New drugs are not enough-drug repositioning in oncology: An update

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Abstract. Drug repositioning refers to the concept of discovering novel clinical benefits of drugs that are already known for use treating other diseases. The advantages of this are that several important drug characteristics are already established (including efficacy, pharmacokinetics, pharmacodynamics and toxicity), making the process of research for a putative drug quicker and less costly. Drug repositioning in oncology has received extensive focus. The present review summarizes the most prominent examples of drug repositioning for the treatment of cancer, taking into consideration their primary use, proposed anticancer mechanisms and current development status.

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1. Introduction

In previous decades, a considerable amount of work has been conducted in search of novel oncological therapies; however, cancer remains one of the leading causes of death globally. The creation of novel drugs requires large volumes of capital, alongside extensive experimentation and testing, comprising the pioneer identification of identifiable targets and corroboration, the establishment of the lead compound, and subsequent studies into efficacy, pharmacokinetics and toxicity. After this arduous process, a minimal number of possible oncology drugs reach clinical trials, a fraction that is considered to be ~5% (1). Then, if the three phases of clinical trials are successful, the new compound can be authorized for use in therapeutic settings. The traditional method of developing new anticancer drugs is a pervasive, stringent and expensive procedure (1,2). Paul *et al* (3,4) estimated that the time of development of a new drug from beginning to end was 11.4-13.5 years, and Adams *et al* (3,4) analyzed that the costs range between 161-1,800 million dollars per pharmaceutical product.

Despite the enormous quantities of money invested in drug discovery, the number of novel molecules introduced into the clinic has not increased significantly. An alternative method in drug development is the consideration of approved known molecules used in non-oncological situations (5). This strategy has previously been termed drug repositioning, drug repurposing, drug reprofiling, therapeutic switching or indication

switching, of which, drug repositioning is the most frequently used. The significant advantage of this strategy is that various characteristics of these drugs, such as their pharmacokinetics, pharmacodynamics and toxicity, are already well known in animals and humans (6). Due to the basis of repurposing, new candidates could be ready for clinical trials faster, and if successfully approved by regulatory authorities, their integration into medical practice could be more agile. Repurposed drugs are generally approved quicker (3-12 years) and at a reduced cost (50-60% compared with novel compounds) (7). Also, while ~10% of new drug applications gain market approval, ~30% of repurposed drugs are approved, giving companies a market-driven incentive to repurpose existing assets (8).

Research into repurposing drugs in oncology has been growing in the past years (9). One example is the Repurposing Drugs in Oncology project, an international collaboration initiated by several researchers, clinicians and patient advocates working in the non-profit sector (10). It is out of the sphere of this article to discuss the strategies for identifying repurposing opportunities (knowledge mining, *in silico* approaches, high-throughput screening). For the analysis of those strategies, the review of Xue *et al* (11) is recommended. At present, >270 drugs are being analyzed for potential antitumor activity; of these, ~29% are on the World Health Organization Essential Medicines List (12). Furthermore, ~75% of these drugs are off-patent, and ~57% exhibited antitumor activity in human clinical trials (11). The purpose and significance of this review is to summarize updated information concerning the most promising drugs for repurposing in oncology, and combining analysis of their structures, the tumors that are affected by them, their diverse mechanisms of action and novel information regarding the clinical trials currently being conducted.

2. Artesunate (ART)

ART is a semi-synthetic byproduct of artemisinin, a sesquiterpene compound isolated from the plant *Artemisia annua* used to treat malaria, generally in combination with other drugs (13). Malaria is caused by *Plasmodium falciparum*, which mostly resides in red blood cells and contains iron-rich heme-groups (14). The proposed mechanism of action for its treatment involves the cleavage of endoperoxide bridges by iron, producing free radicals which damage biological macromolecules, causing oxidative stress in the cells of the parasite (15). Several published case reports and pilot phase I/II trials indicate clinical anticancer activity of this compound in a variety of solid tumors, such as Kaposi's sarcoma, non-small cell lung cancer (NSCLC), and colon, melanoma, breast, ovarian, prostate and renal cancers (16-28). Cases of hepatotoxicity were found when artemisinin was combined with other drugs (29).

The mechanism of action of ART in cancer remains a matter of debate. The cellular response of cancer cells to ART may be due to toxic free radicals generated by an endoperoxide moiety, cell cycle arrest, induction of apoptosis or inhibition of tumor angiogenesis (30). Multiple studies revealed that the inhibitory effect of ART on cancer cells is iron-dependent, and iron-triggered ART radicals are more likely to alkylate cellular proteins covalently (17,31,32). Thus, Zhou *et al* (31) concluded that three modes could be involved in ART alkylation. One of them involves the molecule binding in a specific and noncovalent manner, following which a covalent bond is formed by heme activation. Additionally, ART may non-specifically bind to the surface of proteins, primarily high abundance proteins, with covalent bonds formed by heme activation. The last model proposed involves the drug alkylating heme-containing proteins through heme or amino acid residues nearby. There is no clear consensus on the topic. Currently, five clinical trials are actively recruiting (clinical trial nos. NCT02633098, NCT03093129, NCT03792516, NCT03100045 and NCT02786589).

3. Auranofin (AUF)

Rheumatoid arthritis is defined by persistent inflammation and joint swelling, leading to functional disability (33). AUF is an Au(I) complex containing an Au-S bond that is maintained by a triethyl phosphine group (34). AUF is prescribed for the treatment of rheumatoid arthritis, as it can slow disease progression by inhibiting inflammation and stimulating cell-mediated immunity (35). Also, AUF inhibits phagocytosis by macrophages, as well as the release of lysosomal enzymes and antibodies involved in cytotoxicity (36). The use of AUF is rare today due to the emergence of novel antirheumatic medications. AUF's anticancer properties were observed in a wide range of cancers, such as melanoma, leukemia, gastrointestinal stromal tumor (GIST) and NSCLC, among others (37-39). This organogold compound was also used in combination with other drugs; for instance, AUF enhanced the toxicity of tumor suppressor candidate 2 (TUSC2)/erlotinib synergistically (40). In the presence of AUF, several cancer cell lines exhibited increased susceptibility to the TUSC2/erlotinib combination, undergoing apoptosis.

Furthermore, it was found that those patients with rheumatoid arthritis treated with AUF had lower malignancy rates than those not treated (41). The antineoplastic antitumor effect is attributed mainly to the interaction of AUF with a selenocysteine residue within the redox-active domain of mitochondrial thioredoxin reductase, blocking its activity, and leading to increases in reactive oxygen species (ROS) levels and apoptosis (36). The second primary mechanism is due to the inhibition of the ubiquitin-proteasome pathway. This pathway is required for targeted degradation of proteins within cells, which is upregulated in various cancers (36). A number of the drugs undergoing repositioning affect the PI3K/Akt and mTOR signaling pathways, two pathways which are so interconnected that they could be regarded as a single pathway crucial to numerous aspects of cell growth and survival (42). Disruptions in the Akt-regulated pathways are associated with cancer, and Akt has become a valuable therapeutic target (43). Li *et al* (39) proposed that AUF inhibits the PI3K/Akt/mTOR axis, inducing potent anticancer activity. Currently, one clinical trial is recruiting in order to analyze the combination of AUF and Sirulimus in lung cancer (clinical trial no. NCT01737502).

4. Benzimidazole derivatives (BZMs)

BZMs are heterocyclic organic compounds with structural analogy to nucleotides. They are used as a significant scaffold

for the development of a variety of drugs (44,45). BZM-based compounds are broadly used as anthelmintic drugs with low mammalian toxicity and high effectivity against a wide range of helminth species (46). The mechanism of action of BZMs is based on its specific binding to tubulin, resulting in the disruption of microtubule structure and function, interfering with the microtubule-mediated transport of secretory vesicles in the absorptive tissues of helminths whilst also affecting their structure in tumor cells (47). Additionally, BZMs inhibit glucose uptake, deplete glycogen stores and decrease the formation of ATP, leading to the death of the parasites (48). Certain BZM-based compounds have shown antitumor activity. Including albendazole (ABZ), flubendazole (FLU), mebendazole (MBZ) and omeprazole (OMP).

ABZ. ABZ is a medication used for the treatment of a variety of helminth infestations (49). The antiproliferative effect of ABZ has been observed *in vitro* in hepatocellular carcinoma (HCC) and colorectal carcinoma (CRC) cells, as well as *in vivo* in a xenograft model of peritoneal carcinomatosis (50). ABZ was also active in cells resistant to other microtubule drugs, such as leukemia and ovarian cancer cells (51,52). Its antitumor mechanism of action appears to depend on its ability to interfere with microtubules (53). Another mechanism of antitumor action has been proposed for ABZ; it inhibited vascular endothelial growth factor (VEGF) production and tumor angiogenesis in mice bearing peritoneal ovarian tumors (54). Currently, one clinical trial is recruiting to investigate ABZ in cancer (clinical trial no. NCT02366884).

FLU. FLU is mainly used in veterinary medicine for the treatment of intestinal parasites (55). FLU exhibits antiproliferative effects in leukemia, multiple myeloma (MM), melanoma and breast cancer cells (56). FLU alters microtubule structure, induces apoptosis, inhibits angiogenesis, induces cell differentiation, inhibits cell migration and induces ROS activating autophagy (57,58). In a study of a panel of 26 cancer cell lines, neuroblastoma was identified as a highly FLU-sensitive malignancy (59). The antineuroblastoma activity of FLU involved the mouse double minute homolog 2 inhibitor and p53 activator nutlin-3 (59). In combined regimens, FLU enhanced the cytotoxicity of fluorouracil, doxorubicin, vinblastine and vincristine (56). At present, no clinical studies into the effects of FLU on human malignancies have been conducted (60).

MBZ. MBZ is used to treat several helminths infestations (49). Two different glioblastoma multiforme (GBM) animal models showed a survival benefit of treatment with MBZ (61). Additionally, growth inhibition was found in lung cancer cells (62). Growth inhibition involves the prevention of the polymerization of tubulin (63). MBZ was found to interact with several protein kinases, including inhibiting BCR-ABL (64). Furthermore, MBZ induces apoptosis in melanoma cell lines through phosphorylation of Bcl2 and decreased levels of the X-linked inhibitor of apoptosis (65). Treatment with MBZ was as effective as temozolomide in a human melanoma xenograft model, and displayed strong therapeutic efficacy in animal models of both glioma and medulloblastoma, reaching therapeutically effective concentrations in the brain (65,66). Currently, six actively recruiting clinical trials are ongoing, testing MBZ in different types of tumors either as a single drug or in combination with other compounds (clinical trial nos. NCT03925662, NCT03628079, NCT02644291, NCT02366884, NCT03774472, NCT01837862).

OMP. OMP is a widely used medication for peptide ulcers and other gastrointestinal diseases, and is a selective proton pump inhibitor (PPI) that inhibits acid secretion via specific inhibition of the H^+/K^+-ATPase system found in the parietal cells of the stomach. Jin *et al* (67) found that the OMP inhibits the invasion of breast and pancreatic cancer cells through inhibition of chemokine receptor type 4 transcription. Also, it was found that when it is given as an adjuvant drug for relieving common side effects of chemotherapy, OMP has a synergetic effect in improving chemoradiotherapy efficacy and decreasing rectal cancer recurrence (68). As preliminary laboratory studies have found that PPIs inhibit human fatty acid synthase and breast cancer cell survival, currently, a phase II clinical trial is actively recruiting (clinical trial no. NCT02595372) (69).

5. Chloroquine (CLQ)

CLQ and hydroxyCLQ (HCLQ) are 4-aminoquinolines used to treat malaria and autoimmune disorders, including lupus, rheumatoid arthritis and amebiasis (70,71). CLQ inhibits the enzyme heme polymerase, which converts toxic heme into non-toxic hemozoin. Against rheumatoid arthritis, CLQ mainly inhibits lymphoproliferation and phospholipase A2 (72,73). It also inhibits thiamine uptake (74). A vast body of experimental evidence has demonstrated the efficacy of these two drugs against a variety of malignant tumors (75). Such robust data allow the development of clinical trials for both molecules, suggesting that CLQ may be more efficacious than HCLQ (75). Although the vast majority of clinical data was found in patients with GBM and brain metastases, and in patients with BRAF mutations that block vemurafenib sensitivity, good results have also been found in clinical trials for sarcoma, MM and lung cancer (76-79). Inhibition of autophagic flux is the most studied anticancer effect of CLQ; however, other studies reported CLQ-induced cell death via inhibition of cholesterol biosynthesis (80,81). Additionally, these drugs affect Toll-like receptor 9, p53 and CXC chemokine receptor 4-CXC ligand 12 pathways in cancer cells (82). In the tumor stroma, CLQ was shown to affect the tumor vasculature, cancer-associated fibroblasts and the immunological system (75). Currently, two actively recruiting clinical trials are ongoing, testing CLQ in GBM in combination with other compounds (clinical trial nos. NCT03243461 and NCT02378532).

Mefloquine (MFQ), another member of the quinoline family, has shown cytotoxicity and antiproliferative effects against several types of cancer cells. MFQ also exhibits good *in vivo* tumor growth inhibition as a single agent and effectively synergizes with primary cancer chemotherapeutics in arresting tumor growth (83). The mechanism of action of MFQ includes the inhibition of autophagy, lysosomal disruption, inhibition of various signaling pathways and inhibition of P-glycoprotein (P-gp), a plasma membrane ATP-binding cassette transporter that extrudes cytotoxic drugs (83). Currently, there is one active clinical trial studying MFQ in GBM (clinical trial no. NCT01430351).

