human breast cancer by selective cyclooxygenase-2 (COX-2) inhibitors. BMC Cancer 6:27. https://doi.org/10.1186/1471-2407-6-27

Hernández-Lemus E, Martínez-García M (2020) Pathway-based drug-repurposing schemes in cancer: the role of translational bioinformatics. Front Oncol 10:605680. https://doi.org/10.3389/fonc.2020.605680

Hewlings SJ, Kalman DS (2017) Curcumin: a review of its effects on human health. Foods 6:92. https://doi.org/10.3390/foods6100092

Hirata J, Kikuchi Y, Kudoh K et al (2006) Inhibitory effects of bisphosphonates on the proliferation of human ovarian cancer cell lines and the mechanism. Med Chem 2:223–226. https://doi.org/10.2174/157340606776930727

Hoadley KA, Yau C, Wolf DM et al (2014) Multiplatform analysis of 12 cancer types reveals molecular classification within and across tissues of origin. Cell 158:929–944. https://doi.org/10.1016/j.cell.2014.06.049

Hobbs BP, Barata PC, Kanjanapan Y et al (2019) Seamless designs: current practice and considerations for early-phase drug development in oncology. J Natl Cancer Inst 111:118–128. https://doi.org/10.1093/jnci/djy196

Jin G-H, Xu W, Shi Y, Wang L-B (2016) Celecoxib exhibits an antigastric cancer effect by targeting focal adhesion and leukocyte transendothelial migration-associated genes. Oncol Lett 12:2345–2350. https://doi.org/10.3892/ol.2016.4976

Joshi SN, Murphy EA, Olaniyi P, Bryant RJ (2021) The multiple effects of aspirin in prostate cancer patients. Cancer Treat Res Commun 26:100267. https://doi.org/10.1016/j.ctarc.2020.100267

Kata D, Földesi I, Feher LZ et al (2016) Rosuvastatin enhances anti-inflammatory and inhibits pro-inflammatory functions in cultured microglial cells. Neuroscience 314:47–63. https://doi.org/10.1016/j.neuroscience.2015.11.053

Katayama ES, Hue JJ, Bajor DL et al (2020) A comprehensive analysis of clinical trials in pancreatic cancer: what is coming down the pike? Oncotarget 11:3489–3501. https://doi.org/10.18632/oncotarget.27727

Katsila T, Spyroulias GA, Patrinos GP, Matsoukas M-T (2016) Computational approaches in target identification and drug discovery. Comput Struct Biotechnol J 14:177–184. https://doi.org/10.1016/j.csbj.2016.04.004

Kim B, Kim J, Kim YS (2017) Celecoxib induces cell death on non-small cell lung cancer cells through endoplasmic reticulum stress. Anat Cell Biol 50:293. https://doi.org/10.5115/acb.2017.50.4.293

Kismet K, Akay MT, Abbasoglu O, Ercan A (2004) Celecoxib: a potent cyclooxygenase-2 inhibitor in cancer prevention. Cancer Detect Prev 28:127–142. https://doi.org/10.1016/j.cdp.2003.12.005

Kobayashi Y, Banno K, Kunitomi H, et al (2019) Current state and outlook for drug repositioning anticipated in the field of ovarian cancer. J Gynecol Oncol 30. https://doi.org/10.3802/jgo.2019.30.e10

Kobayashi Y, Kashima H, Wu R-C et al (2015) Mevalonate pathway antagonist suppresses formation of serous tubal intraepithelial carcinoma and ovarian carcinoma in mouse models. Clin Cancer Res 21:4652–4662. https://doi.org/10.1158/1078-0432.CCR-14-3368

Koromina M, Pandi M-T, Patrinos GP (2019) Rethinking drug repositioning and development with artificial intelligence, machine learning, and omics. OMICS 23:539–548. https://doi.org/10.1089/omi.2019.0151

Krishna S, Ganapathi S, Ster IC et al (2015) A randomised, double blind, placebo-controlled pilot study of oral artesunate therapy for colorectal cancer. EBioMedicine 2:82–90. https://doi.org/10.1016/j.ebiom.2014.11.010

Kumar S, Bryant CS, Chamala S et al (2009) Ritonavir blocks AKT signaling, activates apoptosis and inhibits migration and invasion in ovarian cancer cells. Mol Cancer 8:26. https://doi.org/10.1186/1476-4598-8-26

