Review

Cancer drug discovery by repurposing: teaching new tricks to old dogs

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Progressively increasing failure rates, high cost, poor bioavailability, poor safety, limited efficacy, and a lengthy design and testing process associated with cancer drug development have necessitated alternative approaches to drug discovery. Exploring established non-cancer drugs for anticancer activity provides an opportunity rapidly to advance therapeutic strategies into clinical trials. The impetus for development of cancer therapeutics from non-cancer drugs stems from the fact that different diseases share common molecular pathways and targets in the cell. Common molecular origins of diverse diseases have been discovered through advancements in genomics, proteomics, and informatics technologies, as well as through the development of analytical tools that allow researchers simultaneously to screen large numbers of existing drugs against a particular disease target. Thus, drugs originally identified as antitussive, sedative, analgesic, antipyretic, antiarthritic, anesthetic, antidiabetic, muscle relaxant, immunosuppressant, antibiotic, antiepileptic, cardioprotective, antihypertensive, erectile function enhancing, or angina relieving are being repurposed for cancer. This review describes the repurposing of these drugs for cancer treatment.

Drug repurposing

Despite the tremendous resources being invested in cancer prevention and treatment, cancer remains one of the leading causes of mortality worldwide. During the past decade, new technologies such as structure-based drug discovery have been created, hundreds of biotechnology companies have been launched, research expenditure by the US National Institutes of Health has increased by more than two-fold, and pharmaceutical industries have doubled their R&D spending. This investment, however, has not resulted in proportionate quantities of new and novel anticancer drugs. Some of the common anticancer drugs approved by the FDA and their molecular targets are shown in Table 1. These drugs may be classified into two basic categories: non-targeted and targeted. Only one of every 5000–10,000 prospective anticancer agents receives FDA approval and only 5% of oncology drugs entering Phase I clinical trials are ultimately approved [1]. These failure rates underscore the need for alternative efforts for drug development [2]. Furthermore, most of the currently available cancer drugs are highly expensive, provide minimal increase in the overall survival, and are associated with numerous side effects [3].

There has been much discussion on the overall steps involved and the future of the drug discovery process [4]. Drug development requires an average of 13 years of research and an investment of US$1.8 billion to bring a single drug from the bench to a patient's bedside [5] (Figure 1). Drug development, in addition to design and production, comprises examining the efficacy, toxicity, and pharmacokinetic and pharmacodynamic profiles of the drug by cell- and animal-based studies. The next step in drug development is testing the safety and efficacy in human subjects by clinical trials that normally comprise four phases. In general, if the drug is found efficacious in Phase III trials, it receives FDA approval. Most drugs, however, fail to receive FDA approval, even when they exhibit safety in Phase I trials; according to one study, this failure is primarily due to a lack of efficacy in Phase II trials [6]. Success rates for Phase II trials have decreased from 28% in 2006–2007 to 18% in 2008–2009 [7]. It has been suggested that most drugs fail because they did not effectively target the disease for which they were intended [6]. However, because of the common molecular origins of diverse diseases, it is estimated that approximately 90% of approved drugs possess secondary indications and can be used for other purposes [8]. Researchers and clinicians have adopted numerous strategies to reduce the cost and time involved in cancer drug development. One such strategy is to evaluate established non-cancer drugs that have already been approved for noncancerous diseases, whose targets have already been discovered and for which reliable biomarkers indicative of success already exist. This approach, alternatively called 'new uses for old drugs', 'drug repositioning', 'drug repurposing', 'drug re-profiling', 'therapeutic switching', or 'indication switching', has gained considerable attention over the past decade [9,10]. The major advantage of this approach is that the pharmacokinetic, pharmacodynamic, and toxicity profiles of drugs are in general well known because of the preclinical and Phase I studies. Thus, these drugs could be rapidly translated into Phase II and III clinical studies and the

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Table 1. Common anticancer drugs approved by the FDA and their molecular targets[a]