6. Chlorpromazine (CPZ)

CPZ is an antipsychotic agent clinically used for the control of psychosis symptoms (84). CPZ is a phenothiazine, and an antagonist of D2 dopamine receptors in cortical and limbic areas of the brain, and the chemical trigger zone (85). CPZ has antiproliferative activity in primary brain cultures, neuroblastomas and glioma cells (86). The antiproliferative effect of CPZ is due to cell cycle arrest at the G2/M phase. Shin *et al* (87) demonstrated that CPZ modulates the p21 promoter, a regulator of cell cycle progression, via the activation of the tumor-suppressor early growth response 1 independently of p53. CPZ is also able to induce apoptosis-independent autophagic cell death through the inhibition of cell cycle progression via the Beclin-1 dependent pathway and modulation of the Akt/mTOR pathway (88). The reported cytotoxic effects of CPZ were selective to dividing cells, with tumor cells more sensitive than non-tumor cells (89). CPZ can cross the blood-brain barrier and accumulate in the brain, two characteristics which make it an attractive adjuvant in human gliomas possessing genetic alterations such as p53 mutation or PTEN deletion (90). Furthermore, CPZ can circumvent multidrug resistance in cancer cells (91). It has also been reported that CPZ can promote apoptosis in leukemia and lymphoma cells, and enhances the cytotoxic effect of tamoxifen in tamoxifen-resistant human breast cancer cells (92,93). Moreover, it has been proposed as an antitumor drug in CRC via the inhibition of sirtuin-1 (94). Additionally, CPZ was able to inhibit the growth of orthotopic liver tumors and, in combination with the antiparasitic agent pentamidine, produce synergistic inhibitory effects on tumor growth (93,95,96).

7. Clomipramine (CMP)

CMP is a tricyclic drug; its mechanism of action is due to mixed inhibition of norepinephrine and serotonin uptake, as well as acting as an antagonist of certain G-protein coupled receptors (97). It is used in depression and other psychiatric disorders (98). Previous studies demonstrated that CMP had a selective cytotoxic effect on all tested brain tumors, probably as it crosses the blood-brain barrier and is retained in the brain for extended periods (99-102). *In vitro* treatment of human leukemia cell lines with CMP produces apoptosis due to a rapid increase in the production of ROS (103). Mechanistically, it has been shown that CMP exerts its antineoplastic effect vi inhibition of mitochondrial complex III, leading to decreased oxygen consumption and subsequent induction of apoptosis via caspase activation (104). CMP has also been proven to be useful in combination with other drugs, such as imatinib in glioma cells, VRP in drug-resistant tumors and dexamethasone in astrocytoma (101,105,106).

8. Desmopressin (dDAVP)

dDAVP is a synthetic version of vasopressin; it is a medication used to treat central diabetes insipidus as a replacement for endogenous antidiuretic hormone when this molecule is insufficient or non-existent (107). dDAVP limits the amount of water eliminated in the urine, functioning at the renal collecting duct (108). It binds to vasopression receptor 2 (V2R), which signals for the translocation of aquaporin channels, causing increased water reabsorption from the urine (109). This water becomes passively redistributed from the nephron to the circulation by way of basolateral membrane channels (110). As dDAVP also stimulates the release of von Willebrand factor from endothelial cells, by acting on V2R, it is used to treat patients with mild-to-moderate cases of moderate hemophilia A and von Willebrand disease (111). The FDA authorized dDAVP for the treatment of bedwetting in 2017 (112).

The presence of vasopressin receptors has been documented in various human malignancies, including CRC, breast and small cell neuroendocrine tumors (NETs) (113). Alonso *et al* (114) proposed the use of dDAVP in surgical oncology, reporting that dDAVP was capable of inhibiting lung colonization by blood-borne tumor cells in preclinical mouse models of aggressive breast cancer. In a model of subcutaneous tumor manipulation and surgical excision, they found that tumor manipulation produced dissemination to the axillary nodes, increasing the number of metastasis in the lungs by up to 6-fold; perioperative treatment with dDAVP decreased regional metastasis. The percentage of lymph node involvement in manipulated animals was 12% with dDAVP and 87% without treatment (115). Similar outcomes were reported for colon cancer (116). Regarding melanoma, an antimetastatic effect was also observed in a model overexpressing tissue inhibitor of metalloproteinases-1 (TIMP-1) (117). Additionally, perioperative administration of dDAVP significantly prolonged survival in a clinical veterinary trial in dogs with locally advanced mammary cancer (118). It has also found that Ddavp may impair the aggressiveness of residual mammary tumors during chemotherapy (116).

Summarized evidence on mechanisms of action that account for the antitumor activity of dDAVP includes direct cytostatic effects, stimulation of microenvironmental production of angiostatin and endothelial release of von Willebrand factor, a key element in resistance to metastasis (119-121). It was suggested that dDAVP disrupts cooperative interactions between the tumor and endothelial cells during early metastatic progression (120). A phase II dose-escalation trial in patients with breast carcinoma explored the safety and potential utility of perioperative administration of dDAVP in humans (clinical trial no. NCT01606072) (121). At the highest dose level evaluated (2 μg/kg), dDAVP appeared safe when administered in two slow infusions, before and after surgery. Notably, treatment with dDVAP was associated with reduced intraoperative bleeding and a rapid postoperative drop in circulating tumor cells, as determined via quantitative PCR of cytokeratin-19 transcripts. A trial in patients with rectal bleeding due to CRC is ongoing (clinical trial no. NCT01623206). Another research group reported enhanced efficacy of docetaxel-based therapy in combination with dDAVP for the treatment of castration-resistant prostate cancer in an orthotopic model (122,123). The perioperative period is an attractive window of opportunity to reduce the risk of metastatic disease; in this context, dDAVP has emerged as a potential surgical adjuvant in oncology (124).

9. Digoxin (DGX)

DGX is a cardiac glycoside with a long history of use in the treatment of heart failure and arrhythmia (125). DGX acts

by inhibiting the Na^+/K^+ ATPase; such inhibition produces an increase in intracellular sodium levels, and subsequently decreased activity of the Na^+/Ca^{2+} exchanger (126). This produces an increase in the intracellular calcium concentration in myocardiocytes, thereby exerting a beneficial effect in the hearts of patients with heart failure or arrhythmia (127). It was previously reported owed that DGX decreases breast cancer recurrence and aggressiveness (128). However, subsequent research found evidence that the use of DGX increased breast cancer incidence among females in Denmark, which was explained by the fact that DGX is a phytoestrogen (129). Taking this into account, a large cohort study with long-term follow-up reported that DGX reduced the incidence of prostate cancer by 25% in males (130). Also, males who used DGX for >10 years presented a ~46% decrease in the incidence of prostate cancer. These data led to a phase II clinical trial for recurrent prostate cancer (clinical trial no. NCT01162135) (131). Estrogens diminish the levels of androgen, inhibiting prostate cancer (132).

Another mechanism proposed is the inhibition of hypoxia-inducible factor (HIF)-1α synthesis and its target genes, such as VEGF (133). Additionally, the binding of cardiac glycosides to Na^+/K^+-ATPase activates proto-oncogene tyrosine-protein kinase, epidermal growth factor receptor (EGFR) and ERK1/2 phosphorylation, leading to an accumulation of p21/CIPI, consequently inducing cell cycle arrest in cancer cells (134). Frankel *et al* (135) conducted a phase IB clinical trial of DGX + trametinib, reporting good tolerance and high rate of disease control in BRAF wild-type metastatic melanoma. Xia *et al* (136) found that DGX inhibits the growth of chordoma, a rare, slow-growing malignant tumor arising from remnants of the fetal notochord, potentially by inducing the apoptosis of tumor cells via a mitochondrial pathway involving cytochrome c and caspases-3/8. Currently, 21 clinical trials using DGX (either alone or in combination with other drugs) are analyzing its antitumor properties in a variety of tumors.

10. Disulfiram (DSF)

DSF has been used as an alcohol deterrent for >60 years by inhibiting the enzyme acetaldehyde dehydrogenase; it functions by breaking down the acetaldehyde generated from enzymatic degradation of alcohol, producing an intense discomfort to alcohol consumers (137). DSF has received particular attention for its antineoplastic effects, both as a single agent and in combination (138). Some of the cytotoxic effects are due to its binding to divalent cations, interfering with copper- and zinc-dependent processes such as angiogenesis and apoptosis (139). Furthermore, it was reported that DSF suppresses the proteasome and NF-κB pathways, specifically suppressing ubiquitin E3 ligase activity (140,141). DSF also affects epigenetic pathways.

DSF contains thiol-reactive functional groups; this chemistry is effective in blocking the active site of certain enzymes. In prostate cancer, DSF can act as a DNA demethylating agent via inhibition of DNA methyltransferase 1 (142). Furthermore, in primary GBM cells treated with DSF *in vitro,* the expression of kinases such as Polo-like kinase 1 was reduced at both the protein and mRNA levels (143). In ovarian cancer cells, DSF administration produced apoptosis via copper-dependent induction of heat-shock proteins (144). DSF was reported to stabilize a family of inhibitors called IκBs, the main inhibitors of NF-κB, which is dysregulated in cancer (140). Stabilization of IκB has been found to re-sensitize gemcitabine-resistant breast and colon cancer to treatment (145). Similarly, DSF resensitized treatment-resistant GBM cell lines (146). Skrott *et al* (147) found that the molecular target of DSF's tumor-suppressive effects was nuclear protein localization protein 4 (Npl4), a substrate-recruiting cofactor of the cell division cycle (Cdc)48p-Npl4p-ubiquitin fusion degradation protein 1p segregase, which is essential for the turnover of proteins involved in multiple regulatory and stress-response pathways in cells. Cong *et al* (148) proposed a chemoradiation regimen targeting stem and non-stem pancreatic cancer cells with the addition of DSF. Triscott *et al* (149) stated that DSF kills cancer stem cells (CSCs) of a variety of cancer types and propose its use in gliomas. Based on these promising preclinical studies, a randomized phase II clinical study compared the effects of cisplatin alone or in combination with DSF, but no difference was found between treated and control groups (150). Furthermore, a clinical dose-escalation trial of DSF in patients with recurrent prostate cancer did not suggest any clinical benefits (151). However, >15 clinical trials are underway at present for breast, prostate, pancreatic and liver cancers, as well as melanoma and GBM, among other malignant tumors. Currently, seven actively recruiting clinical trials are ongoing testing DSF in GBM alone or in combination with other compounds, plus studies in breast and pancreatic cancers (clinical trial nos. NCT03323346, NCT02671890, NCT03950830, NCT03363659, NCT02678975, NCT03151772 and NCT02715609).

11. Doxycycline (DXC)

DXC is a broad-spectrum bacteriostatic antibiotic commonly used for the treatment of various bacterial infections (152). DXC inhibits translation by binding to the 16S rRNA portion of the ribosome, preventing binding of tRNA to the 30S bacterial ribosomal subunit, which is necessary for the delivery of amino acids for protein synthesis. As a result of these actions, the initiation of protein synthesis by polyribosome formation is blocked (153). This antibiotic has a long half-life and is currently used successfully for the long-term treatment of acne (154). In addition to its antibiotic effects, DXC possesses various non-antimicrobial activities, including its ability to inhibit the activities of various matrix metalloproteinases (MMPs), as well as its inhibition of MMP gene expression (155). MMPs are zinc-dependent enzymes reported to be involved in the initial stages of invasion and metastasis of various tumor cells (156). Lamb *et al* (157) proposed a novel method for the treatment of early cancerous lesions and advanced metastatic disease by selectively targeting CSCs responsible for tumor initiation, maintenance and metastasis. DXC is known to inhibit mitochondrial biogenesis (158). The authors found a strict dependence on mitochondrial biogenesis for the clonal expansion and survival of CSCs (157). Then, the authors tested the ability of DXC to inhibit tumor-sphere formation in a broad panel of cancer cell lines derived from eight different tumor types (breast, ductal carcinoma, ovarian, prostate, lung, pancreatic, melanoma and GBM) and reported inhibitory effects of DXC on all of them (157).

DXC can induce apoptosis in diffuse large B-cell lymphoma cell lines (159). Also, it has been used in human tumor xenografts and other animal models to reduce tumor burden and metastatic cancer cell growth. For example, in pancreatic tumor xenografts, DXC treatment reduced tumor growth by ~80% (160). In a model of breast cancer bone metastasis, DXC reduced bone and bone-associated soft tissue tumor mass by ~60 and ~80%, respectively (161). Wan *et al* (162) showed that DXC, in combination with acetylsalicylic acid (AAS), lysine and mifepristone, can prevent and treat cancer metastasis. Qin *et al* (163) reported that DXC suppressed the proliferation and metastasis of lung cancer cells.

Regarding the mechanism of action of DXC in tumor reduction, one of the strongest DXC targets identified via quantitative proteomic analysis was DNA-dependent protein kinase (DNA-PKcs), which is required for proper non-homologous end-joining DNA in the maintenance of mitochondrial DNA integrity and copy number repair (164). DXC confers resistance to radiosensitivity in tumor-initiating cells (165). DNA-PKcs directly interacts with lymphoid enhancer-binding factor 1, which acts downstream in WNT signaling (166). Alexander-Savino *et al* (167) analysed the gene expression profiles of compounds targeting NF-κB, and discovered that DXC is an inhibitor of the NF-κB pathway in a dose-dependent manner. DXC inhibits tumor necrosis factor (TNF)-induced NF-κB activation and reduces the expression of NF-κB-dependent antiapoptotic proteins, including Bcl2α (167). DXC induces cell death through the activation of caspase-8 and release of cytochrome C, suggesting the involvement of both extracellular and intracellular pathways in apoptosis; through the inhibition of NF-κB, DXC increased ROS in CTCL cells and triggered apoptosis that could be reversed through treatment with antioxidants (167). At present, >40 clinical trials are ongoing, of which six trials are actively recruiting, testing the effects of DXC on lymphoma, breast, uterine and lung cancer, as well as in malignant pleural effusions (clinical trial nos. NCT02874430, NCT02201381, NCT01411202, NCT03465774, NCT02583282 and NCT02341209).