Kuo MT, Savaraj N, Feun LG (2010) Targeted cellular metabolism for cancer chemotherapy with recombinant arginine-degrading enzymes. Oncotarget 1:246–251. https://doi.org/10.18632/oncotarget.135

Lam VK, Bentzen SM, Mohindra P et al (2017) Obesity is associated with long-term improved survival in definitively treated locally advanced non-small cell lung cancer (NSCLC). Lung Cancer 104:52–57. https://doi.org/10.1016/j.lungcan.2016.11.017

Levine M, Downing D (1992) New concepts in the biology and biochemistry of ascorbic acid. J Nutr Med 3:361–362. https://doi.org/10.3109/13590849208997993

Li N, Zhan X (2020) Anti-parasite drug ivermectin can suppress ovarian cancer by regulating lncRNA-EIF4A3-mRNA axes. EPMA J 11:289–309. https://doi.org/10.1007/s13167-020-00209-y

Li X, Zhou J (2018) Impact of postdiagnostic statin use on ovarian cancer mortality: A systematic review and meta-analysis of observational studies: Postdiagnostic statin use and ovarian cancer mortality. Br J Clin Pharmacol 84:1109–1120. https://doi.org/10.1111/bcp.13559

Li Z, Wang Z, Shen B et al (2020) Effects of aspirin on the gastrointestinal tract: pros vs. cons. Oncol Lett 20:2567–2578. https://doi.org/10.3892/ol.2020.11817

Libby G, Donnelly LA, Donnan PT et al (2009) New users of metformin are at low risk of incident cancer: a cohort study among people with type 2 diabetes. Diabetes Care 32:1620–1625. https://doi.org/10.2337/dc08-2175

Lim SH, Kim TW, Hong YS et al (2015) A randomised, double-blind, placebo-controlled multi-centre phase III trial of XELIRI/FOLFIRI plus simvastatin for patients with metastatic colorectal cancer. Br J Cancer 113:1421–1426. https://doi.org/10.1038/bjc.2015.371

Lin C, Lo M, Moody R et al (2018) Doxycycline targets aldehyde dehydrogenase-positive breast cancer stem cells. Oncol Rep. https://doi.org/10.3892/or.2018.6337

Lin JJ, Ezer N, Sigel K et al (2016) The effect of statins on survival in patients with stage IV lung cancer. Lung Cancer 99:137–142. https://doi.org/10.1016/j.lungcan.2016.07.006

Liu J, Zhang K, Cheng L et al (2020) Progress in understanding the molecular mechanisms underlying the antitumour effects of ivermectin. Drug Des Devel Ther 14:285–296. https://doi.org/10.2147/DDDT.S237393

Lochhead P, Chan AT (2013) Statins and colorectal cancer. Clin Gastroenterol Hepatol 11:109–18. https://doi.org/10.1016/j.cgh.2012.08.037 (**quiz e13-4**)

Lohinai Z, Dome P, Szilagyi Z et al (2016) From bench to bedside: attempt to evaluate repositioning of drugs in the treatment of metastatic small cell lung cancer (SCLC). PLoS ONE 11:e0144797. https://doi.org/10.1371/journal.pone.0144797

Ma Q, Gao Y, Xu P et al (2019) Atorvastatin inhibits breast cancer cells by downregulating PTEN/AKT pathway via promoting Ras homolog family member B (RhoB). Biomed Res Int 2019:3235021. https://doi.org/10.1155/2019/3235021

Madsen DH, Bugge TH (2015) The source of matrix-degrading enzymes in human cancer: Problems of research reproducibility and possible solutions. J Cell Biol 209:195–198. https://doi.org/10.1083/jcb.201501034

Mansoori B, Mohammadi A, Davudian S et al (2017) The different mechanisms of cancer drug resistance: a brief review. Adv Pharm Bull 7:339–348. https://doi.org/10.15171/apb.2017.041

Michigami T, Hiraga T, Williams PJ et al (2002) The effect of the bisphosphonate ibandronate on breast cancer metastasis to visceral organs. Breast Cancer Res Treat 75:249–258. https://doi.org/10.1023/a:1019905111666

Micklus A, Muntner S (2018) Biopharma deal-making in 2017. Nat Rev Drug Discov 17:91–92. https://doi.org/10.1038/nrd.2018.1