Year	Drug	Cancer type	Molecular target
1952	Leucovorin	Colorectal	NT
1957	Chlorambucil	CLL, Hodgkin lymphoma, NHL	NT
1963	Vincristine	ALL, Hodgkin lymphoma, NHL, rhabdomyosarcoma, Wilms' tumor	NT
1964	Vinblastine	Breast, head and neck, Hodgkin lymphoma, lung	NT
1969	Cytarabine	ALL, AML, CML, meningeal leukemia	NT
	Procarbazine	Hodgkin lymphoma	NT
1973	Bleomycin	Cervical, Hodgkin lymphoma, lung, MPE, NHL, testicular, vulva	NT
1975	Dacarbazine	Hodgkin lymphoma, metastatic melanoma	NT
1977	Tamoxifen citrate	Breast	Estrogen receptor ↓
1978	Cisplatin	Lung, mesothelioma, ovarian	NT
1979	Daunorubicin	AML, ALL	NT
1988	Ifosfamide	Breast, lung, lymphoma, osteosarcoma, ovarian, testicular	NT
	Methotrexate	ALL, breast, GTD, Hodgkin lymphoma, osteosarcoma	NT
1991	Fludarabine	CLL	NT
1994	Etoposide	Ewing sarcoma, lung, testicular	NT
	Pegaspargase	ALL	NT
1996	Anastrozole	Breast	Aromatase ↓
	Docetaxel	Breast, gastric, head and neck, lung, prostate	NT
	Gemcitabine	Breast, lung, ovarian, pancreatic	NT
1997	Rituximab	CLL, NHL	CD20 ↓
	Toremifene	Breast	SERM
1998	Aldesleukin	Melanoma, renal	IL-2 ↓
	Irinotecan	Colorectal	Topoisomerase I ↓
1999	Denileukin diftitox	Cutaneous T cell lymphoma	IL-2 ↓
	Exemestane	Breast	Aromatase ↓
	Cytarabine	ALL, AML, CML, meningeal leukemia	NT
	Doxorubicin	ALL, AML, bone, bladder, breast, gastric, Hodgkin lymphoma, neuroblastoma, NHL, ovarian, thyroid, Wilms' tumor	NT
	Epirubicin	Breast	NT
2000	Bexarotene	Cutaneous T cell lymphoma	Retinoid X receptor ↑
	Gemtuzumab ozagamicin	AML	CD33 ↓
	Leuprolide acetate	Prostate	GnRH ↑
	Arsenic trioxide	AML	NT
	Temozolomide	Anaplastic astrocytoma, glioblastoma multiforme	NT
2001	Alemtuzumab	CLL	CD52 ↓
	Imatinib	CML, gastrointestinal	CD117 ↓
	Letrozole	Breast	Aromatase ↓
	Capecitabine	Breast, colorectal	NT
2002	Fulvestrant	Breast	SERD
	Ibritumomab tiuxetan	NHL	CD20 ↓
	5-Fluorouracil	Basal cell carcinoma, breast, colorectal, gastric, pancreatic	NT
	Oxaliplatin	Colorectal	NT
2003	Abarelix	Prostate	GnRH ↓
	Bortezomib	Mantle cell lymphoma, MM	Proteasome ↓
	Gefitinib	Lung	EGFR ↓
	Tositumomab and ^{131}I	NHL	CD 20 ↓
2004	Bevacizumab	Colorectal, glioblastoma, lung, renal	VEGFR ↓
	Cetuximab	Colorectal, head and neck	EGFR ↓
	Erlotinib	Lung, prostate	EGFR ↓
	Azacitidine	Myelodysplastic syndrome	NT
	Clofarabine	ALL	NT
2005	Sorafenib tosylate	Liver, renal	PDGFR ↓, VEGFR ↓, CD117 ↓
	Lenalidomide	MM, myelodysplastic syndrome	NT
	Nelarabine	ALL	NT
	Paclitaxel	Breast	NT
2006	Dasatinib	ALL, CML	PDGFR ↓, BCR-ABL ↓, Src ↓
	Panitumumab	Colorectal	EGFR ↓
	Sunitinib malate	Gastrointestinal, renal	CD117 ↓
	Vorinostat	Cutaneous T cell lymphoma	HDAC ↓
	Decitabine	Myelodysplastic syndrome	NT

Table 1 (*Continued*)

Year	Drug	Cancer type	Molecular target
2007	Lapatinib ditosylate	Breast	HER2 ↓, EGFR ↓
	Nilotinib	CML	PDGFR ↓, BCR-ABL ↓, CD117 ↓
	Raloxifene	Breast	SERM
	Temsirolimus	Renal	mTOR ↓
	Ixabepilone	Breast	NT
	Topotecan	Cervical, lung, ovarian	Topoisomerase I ↓
2008	Bendamustine	CLL, Hodgkin lymphoma, lung, MM, NHL	NT
	Plerixafor	MM, NHL	NT
2009	Degarelix	Prostate	GnRH ↓
	Everolimus	Renal, astrocytoma	mTOR ↓
	Ofatumumab	CLL	CD 20 ↓
	Pazopanib	Renal	VEGFR ↓
	Romidepsin	Cutaneous T cell lymphoma	HDAC ↓
	Pemetrexed	Mesothelioma, lung	NT
	Pralatrexate	Peripheral T cell lymphoma	NT
2010	Denosumab	MM, bone	RANKL ↓
	Trastuzumab	Breast, gastric	HER2/neu ↓
	Cabazitaxel	Prostate	NT
	Eribulin mesylate	Breast	NT
2011	Ipilimumab	Melanoma	CTLA 4 ↓
	Vandetanib	Thyroid	HER2 ↓, EGFR ↓
	Vemurafenib	Melanoma	BRAF ↓
	Crizotinib	NSCLC	ALK ↓
	Ruxotitinib	Myelofibrosis	JAK-1 ↓, JAK-2 ↓

[a]Abbreviations: ALK,, anaplastic lymphoma kinase; ALL, acute lymphoblastic leukemia; AML, acute myelogenous leukemia; BCR-ABL, breakpoint cluster region gene on chromosome 22 and Abelson murine leukemia viral oncogene homolog; BRAF, v-raf murine sarcoma viral oncogene homolog B1; CLL, chronic lymphocytic leukemia; CML, chronic myelogenous leukemia; CTLA 4, cytotoxic T-lymphocyte-associated antigen 4; EGFR, epidermal growth factor receptor; GnRH, gonadotropin-releasing hormone; GTD, gestational trophoblastic disease; HER2, human epidermal receptor 2; JAK, Janus-associated kinase; MM, multiple myeloma; MPE, malignant pleural effusion; NHL, non-Hodgkin lymphoma; NSCLC, non-small cell lung cancer; NT, non-targeted; PDGFR, platelet-derived growth factor receptor; RANKL, receptor-activated NF-κB ligand; SERD, selective estrogen receptor downregulator; SERM, selective estrogen-receptor modulator; Src, sarcoma; VEGFR, vascular endothelial growth factor receptor; ↓, downregulation; ↑, upregulation.

associated cost could be significantly reduced. At a time when the revenue of drug research is under extreme pressure, pharmaceutical industries are re-evaluating old drugs for new indications to maximize their return on investment. A more recent estimate indicates that, whereas 10% of new molecular entities make it to the market from Phase II clinical trials and 50% from Phase III, the rates for repurposed compounds are 25% and 65%, respectively [11].

