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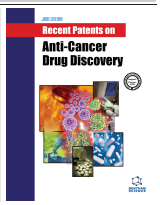
REVIEW ARTICLE

Targeting Cancer Stem Cells with Repurposed Drugs to Improve Current Therapies



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Abstract: ***Background*:** Cancer is a multistep process involving genetic and epigenetic changes in the somatic genome. Genetic mutations as well as environmental factors lead to the initiation, promotion, and progression of cancer. Metastasis allows cancer cells to spread *via* circulatory and lymphatic systems; secondary tumorigenesis typically leads to a fatal outcome. Recent experimental evidence suggests that Cancer Stem Cells (CSCs) play a pivotal role in tumor progression. A tumor is heterogeneous and composed of different cell types. CSCs are a subpopulation of tumor cells possessing abilities to self-renew and differentiate.

***Objective*:** The aim of this study was to present repurposed drugs, and potential candidates, that can serve as anticancer medications intended to target resistant cancer cells, *i.e.* CSCs.

***Methods*:** Research publications, FDA filings, and patents have been reviewed for repurposed drugs or drug combinations that can act to improve cancer treatment and care.

***Results*:** Drugs that act against CSCs include ones approved for treatment of diabetes (metformin & thiazolidinediones), parasitic diseases (chloroquine, niclosamide, mebendazole & pyrvinium), psychotic disorders (thioridazine, clomipramine & phenothiazines), alcoholism (disulfiram), lipid disorder (statins), inflammatory diseases (tranilast, auranofin, acetaminophen & celecoxib), antibiotics (azithromycin), and other disorders. Current research findings advocate the existence of beneficial effects by combining these repurposed drugs, and also through their complementary use with conventional cancer therapies.

***Conclusion*:** Repurposing FDA-approved medications towards cancer care, by targeting the resistant CSCs, will allow for a quicker, cheaper development and approval process. A larger drug library available to physicians will allow for increased efficacy during both first-line and recurrent cancer treatments.

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1. INTRODUCTION

Carcinogenesis is a multistep process. Genetic and epigenetic changes accumulated in the somatic genome of cancer cells lead to tumor initiation, promotion, progression, and metastasis. The cancer cells exhibit hallmark alterations in their physiology, namely: (1) self-sufficiency of growth signals, (2) insensitivity to growth inhibitory signals, (3) evasion of programmed cell death, (4) limitless replicative potential, (5) reprogrammed cellular energetics, (6) induction of angiogenesis, (7) presence of tumor-promoting inflammation, (8) avoidance of immune destruction, (9) maintenance of genome instability and mutation, and (10) activation of tissue invasion and metastasis [1].

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As confirmed during histological examinations, tumors are heterogenous. They are composed of cells at various stages of differentiation as well as non-tumor cells, *e.g.* fibroblasts, immune cells, and endothelial cells, as a consequence of local angiogenesis. In short, not all cells within a tumor are equal. Under the clonal evolution model, malignant tumors are composed of cancer cell variants possessing different genetic profiles created by an accumulation of mutations [2, 3]. The resulting phenotypes, coupled with environmental conditions, give rise to cell plasticity capable of resisting medical intervention [4].

Clonal evolution, alongside competition within the tumor, results in the proliferation of dominant cells that are resistant to therapy and possess the abilities to self-renew and differentiate their progeny. This observed tumor heterogeneity has been explained by the Cancer Stem Cell (CSC) hypothesis. A 2006 workshop of the American Association for Cancer Research settled with a consensus definition of CSC:

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"a cell within a tumor possesses the capacity to self-renewal and to cause the heterogeneous lineages of cancer cells that comprise the tumor" [5]. This was expanded in 2011 by the Working Conference on CSCs that proposed a conceptual and practical framework for CSC terminology. Here, CSCs are defined as "a subclass of neoplastic stem cells that propagate malignant clones indefinitely and produce an overt cancer" [6].

Tumor growth is the direct effect of increased proliferation rates caused by damage to regulatory pathways. Symmetric and asymmetric division models add another layer of complexity when it comes to CSC proliferation. The symmetric model is problematic when targeting CSCs. Asymmetric division yields 1 differentiated and 1 CSC, as opposed to symmetric division's homeostatic population capabilities of producing either 2 differentiated or 2 CSCs, which can act to replenish stem cell populations [7]. Researchers determined that CSCs surviving radiotherapy displayed an increased rate in cell cycle and a loss in the asymmetric division [8]. It is the symmetric division that acts to replenish the CSC population with the most persistent cells selected for their survival ability as a consequence of medical intervention that failed to eradicate all of the CSCs during first-line treatment.