Miranda VC, Braghiroli MI, Faria LD et al (2016) Phase 2 trial of metformin combined with 5-fluorouracil in patients with refractory metastatic colorectal cancer. Clin Colorectal Cancer 15:321-328.e1. https://doi.org/10.1016/j.clcc.2016.04.011

Mo H, Elson CE (2004) Studies of the isoprenoid-mediated inhibition of mevalonate synthesis applied to cancer chemotherapy and chemoprevention. Exp Biol Med (Maywood) 229:567–585. https://doi.org/10.1177/153537020422900701

Mørch LS, Løkkegaard E, Andreasen AH et al (2012) Hormone therapy and different ovarian cancers: a national cohort study. Am J Epidemiol 175:1234–1242. https://doi.org/10.1093/aje/kwr446

Nagaraj AB, Wang QQ, Joseph P et al (2018) Using a novel computational drug-repositioning approach (DrugPredict) to rapidly identify potent drug candidates for cancer treatment. Oncogene 37:403–414. https://doi.org/10.1038/onc.2017.328

Neto EC, Jang INS, Friend SH, Margolin AA (2013) The stream algorithm: computationally efficient ridge-regression via Bayesian model averaging, and applications to pharmacogenomic prediction of cancer cell line sensitivity. Pac Symp Biocomput 27–38. https://www.ncbi.nlm.nih.gov/pmc/articles/PMC3911888/

Newton PT (2019) New insights into niclosamide action: autophagy activation in colorectal cancer. Biochem J 476:779–781. https://doi.org/10.1042/BCJ20190020

Nielsen SF, Nordestgaard BG, Bojesen SE (2012) Statin use and reduced cancer-related mortality. N Engl J Med 367:1792–1802. https://doi.org/10.1056/NEJMoa1201735

Niikura R, Hirata Y, Hayakawa Y et al (2020) Effect of aspirin use on gastric cancer incidence and survival: a systematic review and meta-analysis. JGH Open 4:117–125. https://doi.org/10.1002/jgh3.12226

Nowak-Sliwinska P, Scapozza L, Ruiz i Altaba A (2019) Drug repurposing in oncology: compounds, pathways, phenotypes and computational approaches for colorectal cancer. Biochim Biophys Acta Rev Cancer 1871:434–454. https://doi.org/10.1016/j.bbcan.2019.04.005

Oien DB, Pathoulas CL, Ray U et al (2021) Repurposing quinacrine for treatment-refractory cancer. Semin Cancer Biol 68:21–30. https://doi.org/10.1016/j.semcancer.2019.09.021

Osiri M, Shea B, Welch V et al (2002) Leflunomide for the treatment of rheumatoid arthritis. Cochrane Database Syst Rev. https://doi.org/10.1002/14651858.cd002047

Ottewell PD, Mönkkönen H, Jones M et al (2008) Antitumor effects of doxorubicin followed by zoledronic acid in a mouse model of breast cancer. J Natl Cancer Inst 100:1167–1178. https://doi.org/10.1093/jnci/djn240

Pantziarka P, Bouche G, Meheus L et al (2014) The repurposing drugs in oncology (ReDO) project. Ecancermedicalscience 8:442. https://doi.org/10.3332/ecancer.2014.442

Parenti S, Ferrarini F, Zini R et al (2010) Mesalazine inhibits theÎ²-catenin signalling pathway acting through the upregulation of Î¼-protocadherin gene in colo-rectal cancer cells. Aliment Pharmacol Ther 31:108–119. https://doi.org/10.1111/j.1365-2036.2009.04149.x

Park J, Conteas CN (2010) Anti-carcinogenic properties of curcumin on colorectal cancer. World J Gastrointest Oncol 2:169–176. https://doi.org/10.4251/wjgo.v2.i4.169

Parvathaneni V, Kulkarni NS, Muth A, Gupta V (2019) Drug repurposing: a promising tool to accelerate the drug discovery process. Drug Discov Today 24:2076–2085. https://doi.org/10.1016/j.drudis.2019.06.014

Paul MK, Mukhopadhyay AK (2007) Cancer — the mitochondrial connection. Biologia (bratisl) 62:371–380. https://doi.org/10.2478/s11756-007-0094-4

Pedersen TR, Tobert JA (2004) Simvastatin: a review. Expert Opin Pharmacother 5:2583–2596. https://doi.org/10.1517/14656566.5.12.2583