12. Fenofibrate (FNF)

FNF, a peroxisome proliferator-activated receptor α (PPAR-α) agonist, has been used for decades to treat hypertriglyceridemia and mixed dyslipidemia (168). Multiple studies showed that it may exhibit antitumor effects in B-cell lymphoma, prostate cancer, GBM, mantle cell lymphoma, squamous cell carcinoma, HCC, glioma, melanoma, fibrosarcoma, medulloblastoma, and lung, breast and endometrial cancers (169-171). However, its antitumor mechanisms remain unclear. Li *et al* (169) described the induction of apoptosis in triple negative breast cancer (TNBC) cells via activation of the NF-κB pathway in a PPAR-α-independent manner. Cytoprotective pathways, such as Akt1 and Erk1/2, may also be involved in the antitumor effects of FNF; inhibition of Akt and Erk1/2 pathways led to apoptosis and cell cycle arrest.

One hypothesis in oral cancer suggests targeting mitochondrial metabolism to trigger cell death through decreasing energy production from the Warburg effect (172). Jan *et al* (173) demonstrated that FNF delayed oral tumor development via the reprogramming of metabolic processes. FNF induced cytotoxicity by decreasing oxygen consumption rates, increasing extracellular acidification rates and reducing ATP content (173). Moreover, FNF caused changes in the protein expressions of hexokinase II pyruvate kinase, pyruvate dehydrogenase, and voltage-dependent anion channels (VDACs), all associated with the Warburg effect (174-176). Furthermore, FNF reprogrammed metabolic pathways by interrupting the binding of hexokinase II to VDAC. FBF administration suppressed the incidence rate of tongue lesions, reduced tumor sizes, decreased tumor multiplicity, and reduced the immunoreactivities of VDAC and mTOR. The molecular mechanisms involved in the capacity of FNF to retard tumor growth included downregulation of mTOR via tuberous sclerosis protein (TSC)1/2-dependent signaling through activation of AMPK and suppression of Akt, or via a TSC1/2-independent pathway through direct suppression of raptor (173). Currently, four actively recruiting clinical trials are ongoing, testing FNF in medulloblastoma, and breast and lung cancers (clinical trial nos. NCT01356290, NCT03631706, NCT02751710 and NCT03390686).

13. HIV protease inhibitors (HPIs)

HPIs mimic endogenous peptides and inhibit the active site of HIV aspartyl protease, a viral enzyme responsible for cleaving the Gag-Pol polyprotein (177). This class of drug has been very effective in controlling the effects of HIV in patients, and additionally has been shown to possess antitumor properties, specially nelfinavir (NLV) and ritonavir (RTV). NLV has undergone several preclinical studies in NSCLC, MM, liposarcoma, Kaposi's sarcoma, GBM, prostate cancer, breast cancer, melanoma and thyroid cancer cells with positive results (178). Also, a phase II clinical trial of NLV in combination with chemoradiation for advanced unresectable pancreatic cancer reported acceptable toxicity and promising survival (179). Another trial using NLV in recurrent adenoid cystic cancer of the head and neck showed promising results (180). An extensive number of mechanisms underlying its antitumor activity have been proposed. First, NLV inhibits the PI3K/Akt pathway and cyclin-dependent kinase 2 activity via the degradation of Cdc25A phosphatase (181,182). Another mechanism involves NLV as an inhibitor of heat shock protein 90 (HSP90), suppressing its interaction with Akt (183). Also, the induction of endoplasmic reticulum (ER) stress and autophagy have been implicated (184). Furthermore, NLV was examined as an inhibitor of angiogenesis through the downregulation of HIF-1α (185). Additionally, NLV has been reported to exhibit antiviral activity against specific HPV-transformed cervical carcinoma cells, potentially via the inhibition of E6-mediated proteasomal degradation of mutant p53 (186). There are numerous other possible effects that may explain the anticancer effects described, including MMP-9 and MMP-2 inhibition, increasing radiosensitivity, inhibition of NF-κB, blocking of interleukin (IL)-6, stimulated phosphorylation of signal transducer and activator of transcription 3 (STAT3), decreases in ATP levels, androgen receptors (ARs) and cell survival, upregulation of TRAIL receptor and death receptor 5, Bax upregulation, inhibition of EGFR and insulin growth factor receptor 1, and increased

fatty acid synthase levels (187-194). At present, seven clinical trials are actively recruiting testing the effects of NLV on MM, medulloblastoma, Kaposi's sarcoma, and breast and lung cancers (clinical trial nos. NCT02363829, NCT02024009, NCT01925378, NCT03256916, NCT03829020, NCT02207439 and NCT03077451).

Concerning the antitumor activity of RTV, it was determined that it reduces proliferation and viability, and increases chemosensitivity in MM cell lines (195). Also, it was found that RTV has cytostatic and cytotoxic effects on GBM cells by inhibiting the chymotrypsin-like activity of the proteasome (196). Another study suggested that RTV, via its inhibition of glucose transporter (GLUT)4, decreases glucose consumption, lactate production, and the proliferation of GBM and MM cells *in vitro* (195). Also, RTV may interfere with HSP90 in GBM cells and exert IL-18-inhibiting activities (197). Ikezoe *et al* (198) reported that RTV induces growth arrest and differentiation of human myeloid leukemia cells, and enhances the ability of all-*trans* retinoic acid to decrease the proliferation and increase the differentiation of these cells. It was also found that RTV induced growth arrest and apoptosis of human MM via downregulation of the antiapoptotic protein myeloid cell leukemia 1 (Mcl-1) in these cells. Furthermore, other studies have shown that RTV blocked IL-6-induced activation of STAT3 and ERK signaling in MM cells by inducing growth arrest and apoptosis (198-200).

Clinically, MM responds to standard drug treatment; however, it may acquire drug resistance, subsequently losing its responsiveness to previously effective treatments (201). Drug resistance may be due to the overexpression of P-gp. Another potential cause of drug resistance involves cytochrome P450 3A4 (CYP3A4), which is associated with the metabolism of chemotherapeutic agents. RTV inhibits P-gp and CYP3A4 activity (198). Future studies are required to determine whether RTV can overcome the drug resistance of MM cells in patients. At present, >90% of chronic cases are caused by a chromosomal abnormality that produces the so-called Philadelphia chromosome; this aberration is a consequence of a fusion between the Abl tyrosine kinase gene at chromosome 9 and the Bcr gene at chromosome 22, resulting in a chimeric oncogene, Bcr-Abl, that is responsible for the production of the active Bcr-Abl tyrosine kinase implicated in the pathogenesis of chronic myeloid leukemia (CML) (202). Compounds have been developed to inhibit this aberrant tyrosine kinase, such as imatinib; however, despite impressive results with imatinib, a subset of patients treated with imatinib will develop resistance (203). A total of 6 out of 9 cases of advanced-stage CML with imatinib resistance carried a rare mutation called T315I that caused the substitution of threonine for isoleucine at codon 315 of the Abl protein (204). In 2017, Xu *et al* (205) virtually screened the FDA-approved drug database to identify novel inhibitors for the wild-type and T315I gatekeeper mutant Abl1, finding that RTV could inhibit the T315I mutant Abl1. The only clinical trial so far with published results is a phase II trial of RTV/lopinavir in cases of progressive or recurrent high-grade gliomas that showed no survival benefit (206). However, such results must be revisited, as RTV passes poorly through the blood-brain barrier. RTV must be administered with caution in patients due to interactions with various drugs (207). Careful selection of patients for clinical trials regarding medicine consumption is essential. For example, two drugs mentioned in this review have negative interactions: DSF decreases the metabolism of RTV and statins (STs), increasing the risk of rhabdomyolysis (208,209). At present, three clinical trials are openly recruiting in breast and prostate cancer (clinical trial nos. NCT03890744, NCT04028388 and NCT03066154).

14. Itraconazole (ITZ)

ITZ was developed in 1980 as a triazole antifungal drug (210). In contrast to human cells (which present cholesterol in its cell membrane), fungi contain ergosterol, a product obtained by the demethylation of lanosterol; the mechanism of action of ITZ involves the inhibition of CYP450-dependent 14α-demethylation of lanosterol, which interferes with the fungal ergosterol biosynthesis pathway (211). Its anticancer activity was reported for the first time by Chong *et al* (212), who reported that 14α-demethylase was central for endothelial cell proliferation. Inhibition of WNT/β-catenin signaling was observed in basal cells and examined in melanoma cells. Additionally, ITZ inhibits VEGF- and basic fibroblast growth factor (bFGF)-dependent angiogenesis *in vivo* (212). Concomitantly, ITZ inhibits VEGF receptor 2 (VEGFR2) glycosylation, trafficking and signaling in endothelial cells, leading to the inhibition of migration and tube formation in human vascular endothelial cells (213). Furthermore, *in vivo* experiments demonstrated that ITZ, alone or in combination with pemetrexed, exhibits anticancer activity in NSCLC, basal cell carcinoma and medulloblastoma (214).

Xu *et al* (215) demonstrated that ITZ inhibits cholesterol trafficking in human endothelial cells, leading to inhibition of mTOR. Additionally, Kim *et al* (216) reported that ITZ inhibits the Hedgehog signaling pathway. In GBM cells, the decrease of cholesterol in the cell membrane leads to decreased Akt1 activity, resulting in inhibition of mTOR and subsequent apoptosis (217). Furthermore, the *in vivo* growth of two Hedgehog-dependent tumor models, a medulloblastoma and a basal cell carcinoma, was reduced in animals receiving the antifungal drug (216). The same results were obtained in another study using pleural mesothelioma cells (218).

Another possible mechanism of action involves the effect of ITZ on P-gp expression (219). Positive results in phase II clinical trials for the treatment of lung cancer, prostate cancer and basal carcinoma showed good tolerance and type I toxicity (220,221). Other studies conducted in breast, lung, ovarian or pancreatic cancers also showed promising results (221-224). More clinical trials are currently actively recruiting for different types of tumors using ITZ alone or in combination (clinical trial no. NCT03513211, NCT02749513, NCT03664115, NCT03994211, NCT04018872 and NCT03972748). Cautiousness should be exerted, as there is some evidence that the use of antifungal drugs may interfere with the actions of other anticancer agents, in particular, with rituximab (225).

15. Ivermectin (IVM)

IVM is an antiparasitic drug used to treat numerous types of parasitic infestations, belonging to the avermectin family of medications. It works by causing the parasite's cell membrane to increase its permeability, resulting in paralysis

and death. The avermectins are 16-membered macrocyclic lactone derivatives generated as fermentation products by *Streptomyces avermitilis*. IVM has shown some preliminary antitumor activity (226-229). Jiang *et al* (230) found that IVM reversed the resistance of tumor cells to chemotherapeutic drugs. Mechanistically, IVM exerts these effects mainly by reducing the expression of P-gp via inhibition of the EGFR. IVM binds to the extracellular domain of EGFR, inhibiting its activation and the downstream ERK/Akt/NF-κB signaling cascade. The inhibition of NF-κB leads to reduced P-gp transcription. IVM also inhibits yes-associated protein 1 (YAP1), which acts by activating the transcription of genes involved in cell proliferation and apoptotic suppression (231). An exploration of drugs targeting YAP1 showed that IVM has antitumor properties (232). Also, IVM exhibits karyopherin β1 (KPNB1)-dependent antitumor properties against ovarian cancer (233). KPNB1 encodes nuclear transport factors, and in ovarian cancer cells, IVM was found to block KPNB1 function, causing apoptosis and cell cycle arrest (233). *In vivo* use of IVM with paclitaxel produces a synergistic antitumor effect (233).

IVM was identified as an effective inhibitor of the canonical WNT pathway that acts on a transcriptional factor of the TCF family, blocking colon and lung cancer proliferation; such findings were validated in CRC preclinical models of tumor growth with cell lines and patient-derived primary tumors (234). Kwon *et al* (235) found that treatment with IVM led to transcriptional modulation of genes associated with the epithelial-mesenchymal transition and maintenance of a CSC phenotype in TNBC, resulting in an impairment of clonogenic self-renewal *in vitro*, and inhibition of tumor growth and metastasis *in vivo*. Beyond the aforementioned examples, IVM exerts its antitumor effects in different types of cancer using a wide variety of mechanisms. IVM interacts with several targets, including the multidrug resistance (MDR) protein, the Akt/mTOR pathways, purinergic receptors, p21-activated kinase-1, cancer-related epigenetic dysregulators such as SIN3A and SIN3B, RNA helicase and chloride channel receptors (226).

16. Leflunomide (LFN)

LFN is an inhibitor of the mitochondrial enzyme dihydroorotate dehydrogenase, which plays a central role in the *de novo* pyrimidine synthesis pathway. Therefore, LFN inhibits the duplication of rapidly dividing cells, especially lymphocytes (236). The FDA approved it as an immunomodulatory drug for the treatment of patients with rheumatoid arthritis (237). A number of studies reported that LFN inhibits the growth of several different cell types, including human MM, prostate cancer, NETs, breast cancer and neuroblastoma cells (238-241). Hanson *et al* (242) showed that LFN exhibits potential therapeutic value in treating melanoma. They demonstrated that LFN reduced cell viability in three melanoma cell lines harboring the BRAFV600E mutation. Additionally, they found that LFN affects melanoma cells that do not harbor BRAF mutations, showing that the treatment of LFN with targeted therapies that block components of the proproliferative mitogen-activated protein kinase (MAPK) pathway, such as BRAF (inhibited by vemurafenib) and MAPK kinase (MEK; inhibited by selumetinib), exhibit synergistic antitumor activity in melanoma (242). Caution should be exerted when using LFN in combination, since the concomitant use of LFN and methotrexate (MTX) could produce lethal liver-damage or hepatotoxicity (243).