Targeting CSCs is a critical step in both first-line treatment and in caring for relapse patients. Eliminating CSCs during a patient's initial therapy would serve to reduce the likelihood of future relapse events, whereas targeting these resistant cells in relapse patients will allow physicians more options when planning future treatment regimens. It is common to envision CSCs gaining resistance against medications just as bacterial strains gain antibiotics resistance. However, other conventional cancer therapies also run the risk of becoming ineffective in eliminating these cells. Radiation therapy's mechanism of inducing DNA damage as a means to promote apoptotic pathways can be hindered by CSCs' biases favoring survival [9]. These pro-survival tendencies may be caused by CSCs' primary, constitutive expression of pathways or result from acquired resistance to radiation therapy [10]. Individualized radiotherapy treatments based on CSC biomarkers, *e.g.* human papilloma virus infection status, is one strategy to improve outcomes for head and neck squamous cell carcinoma [11]. In this review, we shall discuss features of CSCs and the potential for their killing by repurposed, also referred to as repositioned, drugs. While we use the term CSCs in our review, we are aware that other investigators may prefer the term tumor-initiating cells or another name to describe these cells.

To link stem cells and cancer together, histological similarities were observed between embryonic and tumor tissues in the nineteenth century. This led to the embryonic rest theory describing how cancers arise from cells with properties similar to those of early embryos. Later investigations proposed cancer cells behaving in a parallel nature to that of normal cell development, but key regulatory processes are impaired. The uncharted cell proliferation seen in cancer is the result of the distortion of normal development, and a lack of coordination between growth and differentiation. In addition, knowledge on stem cell biology in normal tissues has been translated to the concept of CSCs in cancerous tissues [12]. CSCs express plasticity in the form of increased epigenetic and genetic variability [13].

CSCs have been detected in mammals ranging from mice to humans. In their study on hematopoietic malignancies in 1937, Jacob Furth and Morton Kahn provided the first quantitative assay for assessing the frequency of cancer cells for the maintenance of hematopoietic tumor. They showed a single mouse leukemic cell was capable of transmitting the systemic disease through an allograft [14]. By definition, this has to be the CSC of murine leukemia. Like its murine counterpart, the human CSC was first demonstrated in leukemia and then extended to solid tumors. In 1997, Dominique Bonnet and John Dick reported the presence of $CD34^{+}/CD38^{-}$ CSCs in human acute myeloid leukemia [15]. It was discovered that isolated patient CSCs will reconstitute the leukemia when transplanted in immunodeficient mice. In April 2003, Muhammad Al-Hajj and colleagues discovered $CD44^{+}/CD24^{-/low}$ CSCs in human breast cancer. These researchers determined that even just 100 $CD44^{+}/CD24^{-/low}$ cells are capable of producing tumors in mice xenograft models and that alternate phenotypes, seeded in the tens of thousands of cells, were unable to produce tumors [16]. In September 2003, Shelia Singh and colleagues reported the presence of $CD133^{+}$ CSCs in human brain cancer. Brain tumor stem cells (BTSC) were discovered in the cell fraction of neural stem cells possessing CD133 and culture work found these BTSCs had the ability to differentiate into tumor cells phenotypically similar to the patient [17]. These initial studies on CSCs have been expanded to many other cancers in subsequent years.

2. TECHNIQUES TO IDENTIFY CANCER STEM CELLS AND CONTROVERSIES

We have previously mentioned several approaches available to study CSCs [12, 18]. Cell surface antigens, such as CD34, CD44, and CD133, serve as CSC biomarkers. These markers have been used in the isolation of CSCs from leukemia, breast cancer, and many other solid tumors. Researchers have organized a current list of CSC biomarkers for different cancers [19]. In addition to biomarker identification, CSCs can also be characterized by functional assays, namely, the detection of Side Population (SP) and the assessment of Aldehyde Dehydrogenase (ALDH) activity. Both features were first discovered in normal stem cells and then applied to CSCs. The SP assay measures the ability of cells to expel fluorescent dye, namely Hoechst 33342, *via* ATP-dependent drug transporters, including ABCG2, located on the plasma membrane. As analyzed by flow cytometry, cells with fast drug expulsion form a SP distinct from the majority of cells. SPs have been found in many CSCs. Similarly, ALDH is a detoxifying enzyme capable of fulfilling its role of oxidizing aldehydes into carboxylic acids that are further metabolized and removed by the liver. A fluorescent substrate assay using ALDEFLUOR, biodipy aminoacetalde-

hyde (BAAA), allows the isolation of $ALDH^+$ cells. Both SP and ALDH assays involve drug extrusion and metabolism; these properties indicate CSC drug resistance. However, it must be emphasized that biomarkers and functional assays may not characterize all CSCs within a sample as CSCs not exhibiting the screening criteria may be overlooked. On the other hand, these features may inadvertently be detected in normal tissue or stem cells.