Pernice C, Murri D, Valli R et al (2021) Complete response of cutaneous SCC to topical treatment with ascorbic acid solution: a case report. Clin Case Rep 9:1060–1065. https://doi.org/10.1002/ccr3.3585

Pounds R, Leonard S, Dawson C, Kehoe S (2017) Repurposing itraconazole for the treatment of cancer. Oncol Lett 14:2587–2597. https://doi.org/10.3892/ol.2017.6569

PubChem Apricoxib (n.d.) In: Nih.gov. https://pubchem.ncbi.nlm.nih.gov/compound/Apricoxib. Accessed 16 Jun 2021a

Qin Y, Zhang Q, Lee S et al (2015) Doxycycline reverses epithelial-to-mesenchymal transition and suppresses the proliferation and metastasis of lung cancer cells. Oncotarget 6:40667–40679. https://doi.org/10.18632/oncotarget.5842

Rebelo R, Polónia B, Santos LL et al (2021) Drug repurposing opportunities in pancreatic ductal adenocarcinoma. Pharmaceuticals (Basel) 14:280. https://doi.org/10.3390/ph14030280

Rotjanapan P, Dosa D, Thomas KS (2011) Potentially inappropriate treatment of urinary tract infections in two Rhode Island nursing homes. Arch Intern Med 171:438–443. https://doi.org/10.1001/archinternmed.2011.13

Rudin CM, Brahmer JR, Juergens RA et al (2013) Phase 2 study of pemetrexed and itraconazole as second-line therapy for metastatic nonsquamous non-small-cell lung cancer. J Thorac Oncol 8:619–623. https://doi.org/10.1097/JTO.0b013e31828c3950

Sadegh S, Skelton J, Anastasi E et al (2021) Network medicine for disease module identification and drug repurposing with the NeDRex platform. Nat Commun 12:6848. https://doi.org/10.1038/s41467-021-27138-2

Sankpal UT, Goodison S, Jones-Pauley M et al (2017) Tolfenamic acid-induced alterations in genes and pathways in pancreatic cancer cells. Oncotarget 8:14593–14603. https://doi.org/10.18632/oncotarget.14651

Saraei P, Asadi I, Kakar MA, Moradi-Kor N (2019) The beneficial effects of metformin on cancer prevention and therapy: a comprehensive review of recent advances. Cancer Manag Res 11:3295–3313. https://doi.org/10.2147/CMAR.S200059

Sato A (2015) The human immunodeficiency virus protease inhibitor ritonavir is potentially active against urological malignancies. Onco Targets Ther 8:761–768. https://doi.org/10.2147/OTT.S79776

Sawant S, Shegokar R (2014) Cancer research and therapy: where are we today? Int j Cancer Ther Oncol 2:020408. https://doi.org/10.14319/ijcto.0204.8

Scatena C, Roncella M, Di Paolo A et al (2018) Doxycycline, an inhibitor of mitochondrial biogenesis, effectively reduces cancer stem cells (CSCs) in early breast cancer patients: a clinical pilot study. Front Oncol 8:452. https://doi.org/10.3389/fonc.2018.00452

Schmitt CA (2003) Senescence, apoptosis and therapy–cutting the lifelines of cancer. Nat Rev Cancer 3:286–295. https://doi.org/10.1038/nrc1044

Shim JS, Liu JO (2014) Recent advances in drug repositioning for the discovery of new anticancer drugs. Int J Biol Sci 10:654–663. https://doi.org/10.7150/ijbs.9224

Shuch B, Bratslavsky G, Linehan WM, Srinivasan R (2012) Sarcomatoid renal cell carcinoma: a comprehensive review of the biology and current treatment strategies. Oncologist 17:46–54. https://doi.org/10.1634/theoncologist.2011-0227

Siddiqui A, Ceppi P (2020) A non-proliferative role of pyrimidine metabolism in cancer. Mol Metab 35:100962. https://doi.org/10.1016/j.molmet.2020.02.005

Sierra H, Cordova M, Chen C-SJ, Rajadhyaksha M (2015) Confocal imaging-guided laser ablation of basal cell carcinomas: an ex vivo study. J Invest Dermatol 135:612–615. https://doi.org/10.1038/jid.2014.371

Singh HM, Bailey P, Hübschmann D et al (2021) Poly(ADP-ribose) polymerase inhibition in pancreatic cancer. Genes Chromosomes Cancer 60:373–384. https://doi.org/10.1002/gcc.22932