Beyond the aforementioned immunosuppressive effects of LFN, other mechanisms of action have been described. For example, LFN can induce G1 cell cycle arrest via modulation of cyclin D2 and retinoblastoma protein (pRb) expression, and decreasing the phosphorylation of Akt, p70 S6 kinas, and eukaryotic translation initiation factor 4E-binding protein-1 (238). As Ephrins and their receptors (Eph) have been identified as critical regulators of angiogenesis, Chu and Zhang (244) found that LFN has antiangiogenic effects on breast cancer cells via the inhibition of the angiogenic soluble Ephrin-A1/EphA2 system. In supernatants of breast cancer cell lines co-cultured with endothelial cells, soluble Ephrin-A1 was released from breast cancer cells; the co-culture supernatants containing soluble Ephrin-A1 caused the internalization and downregulation of EphA2 on endothelial cells, and activation of human umbilical vein endothelial cells (HUVECs). The soluble Ephrin-A1/EphA2 system functions regulating angiogenesis in breast cancer, but similar results were found in a bladder carcinogenesis model via inhibition of the soluble Ephrin-A1/EphA2 system; Ephrin-A1 overexpression could partially reverse LFN-induced suppression of angiogenesis and subsequent tumor growth inhibition (244). Cook *et al* (240) showed that LFN and its natural metabolites suppress Achaete-scute homolog 1, both at the protein and mRNA level, via a mechanism that is predominately dependent upon the Raf-1/MEK/ERK1/2 pathway. Other mechanisms of action have also been considered, as described by Zhang and Chu (245). Currently, a phase I/II trial of LFN in females with previously treated metastatic TNBC is actively recruiting (clinical trial no. NCT03709446).

17. Lithium (LTH)

LTH has traditionally been used for the treatment of bipolar disorders (BPD). LTH affects all neurotransmitter pathways through highly complex networks. Therefore, it is hypothesized to restore the balance among aberrant signaling pathways in critical regions of the brain (246). It has been shown that the actions of LTH on signal transduction [phosphoinositide hydrolysis, adenylyl cyclase, G protein, glycogen synthase kinase (GSK)-3β, protein kinase C and its substrate, myristoylated alanine-rich C kinase substrate] trigger long-term changes in neuronal signaling patterns that account for the protective properties of LTH in the treatment of BPD (247,248). Through its effects on GSK-3β and protein kinase C, LTH may also modify the level of phosphorylation of cytoskeletal proteins, which leads to neuroplastic changes associated with mood stabilization (248). Chronic LTH regulates transcriptional factors, which in turn may modulate the expression of a variety of genes that compensate for aberrant signaling associated with the pathophysiology of BPD (248,249).

LTH effects on cancer cells have been attributed to the inhibition of GSK3, which impacts multiple cell functions (250). GSK3 inactivates glycogen synthase, a negative regulator of WNT signaling (251). LTH induces anti-invasive,

antimigratory and antiproliferative effects through the inhibition of GSK-3; knockdown of either GSK-3α or GSK-3β produced suppression (252). Additionally, LTH changes the release of neurotransmitters, modulates the activity of several phosphoproteins and directly inhibits inositol monophosphatase (253). A study showed inhibitory effects of LTH on proliferation and growth in prostate cancer cell lines and tumor xenografts via GSK3 inhibition, due to reduced interactions between the transcription factor E2F and DNA that induce S-phase gene expression (254). LTH has also been shown to increase the effect of doxorubicin and etoposide, acting on the cell cycle in prostate cancer cell lines (255). In colon cancer cells, it was suggested that LTH could prevent metastasis through inhibition of lymphangiogenesis, as the inactivation of GSK-3 downregulates Smad3, which reduced expression levels of TGFβ-induced protein, a key mediator of lymphangiogenesis in colon cancer (256). Long-term use of LTH has been associated with nephropathy, and some links between LTH and cancer development have been established (257). However, this fact remains a matter of debate. In a Danish study, overall CRC risk was not affected by the use of LTH, although a slight overall risk for distal colon tumors was seen (258). LTH is accumulated in GBM cells faster and in greater quantities than in neuroblastoma cells, and its levels further increase with chronic exposure (259). Other studies revealed the anti-invasive potential of LTH in GBM cell lines (252,253,259,260). Currently, two actively recruiting clinical trials are ongoing, testing LTH in osteosarcoma, CRC and esophageal cancer (clinical trial nos. NCT03153280 and NCT01669369) (261).

18. Metformin (MET)

MET is a biguanide, widely used for the treatment of type 2 diabetes. Although MET has been used for >50 years, the exact molecular mechanisms of its therapeutic action remain a matter of debate (262). MET induces its antihyperglycemic effects mainly through the blockage of gluconeogenesis. The site of drug action is at the mitochondrial level, mediated by transient and specific inhibition of the respiratory-chain complex 1, inducing a drop in cellular energy charge (263). As a consequence, cellular ATP concentrations fall, and the increase in both ADP/ATP and AMP/ATP ratios triggers AMPK. AMPK coordinates a wide array of compensatory, protective, and energy-sparing responses, ultimately leading to a reduction in hepatic glucose output (264,265). Additional studies are required to understand how MET modulates the respiratory-chain complex 1 (266). Evans *et al* (267) presented evidence that individuals with diabetes treated with MET presented a substantially lower cancer burden than individuals with diabetes treated with other agents, and other studies reached similar conclusions (267-272). The studied populations were patients with type 2 diabetes; therefore, its conclusions may not qualify for nondiabetic subjects. Additionally, these studies were based on retrospective reviews of medical records, and are thus potentially subject to a variety of biases (273). Therefore, the utility of MET in oncology is based on pharmacoepidemiologic data that are considered controversial (274), including studies into prostate cancer risk and MM outcomes (275,276). Despite encouraging *in vitro* and epidemiological data for diverse tumor types, available results from randomized clinical trials on MET are mostly disappointing (277).

The indirect effects of MET on cancer have been described. The proposed mechanisms of action of MET in oncology can be divided into two broad, non-mutually exclusive categories: Indirect and direct (278). Indirectly, MET acts on the liver to inhibit glucose production, producing changes in the metabolic and endocrine circuits that could affect various cellular and molecular processes that influence cancer biology. The most notable change of oncologic relevance is the reduction of hyperinsulinemia, given prior evidence that high insulin levels can stimulate the proliferation of a subset of common cancers (279). MET also influences adipokine levels in cancer biology *in vivo*, but clinical data are needed (280). Previous studies suggested that the immunological or anti-inflammatory modulatory actions of MET are relevant in cancer treatment; however, again there are no clinical data to support or refute these observations (281,282).

Regarding the direct effects of MET on cancer, dozens of *in vivo* and *in vitro* studies have reported direct antineoplastic activity of MET in model systems without providing relevant data for clinical applications (264,278). One study provided evidence regarding the role of AMPK; experiments showed that activation of AMPK is essential in the action of biguanides by showing that the direct AMPK activator A-769662 has antineoplastic activity *in vivo* (283). Other findings suggest the relevance of inhibition of respiratory-chain complex 1 (263,284). Modification in the metabolism of cancer cells in a manner that is influenced by mutations in exposed cancer cells are important consequences of the MET-induced reduction of oxidative phosphorylation, suggesting that rational drug combinations may be a useful approach (285,286). An excellent work published by Pollak (278) demonstrated a rationale for combining biguanides with inhibitors of kinases that control glycolysis. Cancer cells may have a requirement to increase oxidative phosphorylation to counterbalance the diminished glycolysis that appears as a consequence of oncogenic kinase inhibition. With the use of MET, the compensatory increase is attenuated, resulting in the enhanced antineoplastic activity of the kinase inhibitor (287). Another study found that a direct action of MET on cancer cells inhibits growth *in vitro* in association with AMPK activation and inhibition of mTOR, as a consequence of MET-induced energetic stress (288). Other mechanisms have also been proposed, showing contradictory results; it remains to be determined if AMPK activation in cancer cells, due either to the inhibition of oxidative phosphorylation by MET or the direct activation by specific pharmacological activators has antiproliferative or prosurvival consequences (289). Cancer cells functionally deficient in AMPK are less likely to reduce energy consumption in the face of a biguanide-induced reduction on ATP generation, and are therefore more likely to experience a lethal energetic crisis (290). Mutations in genes encoding respiratory-chain complex 1 in cancer cells have also been shown to be hypersensitive to biguanides (284,291). There are two completed trials on multi-histology solid tumors assessing the dose-limiting toxicity of various treatments that include MET with promising results (292,293). Thus, enthusiasm remains for understanding the role of MET in cancer through ongoing clinical research (294). At the moment, >80

actively recruiting clinical trials are open; details can be found in Saraei *et al* (271).

19. Niclosamide (NCS)

NCS is a medication used to treat tapeworm infestations by inhibiting glucose uptake, oxidative phosphorylation and anaerobic metabolism produced in the parasite (295). Mounting evidence indicates that NCS is a noteworthy multifunctional drug with a wide variety of pharmacological activities, due to its capacity to uncouple mitochondrial phosphorylation and modulate a selection of signaling pathways associated with tumor suppression (296). In adrenocortical carcinoma, it was found that NCS inhibits cell proliferation, which was associated with apoptosis, reduction of epithelial-to-mesenchymal transition, β-catenin levels and mitochondrial uncoupling activity (297).

In breast cancer, Fonseca *et al* (298) reported that NCS inhibits mTOR complex 1 (mTORC1) signaling in a breast cancer cell line. A mechanistic study indicated that NCS lowers the cytoplasmic pH and may indirectly lead to inhibition of mTORC1 signaling (299). Wang *et al* (300) found that NCS inhibited the formation of breast cancer spheroids and induced apoptosis. Karakas *et al* (301) reported that NCS enhanced the antitumor activity of the palladium(II) saccharinate complex, leading to enhanced cytotoxic activity in breast CSCs. In TNBC, it was found that NCS alone or in combination with cisplatin suppresses the growth of xenografts of cisplatin-resistant cells (302). Mechanistically NCS reversed the epithelial-mesenchymal transition phenotype, inhibited Akt, ERK and Src signaling pathways, and inhibited the proliferation of both cisplatin-sensitive and cisplatin-resistant TNBC (302).

NCS inhibited the growth of colon cancer cells from human patients both *in vitro* and *in vivo*, regardless of mutations in adenomatous polyposis coli (APC) (303). It was found that NCS inhibited colon cell migration, invasion, proliferation and colony formation *in vitro*, and also reduced liver metastasis in a mouse model (304). Suliman *et al* (305) measured growth inhibition and the apoptosis of three colon cancer cell lines after treatment with NCS, observing that NCS is associated with inhibition of the Notch signaling pathway and increased expression of the tumor suppressor microRNA-200 family. Other studies identified NCS as a selective inhibitor of GBM cell viability, revealing that NCS suppressed WNT, Notch, mTOR and NF-κB signaling pathways (296,305,306). Pre-exposure to NCS significantly diminished the malignant potential of glioma cells *in vivo* (307). Additionally, it was reported that inhibition of STAT3 signaling led to inhibited growth of head and neck cancer cells both *in vitro* and *in vivo*, and enhanced the antitumor effect of erlotinib (308).

The Notch signaling pathway is essential in the generation of hematopoietic stem cells, and activated Notch receptors are cleaved to release the Notch intracellular domain, which moves to the nucleus and binds to transcription factors such as CBF1 to alter gene expression (309). NCS was identified as an inhibitor of endogenous Notch signaling in acute myeloid leukemia (AML) cells (300). Additionally, it was determined that NCS increased the levels of ROS in AML cells. NCS was synergistic with the chemotherapeutic agents cytarabine, etoposide and daunorubicin *in vitro*, and inhibited the growth of AML cells in nude mice (310).

It is estimated that ~20% of patients with NSCLC harbor mutations in the EGFR gene, which promotes cancer cell growth (311). EGFR inhibitors (such as erlotinib) are used, but drug resistance is present in certain cases. It was found that NCS treatment overcomes erlotinib resistance, as NCS in combination with erlotinib potently suppressed the growth of erlotinib-resistant lung cancer cells and increased apoptosis in tumors (312). Additionally, NCS is effective in reducing the radioresistance of human lung cancers *in vitro* and *in vivo*; the mechanism involves inhibition of JAK2-STAT3 activity induced by radiation (313). One study determined that NCS enhanced the suppression of STAT3 in a cell line of NSCLC (314). Another study found that NCS reactivated the tumor suppressor protein phosphatase 2A in NSCLC cells (315). NCS inhibited cell proliferation, colony formation, tumor sphere formation and induced mitochondrial dysfunction by increasing mitochondrial ROS production (315).

It has been reported that NCS can effectively inhibit osteosarcoma cell proliferation, migration, and survival (316). This inhibitory effect is associated with decreased expression of c-Fos, c-Jun, E2F1 and c-Myc. NCS also inhibits osteosarcoma tumor growth in a mouse xenograft tumor model (316). Additionally, NCS produces growth inhibition of ovarian tumor-initiating cells. Subsequently, NCS was found to inhibit ovarian tumor-initiating cells *in vitro* and *in vivo* through alterations of metabolic pathways in ovarian cancer cells (317). King *et al* (318) found that NCS decreased β-catenin transcriptional activity and reduced cell viability in ovarian carcinoma; NCS inhibited tumor growth and the progression of human ovarian cancers in xenograft animal models.