One popular *in vitro* method to study CSCs is the serum-free spheroid culture. Tissue culture cells are usually grown as a monolayer in a nutrient-rich medium containing fetal bovine serum as a source of the necessary growth factors and other components. In lieu of serum, growth factors, including Fibroblast Growth Factor (FGF) and Epidermal Growth Factor (EGF), can induce the cells to grow as spheres in suspension (using non-attached/untreated tissue culture ware). Spheroid cultures mimic the three-dimensional nature of a tissue. Oxygen may be less accessible to the cells located at the interior of a sphere, and the hypoxic condition may modulate their differentiated state towards stemness. Originally developed for neurobiological studies, the spheroid culture can identify stem cells based on their capacity to self-renew and differentiate at the single-cell level; spheroid culture has been adapted for CSCs (we use the term spheroid culture but others may prefer tumorspheres or tumorosphere as well as specific terms such as mammosphere) [20, 21]. There are critiques for spheroid culture. Spheres are prone to aggregate; thus, cell density influences clonality. Furthermore, the quiescent CSCs may be missed using this method [20]. In fact, the quiescent nature of putative normal and CSCs has been utilized for their characterization. These are referred to as label-retaining cells because they can retain labels such as the lipophilic dye PHK26, which is diluted in subsequent cell divisions but not so with slow-dividing cells [22]. CSCs have been isolated from both tumor samples and established cancer cell lines [23]. The advantage of the latter is the absence of non-tumor cells as contaminants; the disadvantage is the additional accumulated changes during the long time period of *in vitro* culture. As an example, our interest in CSCs and SP analysis led us to isolate SPs from the rat C6 glioma cell line, thus deriving putative CSCs from an established cell line [24]. However, the C6 stemness state is dynamic: whereas SPs give rise to both SP and non-SP progenies, as expected, non-SPs can do the same. Thus, CSC plasticity is an interesting topic. MicroRNA, single-cell RNA sequencing, specific bio-imaging reagents, and other modern techniques are being applied to investigations of CSCs [25-27].

Extending CSC studies from *in vitro* to *in vivo*, there are models using strains of immunodeficient mice for xenotransplantation of human CSCs. Limiting dilution analysis yields an estimate of CSC abundance in the tumor sample; sequential transplantation yielding the original tumor will confirm the presence of CSCs. Several murine models have been applied to CSC studies, including nude mice, Non-Obese Diabetic/Severe Combined Immunodeficiency (NOD/SCID) mice, and NOD/SCID interleukin-2 receptor gamma chain null ($Il2rg^{-/-}$) mice. There are critiques believing this approach is overly artificial and non-physiological due to human CSCs not encountering a normal host immune response. Despite such objections, the limiting dilution murine *in vivo* xenograft assay has been held as the gold standard for CSC identification. However, despite being considered the gold standard assay by many in the field, the current model of human tumor growth in immunocompromised mice as a relevant assay for CSC activity is still being questioned [28]. We anticipate better mouse models, such as ones exhibiting human immune response, will enhance CSC research in the near future.

The CSC hypothesis is controversial. A 2019 analysis utilizing ecology's hierarchy of hypothesis approach found empirical support for the CSC hypothesis was only 49.0% [29]. However, there is accumulating evidence favoring the CSC hypothesis.

The presence of CSCs may explain concepts of cancer and therefore be relevant to improving current cancer therapy. The major supporting data are: (1) the presence of CSCs in Minimal Residual Disease (MRD) and (2) the demonstration of CSCs in cell lineage tracing studies of murine tumors. MRD is a term first used in leukemia to denote the small numbers of leukemic cells that remain in the patient after treatment, when the patient is in remission. MRD is the major cause of relapse in cancer and has been applied to solid tumors. Because CSCs have resistance mechanisms, they become enriched after chemo- and radio-therapy and are found in MRD. The presence of CSCs after therapy predicts recurrence; CSCs have major clinical relevance [28]. Lineage tracing is a common technique for studying cell origins in developmental biology. The 2012 tracking of cells expressing fluorescent proteins, *e.g.* Green Fluorescent Protein (GFP), in three different murine solid tumors has been cheered as settling the stem-cell debate [30]. As an example, for murine glioblastoma, a transgene was created to label both the quiescent adult neural stem cells and a subset of the endogenous glioma tumor cells (expressing GFP). The transgene contains a viral thymidine kinase gene that can be targeted by the drug ganciclovir. Glioma was treated with the drug temozolomide (TMZ), but TMZ treatment alone led to the re-growth of a subpopulation of CSCs, that were then controlled by ganciclovir. TMZ-ganciclovir co-treatment impeded tumor development by destroying both cancer cells and CSCs. This study conclusively demonstrates the existence of murine glioma CSC and its selective targeting [31]. Since these are CSCs in solid tumors of murine origin, similar CSCs are assumed to be present in human tumors. CSCs are essential targets for cancer therapy. Thus, the ideal cancer treatment must eradicate bulk cancer cells and CSCs by combining conventional therapy and molecules that specifically target CSCs [32].

3. REPURPOSED DRUGS TARGETING CANCER STEM CELLS

Characteristics of CSCs need to be identified when searching for new treatment strategies. Notably, CSCs become chemoresistant and radioresistant after therapeutic tre-