Sleire L, Førde HE, Netland IA et al (2017) Drug repurposing in cancer. Pharmacol Res 124:74–91. https://doi.org/10.1016/j.phrs.2017.07.013

Srirangam A, Milani M, Mitra R et al (2011) The human immunodeficiency virus protease inhibitor ritonavir inhibits lung cancer cells, in part, by inhibition of survivin. J Thorac Oncol 6:661–670. https://doi.org/10.1097/JTO.0b013e31820c9e3c

Talevi A, Bellera CL (2020) Challenges and opportunities with drug repurposing: finding strategies to find alternative uses of therapeutics. Expert Opin Drug Discov 15:397–401. https://doi.org/10.1080/17460441.2020.1704729

Tang JY, Wu A, Linos E et al (2010) High prevalence of vitamin D deficiency in patients with basal cell nevus syndrome. Arch Dermatol 146:1105–1110. https://doi.org/10.1001/archdermatol.2010.247

Thun MJ, Henley SJ, Patrono C (2002) Nonsteroidal anti-inflammatory drugs as anticancer agents: mechanistic, pharmacologic, and clinical issues. J Natl Cancer Inst 94:252–266. https://doi.org/10.1093/jnci/94.4.252

Tomic T, Botton T, Cerezo M et al (2011) Metformin inhibits melanoma development through autophagy and apoptosis mechanisms. Cell Death Dis 2:e199. https://doi.org/10.1038/cddis.2011.86

Tseng S-C, Huang Y-C, Chen H-J et al (2013) Metformin-mediated downregulation of p38 mitogen-activated protein kinase-dependent excision repair cross-complementing 1 decreases DNA repair capacity and sensitizes human lung cancer cells to paclitaxel. Biochem Pharmacol 85:583–594. https://doi.org/10.1016/j.bcp.2012.12.001

Tsubamoto H, Sonoda T, Ikuta S et al (2015) Combination chemotherapy with itraconazole for treating metastatic pancreatic cancer in the second-line or additional setting. Anticancer Res 35:4191–4196

Tsubamoto H, Sonoda T, Yamasaki M, Inoue K (2014) Impact of combination chemotherapy with itraconazole on survival of patients with refractory ovarian cancer. Anticancer Res 34:2481–2487

Tsubamoto H, Ueda T, Inoue K et al (2017) Repurposing itraconazole as an anticancer agent. Oncol Lett 14:1240–1246. https://doi.org/10.3892/ol.2017.6325

Turanli B, Grøtli M, Boren J et al (2018) Drug repositioning for effective prostate cancer treatment. Front Physiol 9:500. https://doi.org/10.3389/fphys.2018.00500

Ugwueze CV, Ogamba OJ, Young EE et al (2020) Metformin: a possible option in cancer chemotherapy. Anal Cell Pathol (Amst) 2020:7180923. https://doi.org/10.1155/2020/7180923

Van Roon EN, Jansen TLTA, Mourad L et al (2004) Leflunomide in active rheumatoid arthritis: a prospective study in daily practice. Br J Clin Pharmacol 57:790–797. https://doi.org/10.1111/j.1365-2125.2004.02075.x

Verdoodt F, Dehlendorff C, Friis S, Kjaer SK (2018) Non-aspirin NSAID use and ovarian cancer mortality. Gynecol Oncol 150:331–337. https://doi.org/10.1016/j.ygyno.2018.06.018

Vyas S, Zaganjor E, Haigis MC (2016) Mitochondria and cancer. Cell 166:555–566. https://doi.org/10.1016/j.cell.2016.07.002

Wang A, Aragaki AK, Tang JY et al (2016a) Statin use and all-cancer survival: prospective results from the Women's Health Initiative. Br J Cancer 115:129–135. https://doi.org/10.1038/bjc.2016.149

Wang L, Zhang R, Yu L et al (2021) Aspirin use and common cancer risk: a meta-analysis of cohort studies and randomized controlled trials. Front Oncol 11:690219. https://doi.org/10.3389/fonc.2021.690219

Wang S-Q, Zhao B-X, Liu Y et al (2016b) New application of an old drug: antitumor activity and mechanisms of doxycycline in small cell lung cancer. Int J Oncol 48:1353–1360. https://doi.org/10.3892/ijo.2016.3375