Enzalutamide is a novel antiandrogen for the treatment of metastatic, castration-resistant prostate cancer (319). Resistance to enzalutamide therapy was reported to be associated with the expression of AR splice variants, including the AR-V7 isoform; it was found that NCS downregulated AR-V7 expression and inhibited AR-V7 transcription (320). Treatment of NCS + enzalutamide in prostate cancer cells resulted in inhibition of colony formation and growth arrest (321). Furthermore, NCS was reported to have the ability to inhibit mitochondrial function, which is associated with acidic pH in prostate NET cells (322). NCS exhibits pH-dependent toxicity in a castration-resistant prostate NET cell line (322). Additionally, NCS inhibits proliferation and anchorage-independent colony formation in two renal cell carcinoma cell lines, and synergizes with cisplatin and sorafenib both *in vivo* and *in vitro* (323). Recently, the effects of NCS alone and in combination with paclitaxel in cervical cancer were found experimentally (324). NCS significantly inhibited proliferation and induced apoptosis in a panel of cervical cancer cell lines, and inhibited tumor growth in a cervical cancer xenograft mouse model, with it demonstrated that NCS induced mitochondrial dysfunctions by inhibiting mitochondrial respiration, complex I activity and ATP generation, which led to oxidative stress (324). Currently, four clinical trials are actively recruiting for colon and prostate cancer (clinical trial nos. NCT02687009, NCT02687009, NCT03123978 and NCT02807805).

20. Nitroxoline (NTX)

NTX is a widely used antibiotic that is particularly useful for the treatment of urinary tract infections. NTX has gained

considerable attention due to its anticancer properties. These properties have been associated with angiogenesis inhibition by targeting methionine aminopeptidase 2 and sirtuin 1/2, arresting the migration and invasion of cancer cells by affecting cathepsin B, and directly inducing apoptosis (325-327).

NTX demonstrated potent anticancer activity against various types of cancer cells, including lymphoma, leukemia, glioma, and bladder, breast, pancreatic and ovarian cancer cells in a dose-dependent manner (327). Furthermore, NTX effectively and dose-dependently inhibited the growth of urological tumors in orthotopic mouse models (327). Additionally, it was found that NTX sulfate, one of the most common metabolites of NTX, may inhibit the proliferation of T24 cells and HUVECs (327). The results provide evidence for the repurposing of NTX for clinical anticancer applications, particularly for bladder cancer treatment (327). These results, in addition to the known safety profile of NTX and well-defined pharmacokinetic properties, successfully advanced NTX repurposing into a phase II clinical trial in China for non-muscle invasive bladder cancer treatment (clinical trial no. CTR20131716) (327). In another study, Mao *et al* (328) found that NTX induced apoptosis in >40% MM cells within 24 h, which was induced by activation of caspase-3 and inactivation of poly(ADP-ribose) polymerase, an essential enzyme in DNA damage repair. NTX also suppressed prosurvival proteins Bcl-xL and Mcl-1. Moreover, NTX suppressed the growth of MM xenografts in nude mice models. Mechanistically, NTX was found to downregulate tripartite motif-containing protein 25 and upregulate p53 (328).

21. Nonsteroidal anti-inflammatory drugs (NSAIDs)

NSAIDs are a family of drugs used to treat inflammation, mild-to-moderate pain and fever. Probably the best known NSAID is AAS, used since 1897 as an analgesic, antipyretic, and inhibitor of platelet aggregation (329). AAS acts as an acetylating agent that covalently attaches an acetyl group to serine residue S530 in the active site of cyclooxygenase (COX), leading to the inhibition of prostaglandins which are the precursors of thromboxanes (330). A substantial body of evidence has established that AAS has antineoplastic effects *in vitro* (331). Those studies established a close link between inflammation and cancer, suggesting that the anti-inflammatory properties are the central mechanism of action (332). As such, numerous clinical trials have been conducted (333). Cole *et al* (334) performed a meta-analysis of four extensive studies, the Aspirin/Folate Polyp Prevention Study, the Colorectal Adenoma Prevention Study (Cancer and Leukemia Group B), the United Kingdom Colorectal Adenoma Prevention Study and the Association pour la Prevention par l'Aspirine du Cancer Colorectal, concluding that AAS is an active chemopreventive agent in CRC. Additionally, several combinations of AAS with other chemopreventive agents have been evaluated for the prevention of CRC, in addition to clinical studies investigating the use of AAS in treating the dissemination of CRC that leads to liver metastases (clinical trial no. NCT03326791) (333).

In patients diagnosed with Lynch syndrome, which leads to a higher-than-average chance of developing CRC or endometrial cancer, the anticancer efficacy of AAS was determined (clinical trial no. NCT02497820) (333). Additionally, AAS may reduce the risk of metastases and death in patients with lung, prostate, endometrial and breast cancers (335). Another meta-analysis found a decreasing risk of glioma following NSAID treatment, including non-AAS-NSAIDs and AAS; the authors concluded that NSAID use was significantly associated with a lower risk of central nervous system tumors (336). Beyond inhibiting the synthesis of prostaglandin E2 (PGE2), AAS is associated with increased expression of 15-hydroxyprostaglandin dehydrogenase (15-HPGD), leading to the inactivation of PGE2 by another pathway (337). Furthermore, AAS can block PGE2-induced secretion of the C-C motif chemokine ligand 2 and thus the activation of myeloid-derived suppressor cells, thereby causing immune suppression (338).

Immune function is also influenced by AAS, which increases COX-dependent production of resolvin. Resolvins are byproducts of ω-3 fatty acids, which have an essential role in promoting the restoration of normal cell function following inflammation (339). As AASs also decrease platelet aggregation, they could modulate immune function because activated platelets suppress the natural killer cell-mediated lysis of tumor cells (340). It was also demonstrated that AAS activates the NF-κB signaling pathway, inducing apoptosis in models of human cancer (341). At present, >40 clinical trials are actively recruiting using AAS alone or in combination to evaluate its efficacy in cancer treatment (261).

Beyond AAS, there are other NSAIDs, such as celecoxib (CXB), diclofenac (DCF), +-ibuprofen (IBP), ketorolac (KTL), naproxen (NPX), piroxicam (PXM) and sulindac (SLD). Various studies have been conducted using NSAIDs alone or in combination with other drugs for the treatment of cancer (342-344). It is important to note that NSAIDs reduce blood flow to the kidneys, decreasing the elimination of MTX and therefore increasing its blood concentration, what could increase its side effects (345).

CXB is a selective COX-2 inhibitor that was approved by the FDA for the treatment of familial adenomatous polyposis to prevent the formation and growth of colon polyps (261). CXB blocks COX-2 but has little effect on COX-1, and is therefore further classified as a selective COX-2 inhibitor (346). It was found to be useful in the prevention of colon adenomas in a randomized clinical trial, but caused potential cardiovascular events, which limited its advancement (347). It was reported that patients receiving CXB exhibited chemopreventive effects. As determined by a decreased cumulative incidence of advanced adenomas over 5 years (348). Also, preclinical evidence suggests that CXB may provide chemopreventive activity against breast cancer. Clinical trials also showed positive results; two case-control studies illustrated that a standard dose intake of CXB significantly reduced the risk of breast cancer (349,350). CXB inhibits the WNT/β-catenin signaling pathway and its gene products, including survivin and cyclin D1, exhibiting chemopreventive effects against colon cancer (351,352). It is hypothesized that CXB induces several potential antitumor mechanisms, including inhibition of proliferation, induction of apoptosis, immunoregulation, regulation of the tumor microenvironment, antiangiogenic effects, and resensitization of other antitumor drugs (353). Recently, Yu *et al* (354) proposed that the effects of CXB may be due to regulation of tumor autophagy. Currently, 23 actively recruiting clinical trials at different stages are

studying the safety and effectiveness of CXB in a variety of tumor types (355).

Leidgens *et al* (356) demonstrated that DCF induced c-myc inhibition followed by decreased gene expression of GLUT1, as well as decreased lactate dehydrogenase A and lactate secretion, leading to decreased lactate-mediated immunosuppression in a murine glioma model. Another study from the same research group demonstrated that DCF inhibits STAT3 phosphorylation and lactate formation, induces cell cycle arrest at G2/M, and delays tumor growth in an *in vivo* animal model (356). It has also exhibited antitumor activity in a variety of malignant cell lines *in vitro* (357). Arisan *et al* (358) hypothesized that DCF-mediated apoptosis is associated with inhibition of the PI3K/Akt/MAPK signaling axis. DCF also regulates mitochondrial adenine nucleotide transferase and the oxidative phosphorylation complex V, leading to decoupling of oxidative phosphorylation and subsequent reduced ATP generation and cell proliferation (359). In neuroblastoma, DCF enhanced chemotherapy-induced apoptosis via upregulation of p53 (360).

IBP, the most commonly used over-the-counter NSAID, was efficient at decreasing the mitosis rate and inhibited the proliferation of glioma, neuroblastoma, CRC, bladder, breast, lung, pancreatic and gastric cancer cells (361,362). In particular, this drug showed superior effectiveness compared with other NSAIDs in suppressing the proliferation and inducing the apoptosis of human prostate cancer cells at clinically relevant concentrations (361). *In vitro* experiments demonstrated that IBP induces antiangiogenic effects, apoptosis, reduction of cell proliferation, and altered expression of Akt, p53, proliferating cell nuclear antigen, Bax and Blc2 (261).

KTL was proposed to treat oral cancer via inhibition of the ATP-dependent RNA helicase DDX3X (363). Also, KTL salt has shown to suppress early breast cancer relapse (364). KTL is a chiral molecule administered as a 1:1 racemic mixture of the S- and R-enantiomers; the S-enantiomer is considered the active component in pain management with selective activity against COX enzymes (365). The R-enantiomer exhibits activity as an inhibitor of Rac1 and Cdc42. KTL differs from other NSAIDs by functioning as two distinct pharmacologic entities due to the independent actions of each enantiomer. In a recent review, Hudson *et al* (365) summarized the evidence supporting the benefits of KTL administration for patients with ovarian cancer, also discussing how simultaneous inhibition of these two distinct classes of targets (COX enzymes and Rac1/Cdc42 by S-KTL and R-KTL, respectively) may each contribute to anticancer activity.

NPX induced significant inhibition of the effects of the carcinogen azoxymethane, an inducer of colon adenocarcinoma multiplicity in rats (344). Chaudhary *et al* (366) conducted a study using a $Ptch1^{+/-}$/SKH-1 hairless mouse model, which is highly sensitive to ultraviolet-B (UVB) radiation; they found that NPX also works by reversibly inhibiting both COX-1 and COX-2. It has been demonstrated that NPX reduces tumors developed following chronic UVB irradiation of these animals in both basal and squamous cell carcinoma. The mechanism of action of NPX remains a matter of debate. A phase I clinical study is underway to determine the adverse effects and optimal dose of NPX in preventing DNA mismatch-repair-deficient CRC in patients with Lynch syndrome (clinical trial no. NCT02052908) (333).

PXM blocks ornithine decarboxylase induction, inhibiting polyamine production involved in non-melanoma skin carcinogenesis (367). PXM can induce tumor cell apoptosis and suppress MMP-2 activity (368). Actinic keratosis (AK) is a chronic progressive disease that may develop into skin cancer; damage to the skin is multifactorial, but UVB radiation is the paramount factor related to AK pathogenesis (369). Local application of PXM inhibits COX, resulting in blockade of the biosynthesis of PGs and an increase in 15-HPGD expression. Also, the treatment leads to a reduction of proliferation, tumor progression and angiogenesis, as well as an increase in apoptosis (370). Campione *et al* (367,371) found that after topical treatment of AK with PXM, typical epidermal architecture was restored. The efficacy of PXM is related to its activity on both COX enzymes. In a preliminary open-label trial, researchers evaluated the efficacy and tolerability of PXM 1% gel in the treatment of patients affected by AKs; they observed improvement either in the typical features of the AKs or in the perilesional area, observing a healing response in >50% in AKs with the use of PXM (367,371).

Palmerini *et al* (372) analyzed, in a preclinical model of human colon cancer, the action of PXM on cancer progression in $Mlh1^{+/-}$/$APC1638^{N/+}$ mice. PXM diminished the total number of tumors per mice by 80% in the small intestine. Conversely, PXM augmented tumor incidence, multiplicity and volume in the colon. Apoptosis was increased in the epithelium of the large intestine; accordingly, tumors were decreased at this site. In the cecum, PXM increased tumorigenesis, but apoptosis was not diminished, therefore suggesting that other mechanisms play a role in the differential organ-specific effects of PXM on tumorigenesis (372). Further studies are required to elucidate the precise antitumor mechanism of action of PXM.

SLD induces apoptosis and inhibits tumor growth *in vivo* in patients with head and neck tumors (373). Additionally, a substantial reduction was observed in colonic adenomas in patients with familial polyposis (373). Giardiello *et al* (374) reported that SLD decreases the number of adenomas, and Takayama *et al* (375) showed that SLD significantly suppresses the number of aberrant crypt foci in a randomized trial. Sulindac and its metabolites also appear to induce apoptosis in colonic adenomas *in vivo* (375). One clinical trial is actively recruiting to analyze the combination of eflornithine, a medication used to treat African trypanosomiasis, and SLD in reducing the incidence of adenomas and second primary CRCs in patients previously treated for stage 0-III CRC (clinical trial no. NCT01349881).