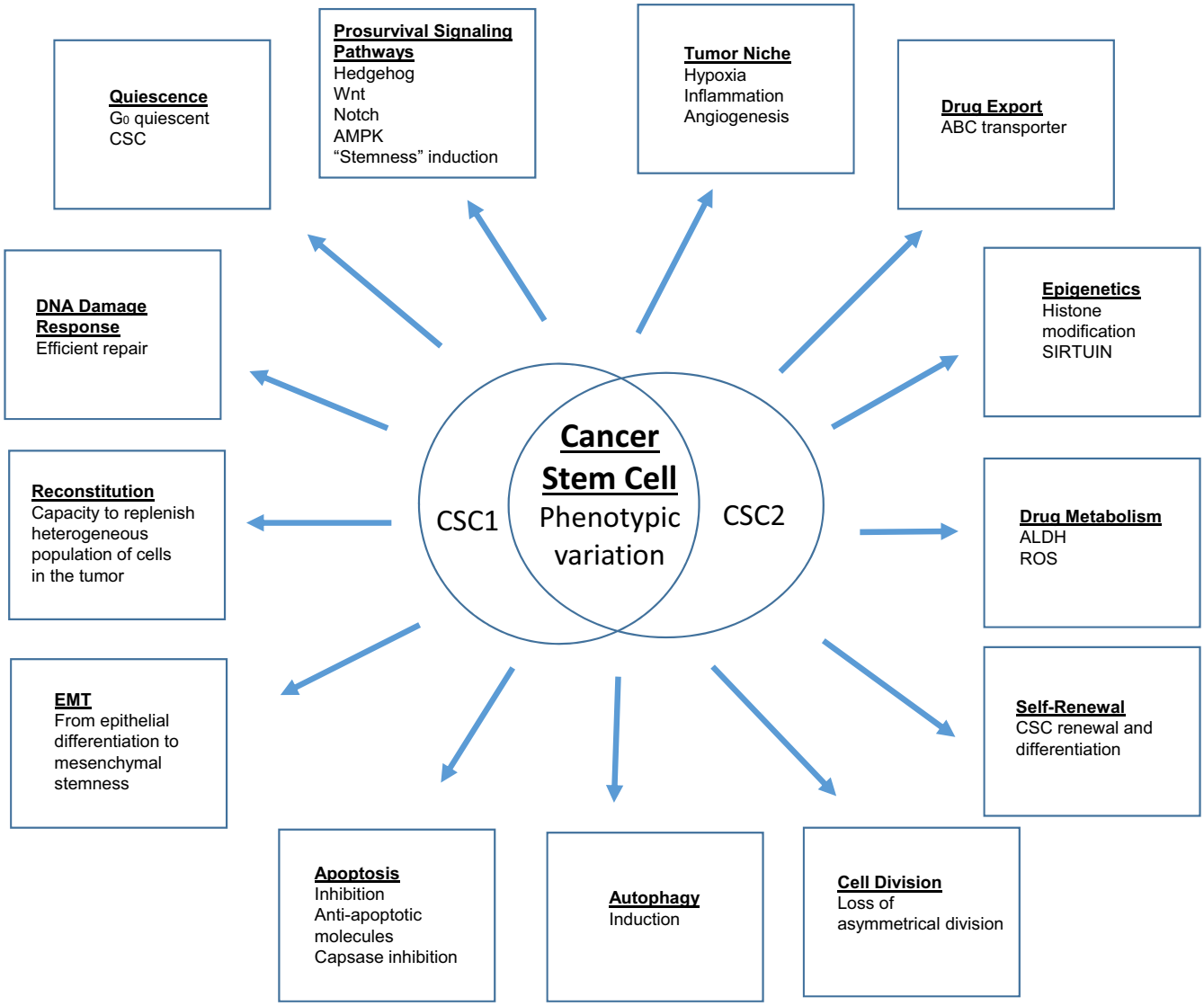

Fig. (1). Characteristic features of the cancer stem cell.

atments. Although conventional therapies can kill the majority of bulk tumor cells, CSCs possess the capacity to reconstitute the tumor. They accomplish this feat *via* many characteristic features, as summarized in (Fig. **1**) (adapted from [18], with modifications). CSCs act *via* activities of drug transporters and metabolism enzymes, plus a DNA repair system activated by genomic instability. They may possess less Reactive Oxygen Intermediates (ROIs), alias Reactive Oxygen Species (ROS), and thus are less susceptible to radiation therapy. Depending on individual cases of cancer, CSCs may arise from either mutated normal stem cells or de-differentiated cancer cells, exhibiting stem cell features. They display pathways of gene expression in common with those of normal stem cells. Therefore, considering therapeutic approaches, molecules targeting CSCs must be capable of differentiating them from the normal stem cells and sparing the latter, otherwise unforeseen problems with normal tissue homeostasis can occur. CSCs display self-renewal, differentiation, high tumorigenicity, and drug resistance. There is an urgent need to develop new therapeutic strategies to control CSC replication, survival, and differentiation. Several signal transduction pathways active in CSCs may be amendable for intervention, including Hedgehog, Wnt, Notch, NF-κB (nuclear factor kappa B), JAK-STAT (Janus kinase/signal transducer and activator of transcription), PI3K/AKT/mTOR (phosphoinositide 3-kinase/AKT/mammalian target of rapamycin), TGF (transforming growth factor)/SMAD, PPAR (peroxisome proliferator-activated receptor) and others, plus crosstalk occurring among different pathways. Therefore, multi-target inhibitors will be one of the main methods to overcome the CSCs and their drug resistance [12, 18, 33, 34].