Several strategies have been used effectively to identify and implement current non-cancer drugs for cancer-related treatment [12]. The first successful strategy is based on the observation that almost all drugs used in human therapy possess more than one target and thus can produce off-target side effects in addition to their principal activity. If these drugs interact with an off-target pathway with sufficient potency, there is a high likelihood that they could be rapidly tested in patients. The second successful strategy is based on the finding that many different diseases share common molecular pathways and targets in the cell. Thus, it is likely that the same drug can be therapeutic for more than one disease.

In the sections that follow, we review some of the most common older drugs that have demonstrated anticancer

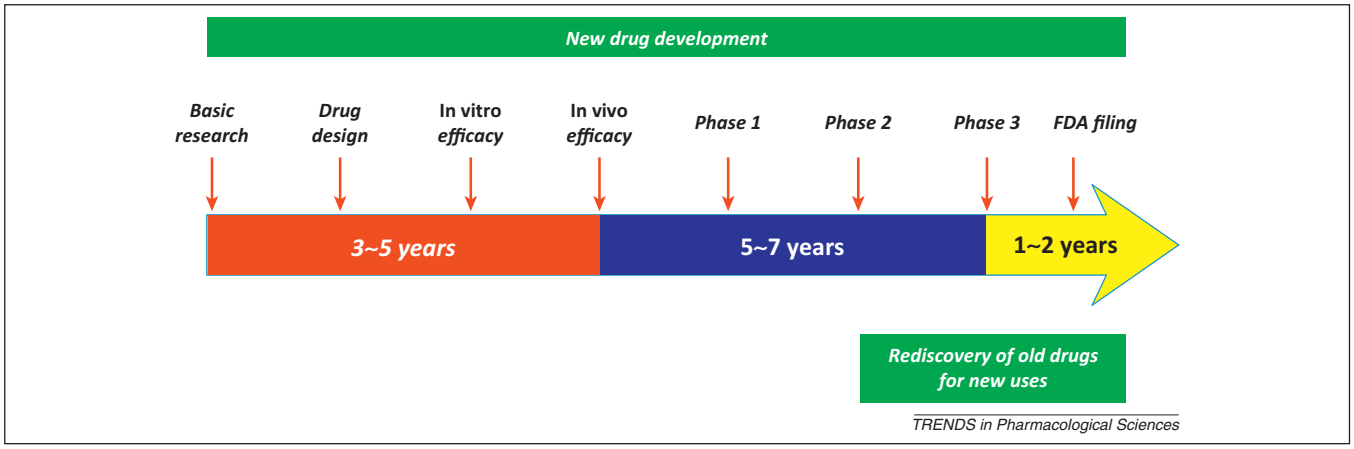

Figure 1. Major steps and estimated time involved in the conventional drug development process, which involves basic research, drug design, testing of safety and efficacy with preclinical and clinical studies, and finally filing for FDA approval. The estimated time of drug development can be significantly reduced by repurposing old drugs.

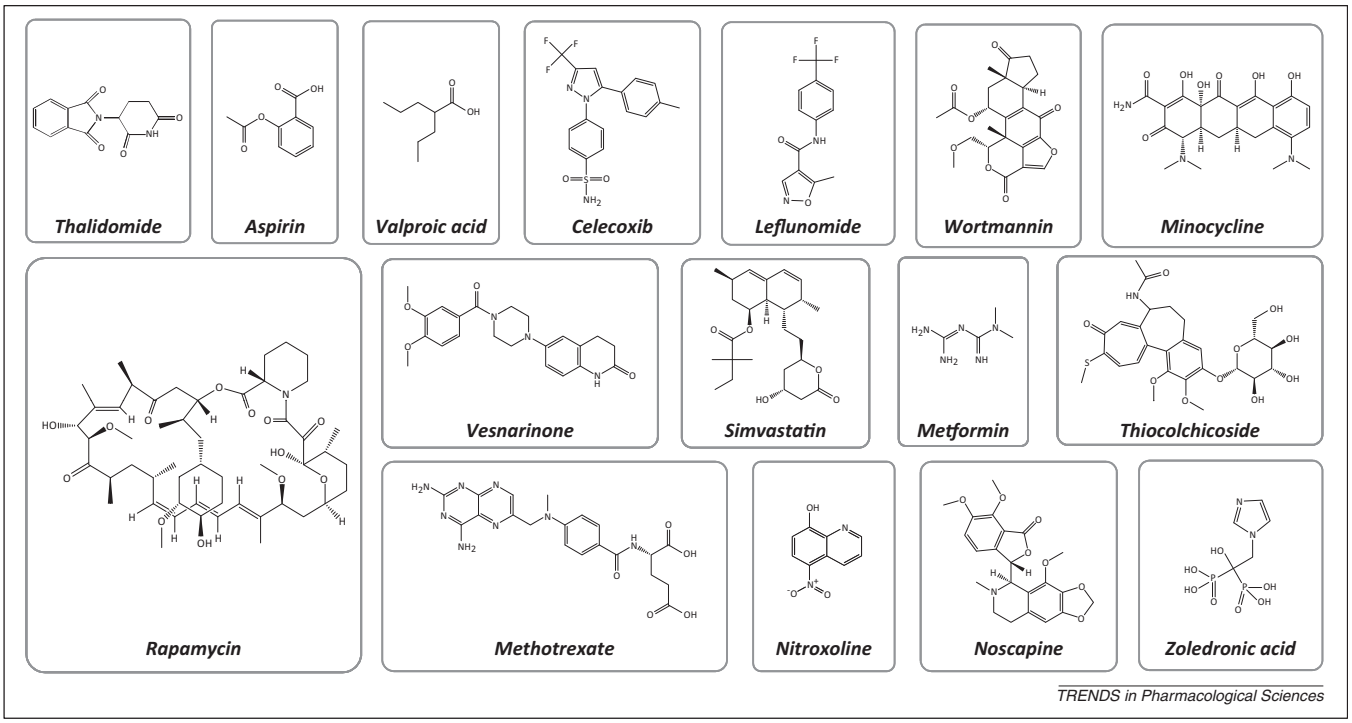

Figure 2. Chemical structure of common non-cancer drugs that exhibit anticancer activity.