22. Phosphodiesterase-5 inhibitors (PDE5Is)

Three PDE5Is, sildenafil (SLD), tadalafil (TLD) and vardenafil (VLD), are approved for the treatment of erectile dysfunction (ED) (376). SLD and TLD are also approved for the treatment of pulmonary arterial hypertension (377). Additionally, there is some evidence of beneficial effects in a variety of clinical conditions, including female sexual arousal disorder, overactive bladder, incontinence, Raynaud's disease, heart failure and stroke (378). Regarding the mechanism of action, it should be stressed that the superfamily of mammalian cyclic nucleotide PDEs constitute a complex family of hydrolases

that catalyze the hydrolytic breakdown of cyclic adenosine monophosphate (cAMP) and cyclic guanosine monophosphate (cGMP) into their biologically inactive counterparts 5'-AMP and 5'-GMP, respectively (379). Inhibition of the breakdown of cGMP, which regulates blood flow in the penis, promotes amelioration of the symptoms of ED. Inhibition of PDE5 activity is emerging as a promising approach via apoptosis and restoration of normal intracellular cGMP levels, thereby resulting in the activation of various downstream molecules to inhibit proliferation, motility and invasion (380).

There are reports in different tumor cell types of increased ROS production and apoptosis following treatment with PDE5Is (381). SLD and VLD induced caspase-dependent apoptosis of B-cell chronic lymphocytic leukemia cells (382). Also, PDE5Is were shown to alter the tumor microenvironment by reducing myeloid-derived suppressor cell function and thus augmenting endogenous antitumor immunity (383). Enhanced tumor suppression and apoptotic activity were seen in a NSCLC cancer orthotopic tumor model following SLD-docetaxel combination treatment (384), as well as with a SLD-capecitabine combination in breast cancer (385) and the combination of SLD-doxorubicin in *in vivo* models of prostate cancer (386). High levels of PDE5 have been described in several types of cancer, such as prostate, lung and breast cancers, CRC and melanoma (387). It was previously demonstrated that PDE5/cGMP/protein kinase G signaling targets the Hippo/tafazzin pathway to maintain the stemness of prostate cancer stem cells, evidencing a new role of PDE5 in governing stem cell features (388). TLD also attenuated TGFβ1-induced fibroblast-myofibroblast trans-differentiation, suggesting a potential role for PDE5Is in preventing stromal enlargement (389).

A retrospective analysis of 4,974 males showed that the prolonged use of PDE5I was associated with a lower incidence rate of prostate cancer (390). The apoptotic and growth-inhibitory activities of PDE5Is have been demonstrated in numerous lung cancer cell lines (391-393). VLD significantly increases the accumulation and enhances the antitumor activity of trastuzumab in a xenograft mouse model of lung cancer (394). Another study showed that SLD was able to enhance the antitumor effects of pemetrexed in NSCLCs, and this effect was further enhanced *in vivo* via co-treatment with the mTOR inhibitor temsirolimus (380). Increased PDE5 expression has been reported in various cell lines deriving from breast cancer (395-397). It was demonstrated that PDE5Is could act as chemopreventive agents due to their ability to suppress 1-methyl-1-nitrosourea-induced mammary carcinogenesis (398). It was reported that SUC metabolites inhibit the MEK/ERK signaling cascade in CRC cell lines, indicating an additional molecular mechanism via which SUC inhibits tumor cell growth (399). Additionally, the treatment of human CRC cells with SLD resulted in cell proliferation inhibition, cell cycle arrest and apoptosis along with increased intracellular ROS levels *in vitro*, causing the reduction of xenograft tumor growth in nude mice (400).

It has been demonstrated that SLD suppresses polyp formation in mice treated with azoxymethane/dextran sulfate sodium (401), highlighting the chemopreventive role of PDE5Is. In both neuroblastoma and hybrid neuroblastoma-glioma cells, both the presence and regulation of PDE5 mRNA during cell differentiation was observed (402). In medulloblastoma cells, PDE5Is interacted with vincristine/etoposide/cisplatin to cause cell death (403). PDE5I promoted autophagy and enhanced chemotherapy-induced DNA damage in a nitric oxide (NO) synthase-dependent manner (404). Oral administration of SLD and VLD selectively improved tumor capillary permeability in gliosarcoma-bearing rats, without changes in normal capillaries (405). Notably, tumor-bearing rats treated with adriamycin in combination with VLD exhibited significantly longer survival than rats treated with adriamycin alone (405). PDE5I enhanced transport and therapeutic efficacy of trastuzumab in hard-to-treat brain metastases from different primary tumors (406). TLD can also enhance the treatment efficacy of the chimeric anti-CD20 monoclonal antibody rituximab by improving the microvascular permeability in an intracranial brain lymphoma mice model (407). In thyroid cancer cells *in vitro*, SLD and TLD diminished proliferation, and at lower doses, they were also able to reduce cellular migration (408). The role of PDE5 in melanoma remains controversial. In a cohort study, males who used SLD for ED exhibited a significantly elevated risk of developing melanoma (394). A case-control study showed that the use of PDE5Is was associated with a modest but significantly increased risk of melanoma (409). Later, a large study failed to find evidence of a positive association between PDE5I exposure and melanoma risk (410). Recently, a meta-analysis revealed an increased risk of malignant melanoma in users of PDE5I (411); however, the inherent limitations of observational studies should be considered. Further studies are needed to evaluate this association properly.

23. Pimozide (PMZ)

PMZ is a neuroleptic drug that selectively blocks dopamine receptor D2, and is used to treat several mental and mood disorders, such as chronic schizophrenia, as it reduces dopamine activity (412). PMZ has been studied as a putative anticancer treatment, showing satisfactory results in melanoma, central nervous system tumors, osteosarcoma, neuroblastoma, myeloproliferative neoplasms, CRC, breast, lung, prostate, ovarian and pancreatic cancers, and HCC (412-423). There are several proposed mechanisms of action. PMZ was previously shown to inhibit the proliferation of the human breast cancer-derived cell line MCF-7 *in vitro* by blocking estradiol-induced growth (418). Additionally, a previous study demonstrated that PMZ is a potential inhibitor of Ran GTPase (Ran), which belongs to the Ras superfamily of small GTPases, and is involved in various aspects of nuclear structure and function, cell cycle regulation, nuclear transport and cell transformation (424). By decreasing Ran mRNA expression, PMZ also reduces the expression of Akt and phosphorylation of VEGFR2 in breast cancer cell lines and HUVECs, leading to increased caspase-3 activation and apoptotic cell death. PMZ also causes a reduction in cell proliferation, migration and invasion *in vitro*, and lung metastasis *in vivo* (424). This may be due to PMZ-induced downregulation of MMPs-1, -2 and -14 (413). In myelogenous leukemia cells, PMZ has gained attention as an anticancer agent by acting as STAT5 inhibitor, as well as an inhibitor of the STAT3 signaling pathway in HCC and suppressing cancer stem-like cell maintenance (413).

Also, it has been demonstrated that PMZ inhibited the growth of HCC cells by disrupting the WNT/β-catenin signaling pathway and reducing epithelial cell adhesion molecule expression (422). Furthermore, it has been reported that PMZ affects CSCs by inhibiting ubiquitin-specific protease and WD repeat-containing protein 48, which are proteins responsible for inhibiting differentiation and maintaining the cell in an undifferentiated state (421). Also, it is of importance to note that PMZ induces ROS generation by suppressing catalase expression (414). Recently, it has been demonstrated that PMZ inhibits P-gp, increasing apoptosis, as well as the expression of pRB and phosphorylated H2AX in KBV20 cells (425). Finally, Chen *et al* (426) reported that PMZ induces a reversible inhibition of proliferation in liver cancer and has an additive activity with sorafenib, which indicates the potential of pimozide as an adjuvant anticancer therapy.

24. Propranolol (PPL)

PPL is a competitive antagonist of the cardiac β1-adrenergic receptor. It competes with sympathomimetic neurotransmitters to bind to receptors, which inhibits sympathetic stimulation of the heart. Block of neurotransmitter binding to β1 receptors on cardiac myocytes suppress activation of adenylate cyclase, inhibiting cAMP synthesis and reducing protein kinase A activation (427). This results in less calcium influx to cardiac myocytes through voltage-gated L-type calcium channels, meaning there is a diminished sympathetic action on cardiac cells, which produces a decrease in heart rate and arterial blood pressure (428). In 2014, PPL was approved by the FDA to treat infantile hemangioma (IH), providing improved treatment outcomes than previous treatments with corticosteroids, interferon, vincristine or cyclophosphamide (429). IH is a common benign tumor of childhood that is potentially disfiguring or life-threatening (430). It is interesting to analyze the mechanism of actions of PPL on IH, as it is an excellent example of all the mechanisms of action of PPL working in an integrated form. Early on, PPL causes vasoconstriction through the inhibition of NO synthesis and release; ~3 days after the beginning of therapy, PPL inhibits the vasodilation mediated by adrenalin, leading to vasoconstriction. At ~1 week later, PPL induces downregulation of angiogenic factors, such as VEGF and bFGF, and promotes remodeling of the extracellular matrix by inhibiting MMP-2 and MMP-9, which are vital for the process of angiogenesis, producing an abundance of TIMPs (155,431). This action, together with the inhibition of the proangiogenic ERK/MAPK cascade, causes the inhibition of angiogenesis. The long-term effects of PPL are characterized by the induction of apoptosis in proliferating endothelial cells, producing tumor regression (432).

Based on its therapeutic actions against IH, PPL is currently being studied for applications in more malignant vascular sarcomas (433). A clinical study found that patients treated for >1 year with PPL exhibit a reduced risk of progression of malignant melanomas and decreased breast cancer mortality (434,435). Currently, *in vitro* studies have found an antiproliferative effect of PPL in several types of cancer, such as breast, pancreatic and brain cancers (436-438).

Although PPL is by itself effective in cancer treatment, its use in combination with radiotherapy or with standard chemotherapy is auspicious. Several malignant tumors have limited sensitivity to radiotherapy. In these cases, a radiosensitizer is required to overcome this problem. Several studies have shown that antagonists of VEGF, COX-2 and EGFR expression can act as radiosensitizers (439-441). Rico *et al* (442) showed that PPL reduced cell viability and migration in a panel of breast cancer cell lines, and that the effect was increased when combined with MET. Furthermore, the combination reduced tumor growth in two immunocompetent models of TNBC, thereby improving survival. Treatment also reduced metastatic growth, with evidence that PPL reduced colonization in the lungs. Another group retrospectively assessed the impact of selective and non-selective β-blockers on tumor proliferation as measured by Ki67 expression (443). Results showed that non-selective β-blockade reduced tumor proliferation by 66% in early-stage breast cancer. Cell line data showed that PPL dose-dependently reduced tumor cell viability. Data from a phase I clinical trial prospectively treated with PPL for 3 weeks showed that Ki67 staining was reduced by 23% (clinical trial no. NCT00502684) (444).

Endothelial cells are very complex cells expressing a variety of molecules and playing an essential role in several functions, including vascular permeability, hemodynamic sensors endothelium-induced vasodilation, and chemical changes (445). Antiangiogenic agents combined with radiation therapy increase treatment effectiveness, killing both cancer and endothelial cells (446). Regarding chemotherapy, when PPL is used in combination with vincristine, its antimitochondrial and antimitotic effects in neuroblastoma cells are increased; the same results were found in an *in vivo* study using a neuroblastoma mouse model (447). A number of preclinical studies combining PPL with chemotherapeutic agents in different tumor cell lines have been conducted, including gemcitabine in pancreatic cancer cells, imatinib in glioma cells, and PTX in TNBC (448). Due to the very advanced stage of the study, it is essential to mention the phase III clinical trials combining PPL and the COX-2 inhibitor Etodolac for the prevention of CRC recurrence and distant metastatic disease (2). As β-blockers have demonstrated their antitumor properties, it has been suggested that α1-blockers such as terazosin, doxazosin and prazosin may also present potential antitumor activity (449). At present, >15 clinical trials using PPL are ongoing.

25. Riluzole (RZL)

RLZ is used in the treatment of amyotrophic lateral sclerosis by reducing glutamate (GLT) release. RLZ preferentially blocks the tetrodotoxin-sensitive voltage-gated sodium channel (450,451); however, the action of RLZ on GLT receptors has been controversial. The close relationship between the cystine/glutamate transporter (xCT) and GLT release has been well-established (452). The xCT system is an amino acid antiporter or exchanger that typically mediates the exchange of extracellular L-cystine and intracellular L-GLT across the cellular plasma membrane (453).

Aside from its original uses, RLZ has been shown to have antitumor effects. The release of GLT in human cancer is well established; for instance, glioma cells show a more aggressive phenotype when releasing an excess of GLT, inducing neurotoxicity in surrounding neurons (454). Similarly, breast

and prostate cancer cells release an excess of GLT, conferring on them a growth advantage (455). Additionally, inhibition of GLT release by RLZ suppresses the proliferation of GLT receptor 1-positive tumor cells *in vitro* and tumor progression *in vivo* (456). For gliomas and other neuronal cancers, inhibition of xCT reduces the invasiveness of glioma xenografts, likely due to a decrease in GLT release to the extracellular space, resulting in reduced excitotoxic death of neurons via excess GLT (457). In the prostate, AR drives prostate cancer; however, inhibiting AR or androgen biosynthesis induces remission for a short time, following which patients acquire a more aggressive castration-resistant condition with reactivated AR-dependent signaling. Downregulating AR expression has been considered as a potential treatment for prostate cancer (458). Wadosky *et al* (458) demonstrated that RLZ downregulates AR-full length, mutant ARs and AR-V7 expression by protein degradation through the ER stress pathway and selective autophagy.