Dietary phytochemicals may be the key multi-target inhibitors needed to target CSCs. The consumption of fruits and vegetables is a common part of the human diet. As omni-

vores, humans also consume various meats and other foods. Bioactive components from plants are non-nutrient dietary phytochemicals that can modulate gene expression and signal transduction pathways. These compounds became known as chemopreventive agents acting upon multiple cellular targets (including the epigenome). For chemoprevention, phytochemicals target inflammation (inflammation may initiate cancer) and cell cycle control (cancer is the loss of growth regulation). Chemopreventive phytochemicals are applicable to cancer care since they may share molecular mechanisms in common with proven cancer therapies. Phytochemicals may modulate cancer development and even metastasis. They may also enhance the activity of conventional chemotherapy. As an example, we showed curcumin (a component of the spice curry) and quercetin (found in apples and onions) can increase the sensitivity of human ovarian cancer cells to the drug cisplatin *in vitro* [35]. Cancer cell drug resistance has led us to target CSCs with phytochemicals [12] and to propose combination treatments using dietary phytochemicals plus repurposed (repositioned) drugs [18].

Drug repositioning exploits novel molecular targets of an FDA-approved drug to treat additional diseases besides its original indication. Just like shared molecular mechanisms between chemoprevention and cancer therapy, the same can be said for cancer therapy and CSCs. Repurposed drugs for cancer and CSCs may be the same compounds (such as metformin) [36]. For cancer therapy and CSC targeting, the combination approach will be beneficial [37]. To our knowledge, the first review on repurposed drugs targeting CSCs was published in 2015 by Junfang Lv and Joong Sup Shim [38]. Availability of existing drug libraries (with about 3,000 compounds) and three repurposed drugs targeting CSC signaling pathways were discussed: niclosamide for Wnt and JAK/STAT, metformin for Notch, and chloroquine for JAK/STAT and Sonic Hedgehog (SHH) pathways. Repurposed drugs targeting CSCs include metformin, niclosamide, chloroquine, disulfiram, tranilast, and the statin drugs simvastatin and lovastatin [12, 18].

In this review, we have updated the list of CSC-targeting repurposed drugs *via* literature and patent searches. In the following sections, the better known repositioned drugs, ones with more supporting publications, will be presented. Table **1** provides a list of drug categories, specific medications, and the origin of CSCs that can be targeted. Since we are acutely aware of the high cost of new anticancer drugs, ("all new cancer drugs enter the market with a price tag that exceeds $100,000 per year," [18]), we intentionally exclude the more recent drugs that target CSCs. As examples, these are the telomerase inhibitor, imetelstat, that inhibits breast and pancreatic CSCs (fast-tracked in 2019 by FDA to Geron, for treatment of adult patients with relapsed or refractory myelofibrosis); the several inhibitors of Smoothened (or Smoo, an essential protein of the SHH pathway) including vismodegib (Roche) and sonidegib (Norvatis) for basal cell carcinoma, and glasdegib (Pfizer) for Acute Myeloid Leukemia (AML) [32]. We also exclude non-human drugs that show CSC-targeting capacity. Examples are the ionophores salinomycin (found in CSC drug screening and used in poultry industry against the parasite protozoan disease coccidiosis) and monensin (against melanoma CSCs, used in the cattle industry, also for coccidiosis) [39, 40]. Other investigators have discussed various CSC-targeting compounds in general [41], in clinical trials [42], and with emphasis on specific areas such as signaling pathways, drug resistance and metabolism [33, 43, 44]. Repurposed drugs targeting specific CSCs have been reviewed for pancreatic and brain CSCs [45-47].

3.1. Metformin

Globally, Diabetes Mellitus (DM) is a prevalent disease affecting an estimated 382 million people across the globe. Type 1 Diabetes Mellitus (T1DM), "childhood diabetes," is an autoimmune disease that destroys insulin-producing beta cell located in the pancreas leading to a deficiency in insulin. Type 2 Diabetes Mellitus (T2DM), "lifestyle diabetes," is caused by insulin insensitivity and accounts for 85-95% of DM. Due to obesity, sedentary lifestyle, smoking and alcohol overconsumption, there is an increase in T2DM incidence worldwide. In 1957, Jean Sterne reported DM treatment with metformin in Paris. Metformin is 1,1-dimethylbiguanide hydrochloride, a synthetic biguanide derived from the herb French lily (*Galega officianalis*); it is the most commonly prescribed drug for T2DM, taken by an estimated 150 million individuals worldwide [48, 49]. Metformin is the old synthetic biguanide that still is the best treatment for T2DM [50]. Metformin lowers blood glucose levels and is safe over a wide range of dosages. DM patients taking metformin have a reduced risk of cancer [51]. Beyond DM, metformin has been repurposed for many diseases, including cancer, cardiovascular disease, and even aging/longevity [49].

Mechanisms of action of metformin have been investigated. Metformin modulates energy metabolism by targeting AMP-activated protein kinase (AMPK), but it also exerts AMPK-independent effects. For DM, metformin yields benefits in relation to glucose metabolism and diabetes-related complications, but the exact mechanisms underlying these benefits are still unclear [52]. For potential therapy of cancer, metformin has been shown to target multiple signaling pathways, such as AMP-activated protein kinase, mammalian target of rapamycin, insulin-like growth factor, c-Jun N-terminal kinase/mitogen-activated protein kinase (p38 MAPK), human epidermal growth factor receptor-2, and NF-κB [53].