activity, regardless of the fact that they were not originally intended for this use. We review drugs that were initially identified as antitussive, sedative, analgesic, antipyretic, antiarthritic, anesthetic, antidiabetic, muscle relaxant, immunosuppressant, antibiotic, antiepileptic, or cardioprotective and drugs designed for hypertension, erectile dysfunction, and angina. These drugs fall into two different categories: (i) drugs that were approved for other uses but whose biological activities are known well enough that they are logically selected for anticancer activities (thalidomide, aspirin, valproic acid [VPA], celecoxib, leflunomide, wortmannin, minocycline, vesnarinone, statins, metformin, thiocolchicoside, rapamycin, methotrexate, bisphosphonates); and (ii) agents identified from a set of approved drugs arbitrarily chosen to examine their specificity for defined cancer targets (nitroxoline, noscapine). Some of these drugs with palliative benefits can also exhibit anticancer activities. These drugs are chemically diverse (Figure 2) and can hit numerous targets in tumor development (Table 2). The diverse cancer targets of these drugs and the molecular mechanisms by which they exert anticancer activities are discussed in this review.

Repurposed non-cancer drugs

Thalidomide

Thalidomide, a derivative of glutamic acid, was originally developed in the 1950s as a sedative hypnotic for the treatment of nausea during pregnancy. However, the drug was withdrawn from the market in 1961 because of its teratogenic effects. Numerous mechanisms were proposed for the teratogenic effects of thalidomide, including antiangiogenic [13] and oxidative DNA-damaging activities [14]. Singhal and colleagues demonstrated that, because of its antiangiogenic activities, thalidomide as a single agent can be used for treating patients with refractory myeloma [15]. This led to successful evaluation of thalidomide in a series of multicenter clinical trials and to final FDA approval of the drug for treatment of multiple myeloma. Recent studies have demonstrated the efficacy of thalidomide against several malignancies, including myelodysplastic syndrome[16], myelodysplasia [17], and acute myeloid leukemia [18].

Research over the past decade has indicated that thalidomide, although initially evaluated because of its potential antiangiogenic effects, can modulate numerous cancer-associated cell signaling pathways. Work from our laboratory and others has demonstrated that, through inhibition of IκB kinase (IKK), thalidomide inhibits the activation of nuclear factor kappa light chain enhancer of activated B cells (NF-κB), which has been linked closely to inflammation and the survival, proliferation, invasion, and metastasis of tumors [19,20]. Further elucidation of the molecular mechanism indicated that the inhibition of NF-κB activation was due to suppression of inhibitor of NF-κB (IκBα) degradation in tumor cells.

Aspirin

Aspirin (acetylsalicylic acid), one of the non-steroidal anti-inflammatory drugs (NSAIDs), has been used as an analgesic to relieve pain, as an antipyretic to reduce fever, and to prevent heart attack and stroke. The first indication for the possible role of aspirin in cancer therapy dates back more than four decades, when Gasic and colleagues demonstrated that platelet reduction by neuraminidase administration in tumor-bearing mice was associated with a 50% reduction in lung metastases [21]. In a subsequent study, the group reported a significant reduction in the number of metastases in tumor-bearing mice by aspirin. Furthermore, inhibition of platelet formation was proposed as the mechanism of action of aspirin. A recent

Table 2. Non-cancer drugs and their mechanism of action for non-cancer and cancer activities[a]

Drug	Original indication (mechanism)	New anticancer indication (mechanism)
Thalidomide	Antiemetic in pregnancy (TNF-α ↓)	Multiple myeloma (NF-κB ↓, STAT3 ↓)
Aspirin	Analgesic, antipyretic (COX-1 ↓, COX-2 ↓)	Colorectal cancer (COX-2 ↓, NF-κB ↓, AP-1 ↓)
Valproic acid	Antiepileptic (GABA ↑)	Leukemia, solid tumors (HDACI ↓, HDACII ↓, NF-κB ↓, IL-6 ↓)
Celecoxib	Osteoarthritis, rheumatoid arthritis (COX-2 ↓)	Colorectal cancer, lung cancer (COX-2 ↓, NF-κB ↓)
Statins	Myocardial infarction (HMG-CoA reductase ↓)	Prostate cancer, leukemia (NF-κB ↓, HMG-CoA reductase ↓)
Metformin	Diabetes mellitus (AMPK ↑[a])	Breast, adenocarcinoma, prostate, colorectal (AMPK ↑[a], NF-κB ↓, TNF ↓, MCP-1 ↓)
Rapamycin	Immunosuppressant (mTOR ↓)	Colorectal cancer, lymphoma, leukemia (NF-κB ↓, IL-6 ↓, IKK ↓)
Methotrexate	Acute leukemia (DHFR ↓)	Osteosarcoma, breast cancer, Hodgkin lymphoma (NF-κB ↓, TNF-α ↓)
Zoledronic acid	Anti-bone resorption (osteoclast ↓)	Multiple myeloma, prostate cancer, breast cancer (CXCR-4 ↓, MMPs ↓, IL-6 ↓, Bcl-2 ↓, Bax ↑, FOXO3a ↑[a])
Leflunomide	Rheumatoid arthritis (DHODH ↓)	Prostate cancer (PDGFR ↓, EGFR ↓, FGFR ↓, NF-κB ↓)
Wortmannin	Antifungal	Leukemia (NF-κB ↓, AP-1 ↓)
Minocycline	Acne	Ovarian cancer, glioma (MMPs ↓)
Vesnarinone	Cardioprotective	Oral cancer, leukemia, lymphoma (NF-κB ↓, IL-8 ↓, VEGF ↓, AP-1 ↓)
Thiocolchicoside	Muscle relaxant (GABA ↓)	Leukemia, multiple myeloma (NF-κB ↓)
Nitroxoline	Antibiotic	Bladder, breast cancer (MetAP-2 ↓)
Noscapine	Antitussive, antimalarial, analgesic (bradykinin ↓)	Multiple cancer types (NF-κB ↓, HIF-1α ↓, Bcl-2 ↓, p21 ↑, p53 ↑, AIF ↑)