Wang Y, Deng W, Li N et al (2018) Combining immunotherapy and radiotherapy for cancer treatment: current challenges and future directions. Front Pharmacol 9:185. https://doi.org/10.3389/fphar.2018.00185

Williamson T, Bai R-Y, Staedtke V et al (2016) Mebendazole and a non-steroidal anti-inflammatory combine to reduce tumor initiation in a colon cancer preclinical model. Oncotarget 7:68571–68584. https://doi.org/10.18632/oncotarget.11851

Wong RSY (2019) Role of nonsteroidal anti-inflammatory drugs (NSAIDs) in cancer prevention and cancer promotion. Adv Pharmacol Sci 2019:3418975. https://doi.org/10.1155/2019/3418975

Wrobel LJ, Le Gal FA (2015) Inhibition of human melanoma growth by a non-cardioselective β-blocker. J Invest Dermatol 135:525–531. https://doi.org/10.1038/jid.2014.373

Xia D-K, Hu Z-G, Tian Y-F, Zeng F-J (2019) Statin use and prognosis of lung cancer: a systematic review and meta-analysis of observational studies and randomized controlled trials. Drug Des Devel Ther 13:405–422. https://doi.org/10.2147/DDDT.S187690

Xin B, Yokoyama Y, Shigeto T, Mizunuma H (2007) Anti-tumor effect of non-steroidal anti-inflammatory drugs on human ovarian cancers. Pathol Oncol Res 13:365–369. https://doi.org/10.1007/bf02940318

Xu Z, Yan Y, Li Z et al (2016) The antibiotic drug tigecycline: a focus on its promising anticancer properties. Front Pharmacol 7:473. https://doi.org/10.3389/fphar.2016.00473

Xue H, Li J, Xie H, Wang Y (2018) Review of drug repositioning approaches and resources. Int J Biol Sci 14:1232–1244. https://doi.org/10.7150/ijbs.24612

Ye S, Lee M, Lee D et al (2019) Association of long-term use of low-dose aspirin as chemoprevention with risk of lung cancer. JAMA

Netw Open 2:e190185. https://doi.org/10.1001/jamanetworkopen.2019.0185

Yue S, Li J, Lee S-Y et al (2014) Cholesteryl ester accumulation induced by PTEN loss and PI3K/AKT activation underlies human prostate cancer aggressiveness. Cell Metab 19:393–406. https://doi.org/10.1016/j.cmet.2014.01.019

Zappavigna S, Cossu AM, Grimaldi A et al (2020) Anti-inflammatory drugs as anticancer agents. Int J Mol Sci 21:2605. https://doi.org/10.3390/ijms21072605

Zeybek ND, Gulcelik NE, Kaymaz FF et al (2011) Rosuvastatin induces apoptosis in cultured human papillary thyroid cancer cells. J Endocrinol 210:105–115. https://doi.org/10.1530/JOE-10-0411

Zhang C, Chu M (2018) Leflunomide: a promising drug with good antitumor potential. Biochem Biophys Res Commun 496:726–730. https://doi.org/10.1016/j.bbrc.2018.01.107

Zhang L, Xu L, Zhang F, Vlashi E (2017) Doxycycline inhibits the cancer stem cell phenotype and epithelial-to-mesenchymal transition in breast cancer. Cell Cycle 16:737–745. https://doi.org/10.1080/15384101.2016.1241929

Zhang X-S, Zhang Y-M, Li B et al (2018) Risk reduction of endometrial and ovarian cancer after bisphosphonates use: a meta-analysis. Gynecol Oncol. https://doi.org/10.1016/j.ygyno.2018.06.012

Zhang Z, Zhou L, Xie N et al (2020) Overcoming cancer therapeutic bottleneck by drug repurposing. Signal Transduct Target Ther 5:113. https://doi.org/10.1038/s41392-020-00213-8

Zhou X-L, Xue W-H, Ding X-F et al (2017) Association between metformin and the risk of gastric cancer in patients with type 2 diabetes mellitus: a meta-analysis of cohort studies. Oncotarget 8:55622–55631. https://doi.org/10.18632/oncotarget.16973

Zhu H, Wei M, Xu J et al (2020) PARP inhibitors in pancreatic cancer: molecular mechanisms and clinical applications. Mol Cancer 19:49. https://doi.org/10.1186/s12943-020-01167-9