Previously, we concluded that: "Probably the most significant drug reported thus far for targeting CSCs is metformin" [18]. Our current assessment is that the statement continues to be true. Metformin's effect on cancer has led to an investigation of its action on CSCs [54]. It inhibits CSC spheroid culture formation. In addition to targeting signaling pathways seen in cancer, it also targets pathways found in CSCs, such as Sonic Hedgehog and Wnt pathways [55].

In 2009, Harvard investigators under the direction of Kevin Struhl first reported that metformin, when tested aga-

Table 1. Repurposed Drugs Targeting Cancer Stem Cells.

Drug Classification	Drug Name	Cancer Stem Cell Tissue Origin	References
Anti-diabetic drugs	Metformin	Breast, prostate, lung	[56-58]
	Pioglitazone	Breast, liver, osteosarcoma, chronic myeloid leukemia	[70-73]
Anti-parasitic drugs	Niclosamide	Breast, ovarian, glioblastoma	[87-89]
	Mebendazole	Acute myeloid leukemia	[96-101]
	pyrvinium	Breast, lung	[109, 110]
	Ivermectin	Breast	[120, 121]
Anti-malaria drug	Chloroquine	Breast, ovarian, lung	[55, 127-130]
Anti-inflammatory drugs	Auranofin	Ovarian, lung	[138, 139]
	Aspirin	Lung	[147]
	Acetaminophen	Breast	[148]
	Celecoxib	Breast, medulloblastoma	[150, 151]
Anti-allergy drug	Tranilast	Breast, esophageal	[155-157]
Anti-cholesterol drugs	Simvastatin	Brain, ovarian	[170, 171]
	Lovastatin	Nasopharyngeal carcinoma	[184]
Anti-alcoholism drug	Disulfarum	Breast, ovarian, glioblastoma, pancreatic, multiple myeloma	[185-191]
Anti-psychotic drugs	Thioridazine	Breast, ovarian, lung, leukemia	[200-204]
	Trifluoperazine	Lung	[209]
	Fluspirilene	Glioma	[210]
	Pimozide	Liver	[211]
	Sulpiride	Breast	[213]
	Clomipramine	Lung	[214]
	Valproic acid	Breast	[216]
Antibiotics	Azithromycin	Breast	[219]
	Doxycycline	Breast	[219]
	Mithromycin	Colorectal	[224]
Differentiating agents	Arsenic trioxide	Acute promyelocytic leukemia	[227]
	Retinoic acid	Acute promyelocytic leukemia, gastric	[228]
Anti-fungal drugs	Itraconazole	Lung	[229]
	Ketoconazole	Glioblastoma	[230]
Iron chelator	Deferiprone	Breast	[231]

inst human breast CSCs, inhibited spheroid formation *in vitro* and reduced tumor volume in nude mice xenograft synergistically with the drug doxorubicin, by blocking both CSCs and non-CSCs [56]. Their finding was later expanded to different drugs (paclitaxel & carboplatin) and CSCs (lung and prostate CSCs) [57]. Others have published confirmatory findings. As an example, in $CD133^+$ prostate CSCs, metformin enhanced their sensitivity to gemcitabine *in vitro* and in nude mice xenografts [58].

Effects of metformin and its molecular mechanisms are continuously being analyzed. Metformin and aspirin combination inhibited migration (cell spreading) of colorectal CSCs [59]. Metformin and other biguanides targeted glioblastoma CSCs by inhibiting Chloride Intracellular Channel 1 (CLIC1) [60]. Furthermore, metformin can increase circulating levels of the peptide hormone Growth/Differentiation Factor (GDF15). This hormone has been shown to reduce food intake and lower body weight through a brainstem-restricted receptor. GDF15 involvement allows metformin to obtain its beneficial effects on energy balance and body weight, major contributors to its action as a chemopreventive agent [61].

In short, the DM medication metformin is the best-known repurposed drug targeting CSCs. There are patents on metformin's use as a cancer therapy, including WO2011031474 to Struhl and colleagues [62], and combinations of metformin and other compounds [63, 64].

3.2. Pioglitazone

In addition to metformin, other DM drugs also target cancer cells and CSCs. A review of potential applications of antidiabetic drugs in cancer treatment is found in reference [65], including Thiazolidinediones (TZDs) and sulfonylurea. TZDs, especially pioglitazone, may be a class of CSC-targeting repurposed drugs.

The application of TZDs to DM has a checkered past [66]. TZDs are known as "the forgotten diabetes medications" [67]. In 1975, the Japanese company Takeda developed 71 analogs of clofibrate in search of hypolipidemic drugs. The first TZD, ciglitazone, with promising lipid and glucose lowering effects, became available in 1982 but was soon withdrawn due to liver toxicity. Another TZD, troglitazone, discovered by Sankyo in 1988 and launched by Glaxo Wellcome in 1997, was withdrawn within 6 weeks in Britain due to rare but potentially fatal hepatotoxicity. It was followed by the FDA pulling troglitazone from the market in 2000. In 1999, FDA approved rosiglitazone from SmithKline and pioglitazone from Takeda for the management of T2DM, as these drugs did not have the same liver safety concerns as troglitazone. Rosiglitazone was able to quickly cap-

ture a major share of the diabetic market, but the cardiovascular risk was soon found. In 2007, FDA required a "black box warning" for ischemic events and Europe recommended non-use [68]. The other TZD, pioglitazone, fares better. It may even have a mild cardioprotective effect, but there may be a risk of bladder cancer. Because of this, France had it withdrawn from the market in 2011. Recent studies suggest pioglitazone may not possess a risk of bladder cancer [67, 69]. Novel TZDs devoid of side effects are being actively pursued because they are an important class of insulin sensitizers for the treatment of T2DM [66].