[a]Abbreviations: AIF, apoptosis-inducing factor; Bax, Bcl-2-associated X protein; CXCR-4, CXC chemokine receptor-4; DHFR, dihydrofolate reductase; DHODH, dihydroorotate dehydrogenase; FGFR, fibroblast growth factor receptor; FOXO, forkhead homeobox type O; GABA, γ-aminobutyric acid; HIF-1α, hypoxia-inducible factor-1α; MCP-1, monocyte chemoattractant protein-1; MetAP, methionine aminopeptidase; MMP, matrix metalloproteinase; ↑[a], activation; ↓, downregulation; ↑, upregulation.

study indicated that a daily dose of 75 mg of aspirin can produce significant beneficial effects against common cancers such as gastrointestinal, esophageal, pancreatic, brain, and lung [22]. In another study [23], daily intake of 75 mg of aspirin for 1–5 years was associated with decreased risk of colorectal cancer.

Preclinical studies have demonstrated the inhibitory effects of aspirin on cyclooxygenase (COX)-1 and COX-2, with the drug exhibiting higher preference for COX-1 [24]. Aspirin has also been shown to inhibit NF-κB activation [25], thus illustrating its anticancer activities in a COX-independent pathway. Furthermore, aspirin has been shown to modulate the production of inflammatory cytokines, to inhibit the activity of activator protein (AP)-1 (a transcription factor closely associated with proliferation of tumor cells) [26], and to modulate numerous molecules linked with tumorigenesis, such as β-catenin, wnt, and tumor necrosis factor (TNF) [27].

In summary, these epidemiological and preclinical studies suggest the potent anticancer activities of aspirin. However, aspirin intake is associated with gastrointestinal and renal toxicities and thus aspirin cannot be administered chronically. Further research is needed to identify safer NSAIDs with minimal gastrointestinal and renal toxicities.

Depakine

Depakine (valproic acid, VPA), a short-chain fatty acid, is used for the treatment of convulsions and migraines. The drug was first identified as exhibiting anticancer activities in human leukemia cells because of its structural similarity with another anticonvulsant that has anticancer activities, 1-methyl-1-cyclohexanecarboxylic acid (MCCA) [28]. In subsequent years, VPA was shown to inhibit histone deacetylase (HDAC) [29]. Altered expression and mutations of genes that encode HDACs have been implicated in tumor growth because they can induce the aberrant transcription of genes regulating crucial cellular functions such as cell proliferation, cell-cycle regulation, and apoptosis. Possibly due to its actions as an HDAC inhibitor, VPA has been shown to inhibit the survival, invasion, angiogenesis, and metastasis of cancer cells [30]. This HDAC inhibitor has also been shown to suppress cytokine production and to modulate inflammatory pathways in cancer cells. For instance, production of interleukin (IL)-6 and TNF-α was suppressed in human monocytic leukemia cells and in human glioma cells by VPA treatment [31]. In prostate cancer cells, suppression in IL-6 production was mediated through inhibition of NF-κB activity [32]. VPA has been shown to increase the acetylation of signal transducers and activators of transcription protein (STAT) 1, which permits binding of STAT1 to NF-κB and reduces NF-κB activity in human melanoma cell lines [33]. Whether VPA modulates inflammatory pathways in cancer patients has not been demonstrated. VPA has been evaluated for safety and efficacy in numerous clinical trials for different leukemias and solid tumors either alone or in combination with other agents [34]. Some of these trials have advanced to Phase II for recurrent glioblastoma, advanced thyroid cancers, acute myelogenous leukemia, relapsed/refractory leukemias, non-small and small-cell lung cancers, B cell lymphoma, breast cancer, melanoma, prostate cancer, and advanced sarcomas (www.clinicaltrials.gov). Overall, these studies suggest VPA as a promising drug to fight cancer, either alone or in combination with other agents. It is expected that the completion of these clinical trials will place this HDAC inhibitor at the forefront of anticancer drugs.

Celecoxib

Celecoxib is a NSAID that helps to relieve the pain and inflammation associated with rheumatoid arthritis (RA) and osteoarthritis. Originally approved by the FDA in 1998, the drug has been shown to interact selectively with and inhibit COX-2, a well-known inflammatory cancer target. Celecoxib has also been shown to exhibit

chemopreventive activities against numerous cancer types because of its COX-2 inhibitory activities. Animal studies have supported the antitumor activities of celecoxib [35]. Some COX-2-independent targets of this drug are NF-κB, AKT8 virus oncogene cellular homolog (AKT), glycogen synthase kinase (GSK) 3β, β-catenin, and cell survival proteins of the inhibitor of apoptosis protein (IAP) and the B cell lymphoma (Bcl)-2 families [36].