RLZ has also been studied in melanoma. Once transformed, melanoma cells release excess GLT (459). Following xCT transport, cystine is reduced into two molecules of cysteine (460). In melanocytes, transport of cystine by xCT is used for cell growth, glutathione production and protection of cells from oxidative stress (453). In the absence of xCT, RLZ's GLT release-inhibitory activity is reduced, producing a decrease in RLZ-mediated antiproliferative effects in metabotropic GLT receptor (GRM1)-expressing tumor cells (457,461). In normal melanocytes, the equilibrium between proliferation and differentiation is tightly regulated (462). However, in melanomas, released GLT is used either for increasing proliferation or promoting antiapoptotic responses resulting from mutations in GRM1, 3 and 5, or ionotropic GLT receptors. There is a direct and proportional association between xCT levels and cell proliferation *in vitro*/tumor progression *in vivo* (463). As a rapid increase in intracellular GLT induces cell death in PC12 cells due to an increase of ROS, RLZ-mediated increases in intracellular GLT may lead to similar consequences to melanoma cells (464). As a response to a rapid increase in GLT-mediated oxidative stress, melanoma cells quickly upregulate xCT expression (457). Melanoma cells under oxidative stress due to serum starvation promptly upregulate xCT protein expression within 2-3 h. Some melanoma cells may survive and acquire resistance to RLZ (465). Therefore, these cells can reduce their dependence on xCT, as shown in RLZ-resistant melanoma cell lines (457). Currently, eight clinical trials are ongoing for different types of tumors.

26. Statins (STs)

STs are drugs used to treat lipid disorders due to their effectiveness in preventing the development of cardiovascular diseases (466). STs inhibit the rate-limiting enzyme 3-hydroxy-3-methylglutaryl-coenzyme A reductase (HMG-CoA) and thus the mevalonate pathway that constitutes the initial step in cholesterol biosynthesis (467). Importantly, data suggest that inhibition of the HMG-CoA may underlie protective effects against cancer, as the mevalonate pathway provides geranylgeranyl pyrophosphate and farnesyl pyrophosphate (468). These compounds are used for the prenylation of proteins, a process critical for directing these proteins to the cell membrane (467,469-471). Interference with this process may be disruptive to cell cycle progression and cell proliferation, thereby mediating antineoplastic effects (472).

One study reported the antitumor properties of lovastatin (LVS) on F3II sarcomatoid mammary carcinoma, a highly invasive and metastatic murine tumor model (473). In female mice, treatment increased tumor latency, and decreased tumor formation and metastatic dissemination to the lungs. The antitumor properties of LVS were strongly associated with inhibition of tumor cell attachment and migration; these actions were prevented by the presence of mevalonate. Incubation of F3II cells with LVS produced a rounded-cell phenotype, lacking cortical actin organization, microtubule disruption and inhibition of integrin-mediated focal contacts in LVS-treated cells. LVS decreases membrane localization of Rho, a signaling molecule that requires geranylation for membrane association and activation (474). Also, LVS induces dose-dependent inhibition of the secretion of urokinase, a key proteolytic enzyme during tumor invasion and metastasis, and a significant increase of tissue-type plasminogen activator, a marker of good prognosis in mammary cancer (475).

STs affect the small GTPase Rho, which requires attachment to cell membranes for proper signaling activity. Chimaerins are GTPase-activating proteins (GAPs) that accelerate GTP hydrolysis from Rac, another GTPase of the same family (476). F3II cells transfected with the β2-chimaerin GAP domain exhibiting low intracellular levels of active Rac-GTP were exposed *in vitro* to a panel of STs. Transfected cells were more sensitive to the cytostatic effects of LVS, simvastatin, atorvastatin and rosuvastatin than untransfected controls with high Rac-GTP levels. Transfected tumor cells also showed a higher capacity for detachment from the substrate and apoptosis after ST exposure (477). STs may affect gliomas by altering the mevalonate pathway, with subsequent modulations on the RAS-RAF-MEK-ERK or Akt signaling pathways (478). Combination treatment of STs with azathioprine, a compound that specifically blocks Rac1 activation, demonstrated an enhanced growth-inhibitory effect on F3II cells (477). Observational studies and meta-analyses have investigated the relationship between cancer incidence and ST use (479,480). Studies of all cancer types, as well as specific cancers, are inconsistent, although several studies suggest a positive association with reduced incidence of gastrointestinal cancers. One meta-analysis, including 7,611 patients with gastric cancer in 26 randomized controlled trials and eight observational studies, found a 27% risk reduction associated with ST use (481). Similarly, other meta-analyses have reported that statin use is associated with a reduced risk of esophageal cancer, HCC and other prevalent cancer types, including breast cancer and CRC (482-484). However, other cohorts and case-control studies, as well as meta-analyses, have reported only weak or no significant correlation between reduced cancer risk and statin use (485,486). In summary, studies published up to this point have reported conflicting results, and are overall inconclusive. It should be emphasized that most clinical trials that have been analyzed have endpoints relating to cardiovascular disease. A possible role for STs in cancer prevention can only be determined through carefully designed clinical trials with a sufficiently long follow-up and cancer incidence as a primary endpoint. At present, ~160

clinical trials are evaluating the effect of STs in cancer, both as a therapy and as a biomarker regarding the association between ST use and cancer incidence.

27. Thalidomide (THL)

THL is a classic example of drug repositioning in oncology (487). It was developed and commercialized as a sedative, and shortly after it was prescribed to mitigate nausea and vomiting in pregnancy. It was launched to the market in 1957, and soon after its popularization, it was observed that thousands of newborns presented severe limb defects such as amelia and phocomelia. As a consequence, it was banned in 1961 (488,489). Currently, it is known that the reason for these limb malformations is the binding of THL to cereblon, a protein required in normal morphogenesis (490). Such binding promotes the recruitment of the DNA-binding protein Ikaros and zinc-finger protein Aiolos to the E3 complex, leading to substrate ubiquitination and degradation (490).

Starting in the 1990s with the research of D'Amato *et al* (491), it was found that THL possesses anticancer properties. Subsequently, a clinical trial in patients with MM was carried out with positive results, ending in the approval of its use by the FDA in combination with dexamethasone in newly diagnosed MM patients (492). At present, it is known that THL inhibits the production of TNFα, altering the mechanisms of intracellular transduction by inhibiting NF-κB activation and the synthesis of IL-6, affecting cell proliferation, inflammation, angiogenesis and apoptosis (493). Furthermore, THL affects VEGF levels by downregulating its expression (494). After FDA approval, new analogs of THL with fewer side effects and increased potency were developed and assayed, including lenalidomide (LDM), and pomalidomide (PLM), all belonging to the class of drugs known as immunomodulatory drugs (IMiDs) (495).

In 2003, the FDA granted fast-track status to LDM for the treatment of relapsed or refractory MM. It has been shown that LDM has antitumor activity in a variety of types of lymphoma and leukemia (496). LDM in combination with dexamethasone possesses even higher activity, and the addition of a monoclonal antibody appears to improve efficacy even further (497). Then, in 2015 and 2016, four different combinations of LDM, dexamethasone plus a third drug were approved for relapsed/refractory MM, with carfilzomib, ixazomib, elotuzumab and daratumumab as the third compound (498). Fan *et al* (499) have described the mechanism of action of LDM-the combination of LDM and cereblon recruits new substrates (Ikaros, Aiolas and glutamine synthetase) that bind to the cereblon-CRL4 complex, leading to increased ubiquitination and proteasome-dependent degradation, thus resulting in anti-MM activity.

PLM was approved in 2013 as a treatment for relapsed and refractory multiple MM; however, patients treated with IMiDs should be monitored for the risk of infections (500). The possibility of cardiovascular and thrombotic complications should also be considered. However, Bringhen *et al* (501) analyzed 1,146 individual patient data to assess toxic deaths during induction treatment with first-generation novel agents THL, LDM and bortezomib, finding a significant reduction in toxicity-related mortality compared with conventional chemotherapy. At present, >60 clinical trials into different types of tumor or clinical settings are being conducted using these compounds (502).

28. Valproic acid (VPA)

VPA is a drug used as an anticonvulsant, and is also utilized in bipolar disorder and the prevention of migraine headaches (503). Although the mechanism is not entirely understood, it is hypothesized that its anticonvulsant action is due to the blockade of voltage-gated sodium channels and augmented levels of γ-aminobutyric acid (504).

Histone acetylation and deacetylation are processes via which the lysine residues at the N-terminal tail of the histone of the nucleosome are acetylated or deacetylated as a critical process of gene regulation (505). The reactions are catalyzed by the enzymes histone acetyltransferase (HAT) or histone deacetylase (HDAC), respectively (506). VPA is an HDAC inhibitor, and histone deacetylation is associated with gene silencing (507). Deacetylation allows the histones to wrap DNA tightly, preventing access to transcription factors, leading to transcriptional repression (506,508-510). The overexpression and increased activity of HDACs are characteristic of tumorigenesis and metastasis, suggesting an important regulatory role of histone deacetylation on oncogene expression (511). VPA has been shown to have antitumor activity (512).

The nature of the association between HDAC-mediated epigenetic regulation, and autophagy induction or suppression remains mostly unknown. It was found in lymphoma cells that HDAC inhibition by VPA is indispensable for the autophagy-enhancing effects demonstrated when used in combination with the mTOR inhibitor temsirolimus (513). Also, patients who have AML benefit from the apoptotic induction in tumor cells using VPA (514). Additionally, VPA suppresses prostatic tumor growth by increasing androgen sensitivity and augmenting cellular prostatic acid phosphatase via histone acetylation, leading to dephosphorylation of ErbB-2 (515). Moreover, studies showed that VPA induces the expression of cyclin D2, a crucial cell cycle regulatory gene that is mostly absent in prostate cancer (516). VPA has also been tested in head and neck squamous cell carcinoma, where it was demonstrated to increase p21, thus affecting cancer cell viability, differentiation marker expression and growth (517).

Studies combining VPA with MTF have demonstrated their synergistic anticancer effect, likely due to the p53 signaling pathway, which induces cancer cell apoptosis (518). Another synergetic combination of VPA and ellipticine (a topoisomerase II inhibitor) induces apoptosis in neuroblastoma cells, due to increasing histone H3 and H4 acetylation (519). VPA also exhibited its anticancer effects on bladder cancer in combination with melatonin, demonstrating a synergetic effect by activating apoptotic, necrotic and autophagy-associated genes (520). Another combination study has shown that VPA increases thymidine phosphorylase levels in breast cancer cells, thus synergizing the effects of capecitabine (521). Effects of VPA on pancreatic and colon cancer were associated with reduced levels of amyloid precursor protein (APP); lowering the levels of APP was associated with the activation of the chaperone GRP78 in cancer cells (521). DNA damage and apoptosis through ROS production have been proposed as additional mechanisms of VPA in pancreatic and cervical

cancer (522). Abdelaleem *et al* (523) summarizes the evidence concerning the antitumor effects of VPA on gliomas. At present, >14 clinical trials are investigating the effectiveness of VPA in a wide variety of malignant tumors, such as pancreatic, bladder, cervix, thyroid and prostate cancers (412).

29. Verapamil (VRP)

VRP, an L-type calcium channel blocker, is used for the treatment of high blood pressure, angina and supraventricular tachycardia by blocking voltage-dependent calcium (Ca_v) channels. There is compelling evidence that Ca_V channels are expressed in various cancers at the gene and protein levels (524). Sun *et al* (525) reported that LNCaP prostate cancer cells displayed Ca^{2+} transients following stimulation with 5α-DHT, which were inhibited by VRP. VRP has been shown to induce growth inhibition in meningioma cell cultures, as well as in a mouse xenograft model (526). Additionally, VRP combined with hydroxyurea or RU486 increased meningioma growth inhibition *in vitro* by inducing apoptosis and G1 cell cycle arrest, and *in vivo* by affecting microvascular density (527). Hajighasemi *et al* (528) found that VRP downregulated the production of VEGF in human peripheral blood mononuclear cells. VRP has exhibited antiproliferative effects on breast cancer cells in a mouse model (529). In a prospective study of 99 patients with anthracycline-resistant metastatic breast carcinoma, VRP showed positive survival effects. In advanced NSCLC, VRP improved the survival of patients when administered alongside vindesine and ifosfamide (530). However, there are controversial results concerning the anticancer properties of VRP (531,532).

As mentioned previously, tumor cells develop a form of drug resistance known as MDR, which is linked to the expression of P-gp. VRP is also an inhibitor of P-gp that, when combined with chemotherapeutics, can help to induce intracellular drug accumulation (533). Another reported mechanism involves autophagy. Autophagy is a natural, highly regulated process that involves orderly degradation and recycling of cellular materials (232). It has been debated as to whether autophagy acts as a tumor suppressor or as a factor that helps the survival of malignant cells. However, it has been shown that autophagy is more likely to act as a tumor suppressor, according to several models (534). VRP led to an accumulation of autophagy-like structures (535). VRP stimulates autophagy, involving a switch toward aerobic glycolysis and enhanced lactate production (535). VRP can reduce intracellular glucose levels with a reduction of lactate products (535). These produce two effects in the cancer cell; first, depriving the cells of substrates for anaerobic glycosylation, and secondly, producing a reduction of lactate products that maintain an acidic pH and facilitate tumor growth (536). Other mechanisms also play a role in the antitumor effects of VRP, such as reduced angiogenesis (535-538). Further investigation is needed. Currently, one clinical trial is open and actively recruiting analyzing the effect of brentuximab, dedotin, cyclosporine and VRP in patients with relapsed or refractory Hodgkin Lymphoma (clinical trial no. NCT03013933).