Mechanisms of action of TZDs have been investigated. Their activity is mediated *via* the Peroxisome Proliferator-Activated Receptors (PPARs). The three major types are PPARα, PPARβ/δ and PPARγ, with TZDs binding especially to the third type. These are nuclear receptors. Ligand bound PPARγ forms a heterodimer with the Retinoid X Receptor (RXR), migrates to the cell nucleus and recognizes the specific gene sequences known as Peroxisome Proliferator Response Elements (PPREs) and modulate gene expression, including the production of adipokines by fat tissues. The end result is the regulation of insulin sensitivity by TZDs. As transcriptional factors, PPARs are targets in the management of metabolic syndrome and T2DM [66].

TZDs target CSCs. In breast CSCs that form a spheroid culture *in vitro*, these "mammospheres" were inhibited by pioglitazone. Pioglitazone inhibited the expression of Notch pathway gene products in breast CSCs; it also inhibited the expression of proinflammatory cytokine Interleukin-6 (IL-6) expression in tumor-associated fibroblasts (thus potentially affecting the CSC niche or microenvironment) [70]. Both *in vitro* and *in vivo* immunodeficient mice studies using rosiglitazone to treat CSCs had been performed. For osteosarcoma, rosiglitazone induced growth arrest and differentiation in cell culture; it also decreased tumor size *in vivo*. For molecular mechanisms, rosiglitazone inhibited the Wnt and Hippo-YAP pathways [71]. For liver cancer or Hepatocellular Carcinoma (HCC), rosiglitazone inhibited liver CSC spheroids ("hepatospheres") in cell culture and decreased tumor size in mice. TZD action involved Reactive Oxygen Species (ROS) [72].

Significantly, targeting CSCs has been achieved in human patients with Chronic Myeloid Leukemia (CML) [73]. In three patients with chronic residual disease after imatinib (kinase inhibitor drug) treatment, the addition of pioglitazone to target leukemic CSCs led to remission. Hence, there are current efforts to obtain better TZDs to target CSCs [74]. With respect to patents, WO2009088992 is one concerning TZDs with an application towards cancer [75].

3.3. Niclosamide

Even though we have just discussed anti-diabetic TZDs as the second group of drugs in this review, we consider niclosamide as the second most significant repurposed drug that targets CSCs after metformin [18]. Niclosamide is a lipophilic salicylanilide with two benzene rings. Its IUPAC name is 5-chloro-N-(2-chloro-4-nitrophenyl)-2-hydroxybenzamide. Niclosamide was first reported in 1958 as a molluscicide. Scientists at Bayer screened over 20,000 molecules against the snail species (*Biomphalaria glabrata*) that serves as an intermediate host to blood flukes (agent of the important parasitic disease schistosomiasis) to find the compound, named Bayluscide [76]. Soon afterwards, niclosamide was shown to act against tapeworms (cestodes); FDA approved its human use in 1982. As a common anthelminthic (especially for tapeworms), niclosamide is on the World Health Organization's list of essential medicines [77]. Millions of patients have been treated with this drug [78]. (Despite this, in 1996, niclosamide, sold in the US under the brand name Niclocide, was voluntarily withdrawn from the market by Bayer in favor of a better replacement, praziquantel). In addition to tapeworms, niclosamide may be beneficial to a variety of diseases: Parkinson's disease, T2DM, lupus, rheumatoid arthritis, antibacterial and antiviral activities. Niclosamide is "a drug with many (re)purposes" [79]. With respect to its anti-microbial potentials, niclosamide targets the tuberculosis bacterium and the human immunodeficiency virus [80]. It has also gained notice for its potential to target the pandemic COVID-19 (coronavirus disease 2019) infectious agent SARS-Cov-2 (severe acute respiratory syndrome coronavirus-2) [81]. "Niclosamide for mild to moderate COVID-19" is an ongoing clinical trial at Tuft Medical Center (NCT04399356).

In an early clinical trial, niclosamide has been shown to be an effective, nontoxic agent for the therapy of tapeworm infections. It inhibits oxidative phosphorylation in cestode mitochondria. The scolex and proximal segments of tapeworms are killed on contact, with the scolex separated from the intestinal wall and then evacuated in the feces [82]. Despite its wide use as an anthelmintic drug, the exact mechanism of action is still unclear [78]. Niclosamide has been shown to target cancer and CSCs by blocking multiple signaling pathways (including Wnt, Notch, STAT3 & NF-κB) [83, 84]. It has been noticed that a particular developmental stage of tapeworms (metacestodes) has a resemblance to cancer. Both cancer cells and metacestodes show uncontrolled proliferation, invasion, and metastasis, and are difficult to kill without causing damage to the surrounding tissue. This similarity suggests the same drug will be capable of treating both diseases [85]. In a bizarre clinical case, *Hymenolepis nana* tapeworm-derived cancer cells were the cause of death of a 41-year-old AIDS patient [86].