In patients with familial adenomatous polyposis, 6 months of twice-daily treatment with 400 mg of celecoxib was found to produce a significant reduction in the number of colorectal polyps [37]. On the basis of results from a National Cancer Institute-sponsored Phase II trial, the drug was approved by the FDA for the prevention of polyps in patients with familial adenomatous polyposis (FAP) in December 1999 [37]. However, the recommended dose for the prevention of FAP (800 mg/day) is higher than that for patients with osteoarthritis (200 mg/day) or RA (200–400 mg/day). The putative gastrointestinal, renal, and cardiotoxic effects associated with this drug are one of its major drawbacks and, therefore, caution is required while taking this NSAID as an anticancer drug alone or in combination therapies.

Additionally, short-term COX-2 inhibition by celecoxib was associated with antitumor activity in primary breast cancer tissue in a recent study. The drug exhibited antiproliferative activities as reflected by a reduction of Ki-67-positive cells. It was concluded that COX-2 inhibition should be considered as a treatment strategy for further clinical testing in primary breast cancer.

Statins

Statins are a group of cholesterol-lowering agents that inhibit 3-hydroxy-3-methylglutaryl-coenzyme A (HMG-CoA) reductase, a rate-limiting enzyme in the cholesterol biosynthesis pathway. Statins are used to lower the endogenous synthesis of cholesterol in patients at high risk of myocardial infarction. Owing to their HMG-CoA reductase inhibitory activities, statins reduce the concentration of downstream byproducts including mevalonate and farnesyl and geranylgeranyl pyrophosphate. Because tumor cells depend heavily on sustained availability of these molecules, statins represent promising cancer therapeutics. One of our studies showed that simvastatin can potentiate TNF-induced apoptosis through downregulation of NF-κB-regulated antiapoptotic gene products in chronic myeloid leukemia cells [38]. In a subsequent study, we found that of the six statins, only the natural statins (simvastatin, mevastatin, lovastatin, and pravastatin), and not the synthetic statins (fluvastatin and atorvastatin), were able to inhibit TNF-induced NF-κB activation in chronic myeloid leukemia cells [39]. The antitumor activities of statins are supported by studies in animal tumor models in which statins have been found to reduce the incidence and growth of tumors [40].

Observational studies in humans support the chemopreventive effect of statins, showing significant reduction in the overall risk of cancer. In a case-control study, use of statins, in particular simvastatin (≥40 mg/day for 2–5 years), was associated with a significantly reduced incidence of colorectal cancer [41]. These doses are well within the range recommended for patients with coronary heart disease. A population-based case-control study was designed to assess the efficacy of statin use in patients with adenocarcinoma of the colon or rectum [42]. The use of statins was not associated with reduced risk of colorectal cancer. The risk of stage IV cancer was, however, significantly lower among statin users than among non-users. In another study, 5 years of long-term statin therapy was not associated with significant reduction in colorectal cancer risk [43]. Further clinical studies are thus required to demonstrate the efficacy of statins in cancer patients.

Metformin

Metformin has been widely used for more than 30 years in the treatment of type 2 diabetes. At the molecular level, metformin has been shown to activate AMP-activated protein kinase (AMPK), a key regulator of cellular metabolism. The fact that mammalian target of rapamycin (mTOR), a master gene involved in cancer cell survival, is negatively regulated by AMPK has led many researchers to evaluate the efficacy of metformin in patients treated with this drug [44]. Studies indicate that metformin can also reduce mTOR signaling independent of AMPK by inhibiting Ras-related GTPase (Rag)-mediated activation of mTOR [45]. Extensive preclinical and clinical studies over the past decade have demonstrated the antitumor properties of this drug.

In patients with diabetes and at the dose of metformin used by these patients (250–500 mg/day), the drug has been shown to reduce the risk of cancer. A large prospective study [46] indicated that the incidence of gastroenterological cancer in patients with diabetes was reduced by a daily dose of metformin (500 mg/day). A recent systematic review and meta-analysis indicated that metformin was associated with a substantially lower risk of all-cancer mortality and incidence in patients with diabetes [47]. A relationship between long-term use of metformin and decreased risk of breast cancer in women with type 2 diabetes was demonstrated in an observational study [48]. Furthermore, diabetes patients with breast cancer receiving metformin and neoadjuvant chemotherapy had a higher pathological complete response rate than did patients with diabetes not receiving metformin [49]. The therapeutic potential of metformin in prostate, breast, endometrial, and pancreatic cancers is currently being evaluated in several clinical trials, some of which have advanced to Phase III (e.g., NCT01101438, NCT01864096).

Rapamycin

Rapamycin (sirolimus) is a lipophilic macrolide and an allosteric inhibitor of the mTOR pathway that was approved as an immunosuppressant in 1999 for the prevention of allograft rejection. Because mTOR is frequently upregulated in many tumor types [50], rapamycin has been heavily investigated for its anticancer properties. However, the immunosuppressant nature of rapamycin makes it somewhat paradoxical. In one study, the drug suppressed colony formation of leukemic progenitor cells in patients with acute myeloid leukemia [51]. The drug has also been shown to be efficacious in patients with imatinib-resistant chronic myelogenous leukemia [52]. Patients

showed a positive response and a decrease in vascular endothelial growth factor (VEGF) mRNA levels in circulating leukemic cells. The side effects during rapamycin treatment were mild in most patients.