30. Zidovudine (AZT)

AZT is an analog of thymidine synthesized in 1964 as a potential anticancer agent, but which failed at that time to have positive results (539). In 1983, a retrovirus known as HIV was identified as the cause of AIDS. AZT proved to be a potent inhibitor of retroviruses, and following several studies, was approved for the treatment of HIV (540). AZT blocks the replication of HIV-1 by inhibiting reverse transcriptase (RT); AZT is phosphorylated intracellularly to AZT-triphosphate (AZT-TP) by thymidine kinase, and then is integrated into viral DNA, blocking chain elongation (541). Telomeres are the extremes of the chromosomes; their DNA consists of repetitive sequences, protecting the chromosomal ends. In each cell division, every chromosome is duplicated, but DNA polymerases cannot copy all bases in the 3' end after primer removal, which results in the loss of a certain number of telomeric sequences in every cycle. Then, telomeres shorten progressively; when telomere length is critical, the cell enters into senescence and apoptosis (542). In the case of germinal or stem cells, they do not have an incomplete replication process; to solve this issue, the vast majority of organisms use a specific mechanism to maintain telomere length, executed by a specialized holoenzyme called telomerase (543). Telomerase is also an RT (structurally similar to HIV RT) comprised of a main catalytic subunit (hTERT) and an RNA (hTR) that acts as a template for the addition of telomeric sequences at the DNA 3' end. Telomerase is inactive in most somatic cells; however, it is active in 85-90% of human tumors (544). The fact that hTERT is a functional catalytic RT led to a study concerning the possibility of inhibiting this enzyme in cancer cells using viral RT inhibitors such as AZT. It was demonstrated that AZT was preferentially incorporated into telomeric DNA rather than non-telomeric DNA and, for the first time, that telomere shortening caused by AZT was irreversible (545,546). Numerous other studies observed similar results (541,547-550). Synergistic interactions were seen, with AZT promoting the effects of cisplatin, paclitaxel and 5-fluorouracil (551-553).

In 2001, the effects of chronic *in vitro* AZT exposure on a mouse mammary carcinoma cell line were investigated (554). Treatment with AZT for ≥30 passages completely inhibited telomerase activity, inducing progressive telomere shortening that led to cell senescence and apoptosis. Regarding the antitumor mechanism, AZT-TP is also incorporated into eukaryotic DNA in place of thymidine, having low affinity for DNA polymerases α, β and γ, and high affinity for RT (555). Several non-telomeric telomerase functions have been described, such as transcriptional modulation of the WNT/β-catenin signaling pathway and RNA-dependent RNA polymerase activity; it was concluded that the inhibition produced by AZT was a mix of effects between canonical and non-canonical functions (556,557). Recently, Song *et al* (558) demonstrated that AZT decreased angiogenesis by reducing receptor tyrosine kinase signaling in endothelial cells.

Currently, AZT is employed in the treatment of numerous virus-associated human cancers, including Epstein-Barr-associated lymphoma, AIDS-related Kaposi sarcoma, primary central nervous system lymphoma, Kaposi sarcoma-associated primary effusion lymphoma and adult T cell leukemia (559). As of 2019, >20 clinical trials are ongoing studying AZT in the treatment of Kaposi's sarcoma, lymphoma, leukemia and other tumors in patients with AIDS. AZT has been tested in phase I and II clinical trials for other types of tumor, either alone or in combination, showing some tumor regression (560-564). In 2012, it was demonstrated that AZT was effective against two

Table I. Drug repositioning in oncology.

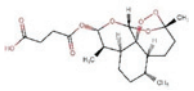
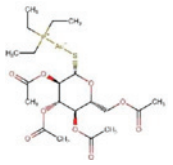
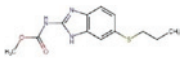
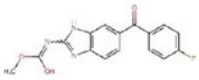
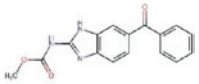
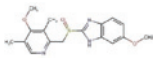
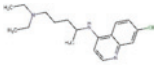
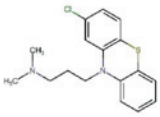
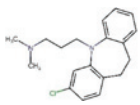
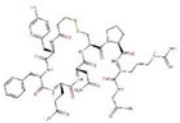
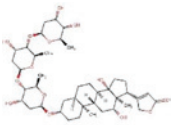
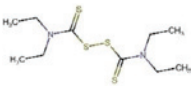
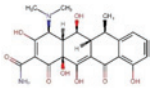
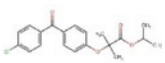
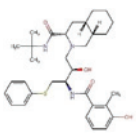
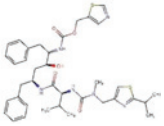
Drug name (class of drug)	Primary use	Potential anticancer treatment applications	Clinical trial identifier	Chemical structure
Artesunate	Malaria	Kaposi's sarcoma, NSCLC, melanoma, breast, ovarian, prostate and renal cancers	NCT02633098	
Auranofin	Rheumatoid arthritis	Melanoma, leukemia, gastrointestinal stromal tumor, NSCLC	NCT01737502	
Albendazole (BZM)	Helminths infestation	CRC, leukemia, liver and ovarian cancers	NCT02366884	
Flubendazole (BZM)	Intestinal parasites	Leukemia, melanoma, myeloma, neuroblastoma, breast cancer	-	
Mebendazole (BZM)	Helminths infestation	GBM, melanoma, glioma, medulloblastoma	NCT03925662	
Omeprazole (BZM)	Gastrointestinal disease	CRC, breast and pancreatic cancers	NCT02595372	
Chloroquine	Malaria, lupus, amebiosis, rheumatoid arthritis	GBM, NSCLC, pancreatic and breast cancers	NCT03243461	
Chlorpromazine	Psychosis	Glioma, neuroblastoma, leukemia, lymphoma, CRC, breast and liver cancers	NCT03021486	
Clomipramine	Depression and other psychiatric disorders	Glioma, astrocytoma	-	
Desmopressin	Central diabetes insipidus	CRC, lung and breast cancers	NCT01623206	
Digoxin	Hearth failure and arrhythmia	Breast, prostate, and head and neck cancers	NCT01763931	
Disulfiram	Alcohol deterrent	GBM, CRC, melanoma, prostate, ovarian, breast, pancreatic and liver cancers	NCT03323346	
Doxycycline	Bacterial infestation	GBM, melanoma, breast, ovarian, lung, prostate and pancreatic cancers	NCT02775695	
Fenofibrate	Hypertriglyceridemia and mixed dyslipidemia	Medulloblastoma, breast and lung cancers	NCT01356290	
Nelfinavir (HPI)	AIDS	Myeloma, sarcoma, GBM, melanoma, head and neck, pancreatic, breast, lung, thyroid and prostate cancers	NCT01065844	
Ritonavir (HPI)	AIDS	MM, glioma, breast cancer, chronic myeloid leukemia	NCT01009437	

Table I. Continued.

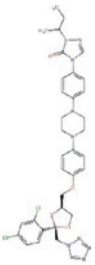
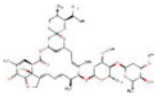
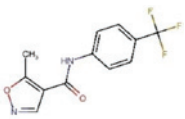
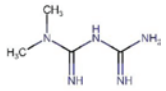
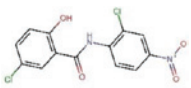
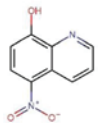
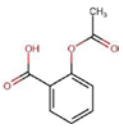
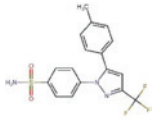
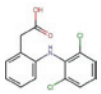
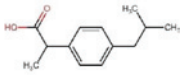
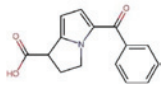
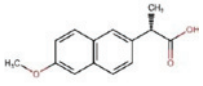
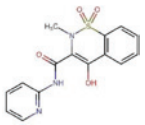
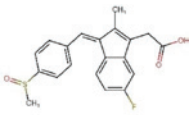
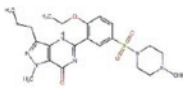
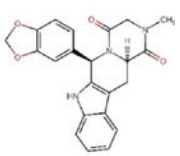
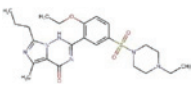
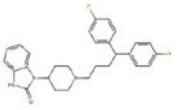
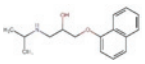
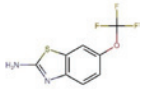
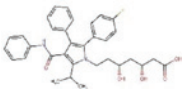
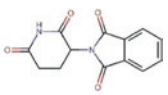
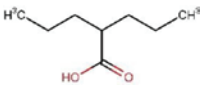
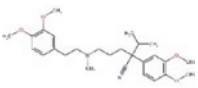
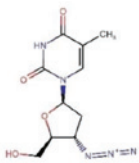
Drug name (class of drug)	Primary use	Potential anticancer treatment applications	Clinical trial identifier	Chemical structure
Itraconazole	Antifungal	NSCLC, GBM, medulloblastoma, basal cell carcinoma, breast, lung, prostate, ovarian and pancreatic cancers	NCT00769600	
Ivermectin	Parasitic infestation	TNBC, CRC, lung and ovarian cancers	NCT02366884	
Leflunomide	Rheumatoid arthritis	Myeloma, melanoma, NET, TNBC, neuroblastoma, prostate, bladder and breast cancers	NCT03709446	
Lithium	Depression	Osteosarcoma, leukemia, CRC, GBM, prostate, thyroid, lung, stomach, esophageal brain, and head and neck cancers	NCT03153280	Li(OH)
Metformin	Type 2 diabetes	CRC, NSCLC, breast, bladder, endometrial, lung, prostate and pancreatic cancers	NCT02285855	
Niclosamide	Tapeworm infestation	NET, NSCLC, TNBC, acute myeloid leukemia, osteosarcoma, adrenocortical carcinoma, glioma, ovarian, prostate, lung, and head and neck cancers	NCT02807805	
Nitroxoline	Urinary tract infections	Non-muscle invasive bladder cancer	CTR20131716	
Acetylsalicylic acid (NSAID)	Analgesic, antipyretic, platelet aggregation inhibitor	CRC and CRC liver metastases	NCT03326791	
Celecoxib (NSAID)	Familial adenomatous polyposis	CRC, lung, breast, prostate, bladder, and head and neck cancers	NCT02429427	
Diclofenac (NSAID)	Antipyretic, anti-inflammatory, analgesic	Glioma, skin cancer	NCT04091022	
Ibuprofen (NSAID)	Antipyretic, anti-inflammatory, analgesic	Glioma, neuroblastoma, CRC, prostate, bladder, breast, lung and gastric cancers	NCT02141139	
Ketorolac (NSAID)	Antipyretic, anti-inflammatory, analgesic	Oral, head and neck, and breast cancers	NCT02470299	
Naproxen (NSAID)	Antipyretic, anti-inflammatory, analgesic	CRC, basal and squamous cell carcinoma	NCT02052908	

Table I. Continued.

Drug name (class of drug)	Primary use	Potential anticancer treatment applications	Clinical trial identifier	Chemical structure
Piroxicam (NSAID)	Antipyretic, anti-inflammatory, analgesic	Skin cancer	-	
Sulindac (NSAID)	Antipyretic, anti-inflammatory, analgesic	Colorectal neoplasms	NCT01349881	
Sildenafil (PDE5I)	Erectile dysfunction	NSCLC	NCT00752115	
Tadalafil (PDE5I)	Erectile dysfunction	HCC, metastatic pancreatic cancer	NCT03785210	
Vardenafil (PDE5I)	Erectile dysfunction	Gliomas and brain metastases	NCT02279992	
Pimozide	Several mental/mood disorders	Breast, lung, prostate, ovarian and pancreatic cancers, CRC, HCC	-	
Propranolol	Infantile hemangioma	Breast cancer, CRC	NCT00888797	
Riluzole	Amyotrophic lateral sclerosis	Melanoma, breast and prostate cancerc	NCT02796755	
Statins	Cardiovascular diseases	HCC, CRC, prostate cancer	NCT04026230	
Thalidomide	Nausea and vomiting of pregnancy	Prostate cancer, lymphoma, leukemia, MM	NCT00450008	
Valproic acid	Anticonvulsant, bipolar disorder, migraine headaches	Lymphoma, myeloid leukemia, CRC, glioma, thyroid, cervical, bladder, head and neck, prostate and pancreatic cancers	NCT00670046	
Verapamil	High blood pressure, angina, tachycardia	NSCLC, meningioma, breast cancer	NCT00706810	
Zidovudine	AIDS	Lymphoma, MM, breast cancer	NCT00854581	

One example of a notable clinical trial is provided for each drug. BZM, benzimidazole derivative; HPI, HIV protease inhibitor; NSAID, nonsteroidal anti-inflammatory drug; PDE5I, phospodiesterase-5 inhibitor; CRC, colorectal carcinoma; HCC, hepatocellular carcinoma; GBM, glioblastoma multiforme; MM, multiple myeloma; NET, neuroendocrine tumors; NSCLC, non-small cell lung cancer; TNBC, triple negative breast cancer.

human MM cell lines *in vitro* in a dose- and time-dependent manner, promoting cell cycle arrest in S phase. AZT is extremely promising. However, additional clinical studies are required to search for the full potential of AZT in a clinical setting (565).

31. Concluding remarks

Developing more effective cancer treatments requires not only the classical design of new molecules, but also intelligent searches for new antitumor medications by repurposing old drugs already approved for other uses. Such an approach has certain advantages; the development of a new drug is costly and timely, whereas drugs that are already approved have defined safety and pharmacological profiles. A drug with a long clinical history in humans has properly defined pharmacokinetic and pharmacodynamics data, including target identification, toxicity profiles, recommended dosage schemes and the consistent recognition of adverse effects, often meaning that development for an oncological indication can begin at a later stage, such as phase IIA. Furthermore, repositioned molecules often are approved quicker with reduced cost. However, there are some hurdles in the path, mainly the interests of companies and the costly remaining phases of the clinical trials prior to final approval. This review underlines the most promising drugs for repurposing, which are summarized in Table I, and although more research is needed, repositioning could pave the way to new, improved and more effective treatments for patients with cancer.

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Availability of data and materials

Not applicable.

Authors' contributions

All authors contributed intellectually to the research, drafting and editing of the manuscript, and approved the final version of the manuscript to be published.

Ethics approval and consent to participate

Not applicable.

Patient consent for publication

Not applicable.

Competing interests

The authors declare that they have no competing interests.

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