Interest in the anticancer activities of rapamycin has stimulated researchers to develop new semisynthetic rapamycin analogs (rapalogs) such as everolimus, temsirolimus, and deforolimus (ridaforolimus) with high specificity, better solubility, and minimal adverse effects[53]. Temsirolimus was approved for the treatment of renal cell carcinoma by the FDA and the European Medicines Agency in 2007.

Methotrexate

Methotrexate is a folic acid analog that inhibits dihydrofolate reductase, an enzyme needed for DNA synthesis, repair, and cellular replication. In the early 1950s, when methotrexate was first proposed as a treatment for leukemia, its dihydrofolate reductase inhibitory effects were shown to contribute to its antitumor activities [54]. Studies in subsequent years proved the antitumor efficacy of this drug in a wide range of malignancies, including breast, ovarian, bladder and head and neck cancers [55]. In 1988, the drug was approved by the FDA for the treatment of osteosarcoma, breast cancer, acute lymphoblastic leukemia, and Hodgkin lymphoma.

Methotrexate has also been found to target inflammatory pathways. In our own laboratory, the drug was found to suppress NF-κB activation through the release of adenosine in cancer cells. The drug decreases the production of TNF-α and chemokines and exhibits antiangiogenic properties that may also contribute to its anti-inflammatory profile [56].

Bisphosphonates

Bisphosphonates are a class of drugs most commonly prescribed to treat osteoporosis (bone destruction). These drugs have been widely used to prevent bone loss and to reduce the risk of skeletal complications because of their proven efficacy in inhibiting osteoclast-mediated bone resorption [57]. Because of anti-bone-resorptive effects, bisphosphonates are now being used to ameliorate cancer-related bone loss in patients. Bisphosphonates inhibit farnesyldiphosphate synthase in the mevalonate pathway and thereby prevent protein prenylation of small GTPase signaling proteins required for osteoclast function [58]. Numerous bisphosphonates have been developed over the years, including etidronate, clodronate, tiludronate, pamidronate, alendronate, ibandronate, risedronate, and zoledronic acid.

Preclinical and clinical studies have shown that bisphosphonates possess various antitumor effects in numerous cancer types, including multiple myeloma, breast cancer, prostate cancer, and osteosarcoma [59]. The efficacy of bisphosphonates in ameliorating cancer-related bone loss in patients with metastatic bone disease and multiple myeloma has been well established [60]. In a recent, large randomized clinical trial involving 1970 multiple myeloma patients, zoledronic acid was found to suppress bone loss [61]. The benefits of zoledronic acid in improving overall survival rates of patients with multiple myeloma were evident from another recent study [62]. Zoledronic acid was found effective in preventing or delaying skeleton-related events in patients with advanced cancer metastasis to bone or myeloma. Bisphosphonates, alone or as adjuvants, were also found efficacious in preventing bone metastases and overall progression of disease in patients with breast cancer [63], prostate cancer [64], and osteosarcoma [65].

Zoledronic acid is now approved for the treatment of metastatic bone disease [66]. However, the recommended doses for treating bone metastases are much higher than those required for the treatment of postmenopausal osteoporosis. Furthermore, the adverse effects associated with these drugs, such as renal toxicity, osteonecrosis of the jaw, and gastrointestinal problems, deserve attention.

Other non-cancer drugs

In addition to the drugs discussed above, numerous other non-cancer drugs have demonstrated anticancer activities. Leflunomide is an immunomodulatory drug often used as a first-choice disease-modifying antirheumatic drug [67]. In addition to its inhibitory effects on dihydroorotate dehydrogenase, the drug has been shown to be a potent inhibitor of tyrosine kinases, epidermal growth factor receptor, and fibroblast growth factor receptor [68]. Because activation of these kinases is often associated with various forms of cancer, leflunomide represents a potentially important cancer therapeutic.

Wortmannin is a fungal metabolite that was originally reported for its anti-inflammatory activity. It is an irreversible inhibitor of phosphoinositide 3-kinase (PI3K) that forms a covalent bond in the ATP-binding cleft of the kinase [69]. The PI3K pathway is frequently activated and is involved in the pathogenesis of numerous cancer types. Because of the inhibitory effects of wortmannin on the PI3K pathway, this fungal metabolite could play a role in future cancer therapeutics.

Minocycline is a lipophilic semisynthetic derivative of the tetracycline group of antibiotics originally prescribed for the treatment of severe acne and approved by the FDA in 1971. Recent studies have demonstrated that minocycline has anticancer activities against ovarian cancer, glioma, and numerous other cancer types [70].

Vesnarinone, a synthetic quinolinone derivative with inotropic effects, was originally developed to treat cardiac failure. Because of its antiproliferative, differentiation-inducing, and apoptosis-inducing properties, the drug has exhibited activities against several human malignancies, including leukemia and several solid tumors [71].

Thiocolchicoside is a semisynthetic drug derived from colchicoside that has been used for more than 35 years as an analgesic, a muscle relaxant, and a treatment for numerous orthopedic, traumatic, and rheumatological conditions [72]. Studies over the past decade have indicated the anticancer potential of this drug [73–75]. Mechanistically, thiocolchicoside has been shown to inhibit the NF-κB signaling pathway in cancer cells [73]. We found that the drug inhibited the phosphorylation, ubiquitination, and degradation of the IκBα subunit of NF-κB that was linked with suppression of IKK activation and p65 nuclear translocation [73]. However, further studies using animal

models and human studies are needed to prove the anticancer potential of this fascinating muscle relaxant.

Nitroxoline is an antibiotic that is used to treat urinary tract infections. In an attempt to identify potent anticancer agents from a library of 175,000 chemical compounds, nitroxoline was recently found to possess potent antiangiogenic activity [76]. The anticancer activity of nitroxoline was shown by another recent study [77]. Among six different compounds tested, nitroxoline was one of the potent agents against lymphoma, leukemia, and pancreatic cancer cells [77].

Noscapine is a natural non-opiate alkaloid known to possess antitussive (cough suppressant), antimalarial, and analgesic properties. Studies over the past 5 years have demonstrated the anticancer activities of this drug [78,79]. The most common mechanisms implicated in the anticancer activities of noscapine include inhibition in microtubule assembly [80], suppression of the expression of hypoxia-inducible factor-1α [78] and Bcl-2 [81], induction of the expression of p21 and p53 [82], and activation of c-Jun NH_2-terminal kinase [83]. Clinical data on the anticancer activities of noscapine are limited, however.

Perspective and future directions

During the past decade, interest in finding new uses for old drugs has grown among clinicians and researchers. In this review, we have discussed several defined drugs and two drug classes (statins and bisphosphonates) that have shown anticancer activities and palliative benefits in cancer patients. Only a few of these drugs (thalidomide, celecoxib, methotrexate, and zoledronic acid) have been approved for cancer patients, however. The rationale for evaluating the anticancer activity of most of these non-cancer-approved drugs came from previous knowledge of their biological activities on cancer targets and the fact that they have passed significant numbers of toxicity tests and thus have known safety. The possibilities of failure for reasons of adverse toxicology are minimal.

Although drug repurposing should significantly reduce the money and time associated with new cancer drug development, there are numerous points that deserve attention. The approved non-cancer drugs cannot be tested blindly in cancer patients without valid mechanistic insight into their possible efficacy. Only a few non-cancer drugs (e.g., thalidomide) have progressed straight to cancer patients. Identification of similar drugs would obviously be immensely valuable. Because in most cases the real mechanism of action of drugs in the human body is unknown, it may be worth examining the efficacy of approved and abandoned drugs with defined biological activities (e.g., thiocolchicoside, nitroxoline) directly in cancer patients. When considering drugs for repurposing, we recommend extra care in selecting only those abandoned drugs whose non-cancer activities have been demonstrated using reliable end points and that have properly defined pharmacokinetic and pharmacodynamic data. The drugs discussed in this review have been approved for other purposes, have well-defined pharmacokinetic and pharmacodynamic properties, and have well-characterized cancer targets.

Considering the fact that the hurdles associated with Phase II and III trials have not changed over the years and that these trials are the most expensive in drug development, it is unknown whether repurposing failed Phase II or approved drugs would save money and time. However, there are many places along the drug development process where the strategy of repurposing an old drug for a new anticancer indication could save time and expense. The period of preclinical and Phase I testing is extensive. Drugs that successfully complete this testing are approved for Phase II testing. If drugs fail in a Phase II trial, this is usually because they did not effectively treat the disease for which they were intended. However, because these drugs modulate various targets in the preclinical models and had passed Phase I toxicity testing in humans, it is possible that these drugs could still be effective but needs testing against the right disease, such as cancer. Some of the drugs discussed in this review, such as wortmannin and thiocolchicoside, have shown activity only in preclinical studies. Whether these observations will translate into the clinic remains to be seen. If they are unsuccessful, we believe that, through careful analysis of the observations, it might be possible to use their chemical structures or targets to develop new anticancer drugs. We believe that exploring the utility of a known drug with known molecular targets and biological effects has less risk of failure than does developing a new molecule with untested biological effects. This line of thought was probably the basis for the following statement made by James Black, pharmacologist and winner of the 1988 Nobel Prize in Physiology or Medicine: 'the most fruitful basis for the discovery of a new drug is to start with an old drug' [84]. In most cases, it is uncertain whether drug doses, formulations, and routes of administration similar to those used for the original indication are needed for a new anticancer indication. If the new drug doses are not readily achievable in humans, further modifications of the original structure might be needed to achieve the pharmacokinetic and pharmacodynamic profiles suitable for new oncology indications. Furthermore, the approved drugs are surrounded by regulatory standards and intellectual property issues that could impede commercialization for new anticancer indication. Given the demonstrated successes of the bedside-to-bench approach highlighted in this review, we believe that each of these challenges deserves further extensive research throughout the drug discovery community.

Concluding remarks

In summary, starting with an existing old drug with a known clinical history can significantly reduce the time and cost associated with the development of new drugs for the prevention and treatment of cancer. We hope that drug repurposing will play a high-impact role in developing new cancer drug therapies and bringing these therapies rapidly to patients who are in great need of medicine to cure this deadly disease. Drug repurposing offers an opportunity to significantly advance basic understanding throughout the drug design process and to establish novel collaborations between academic and industry scientists. Indeed, such collaborative approaches are already under way. For instance, the National Institutes of Health, via its National

Center for Advancing Translational Sciences, has collaborated with eight companies to test 58 abandoned drugs for new uses. Similarly, the UK Medical Research Council is spending US$15 million so that UK researchers can study 22 abandoned compounds [85]. Although some libraries of FDA-approved drugs have been screened in the past, there is currently not one definitive source of all of these molecules that researchers can access for themselves. We encourage the development of a comprehensive library of compounds that have failed the drug discovery process for reasons other than toxicity as well as active non-cancer drugs that is easily available to researchers. Such efforts will enhance the productivity of the drug discovery process.

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