CSC-targeting activity of niclosamide was discovered in drug screening, as seen in the following examples. In ovarian and breast CSC drug screenings *in vitro*, niclosamide was selected from 1,258 drugs (LOPAC chemical library). Using CSCs from the cisplatin-resistant ovarian cancer line, the selected niclosamide inhibited tumor xenografts in NOD/SCID mice [87]. Similarly, it inhibited breast CSC tumor xenografts [88]. In a separate screening of 160 compounds (Killer Plate compound library), niclosamide was selected to target glioblastoma CSCs; niclosamide-pretreated CSCs had inhibited tumor growth in xenografts, and synergistic effects between niclosamide and temozolomide were predicted. The mechanisms were simultaneous inhibition of multiple pathways (Wnt, Notch, mTOR and NF-κB) [89].

Niclosamide works together with standard chemotherapeutic agents. Niclosamide and cisplatin combination inhibited the spheroid formation of breast CSCs and decreased tumor size in immunodeficient mice [90]. However, for applications such as CSCs, availability may be a concern. Niclosamide is only partially absorbed from the gastrointestinal tract, synthesizing its derivatives (after structure-activity analysis) may yield novel compounds with improved bioavailability for CSC targeting and cancer therapy [83]. Another approach is an improvement in niclosamide delivery [91]. With respect to patents, WO2012143377 is one concerning niclosamide and cancer metastasis [92].

3.4. Mebendazole

Besides niclosamide, several other anthelmintics target CSCs, including mebendazole (MBZ). MBZ belongs to the group of benzimidazoles (BZs). BZs are low-dose broad-spectrum anthelmintics with a high therapeutic index and selective toxicity for helminths. Their primary mode of action involves interaction with the eukaryotic cytoskeletal protein, tubulin. Because of this, Ernest Lacey marveled at "the paradox of the interaction of BZs with a ubiquitous protein and the evidence for their selective toxicity for helminths" [93]. BZs bind to parasitic worm tubulin with a higher affinity than mammalian tubulin; hence they have extensive veterinary applications. However, their heavy use to control gastrointestinal parasites of livestock has led to widespread BZ resistance in target parasite species [94]. Human use of BZs followed the veterinary use. FDA approved MBZ in 1974. Currently, both MBZ and albendazole are on the WHO essential medicines list [77], but flubendazole was only approved for veterinary use. In the world, about 1.5 billion people are at risk for Soil-Transmitted Helminths (STHs); WHO has proposed preventive chemotherapy to treat at-risk children and adults with MBZ (such as a single dose of 500 mg) at regular intervals [95].

MBZ has been shown to target cancer and CSCs. In addition to binding to beta tubulin and inhibition of tubulin polymerization, it induces apoptosis, inhibits angiogenesis and multiple signaling pathways, such as Sonic Hedgehog and MAPK. Thus, MBZ is a "dirty drug" acting on a wide range of pro-tumoral mechanisms; it may complement anticancer drugs with more precise targets [96]. Both MBZ and flubendazole may target cancer [97, 98]. For example, flubendazole inhibited breast CSCs and tumor metastasis *in vivo* by inhibiting STAT3 [99]. In 2011 in Sweden, MBZ treatment to a 74-year-old patient with metastatic colon cancer led to remission [100]. In a screening of a small molecule drug library (about 1,200 compounds), MBZ was found to induce differentiation of primary leukemia blast cells from acute myeloid leukemia patients [101].

In summary, the findings described above confirm mebendazole as an ideal candidate for drug repurposing for CSC targeting and cancer therapy [96]. With respect to patents, WO2018138510 and WO2019109074 involve MBZ, cancer and cancer metastasis [102, 103].

3.5. Pyrvinium

Another anthelmintic that targets CSCs is pyrvinium. In 1955, pyrvinium received FDA approval for enterobiasis treatment in adults and children. Enterobiosis is caused by infection of the nematode *Enterobius vermicularis*, commonly known as the pinworm. Several forms of pyrvinium are available, including pyrvinium pamoate (PP). Besides pinworm, PP is active against the parasitic protozoan *Cryptosporidium parvum* [104, 105].

PP has been repurposed first as a cancer treatment, then as an agent against CSCs. It inhibits efficient ATP production by suppressing the NADH-fumarate reductase system, one that mediates a reverse reaction of the mitochondrial electron-transport chain complex II in parasitic helminths and CSCs under hypoxic conditions (tumor niche) [106, 107]. PP inhibits multiple pathways such as STAT3, PI3K, Wnt, Hedgehog, and Hippo. It inhibits unfolded protein response and autophagy. The drug also suppresses mitochondrial electron complex chain I (leading to energy depletion) [106, 108].

Effects of PP on CSCs are seen in specific examples. PP promoted apoptosis of lung CSCs [109]. It inhibited breast CSCs *in vitro* (decrease of CD44 and $ALDH^+$ cells) and *in vivo* (decrease tumor size) [110]. With respect to existing patents, US20090099062 involves pyrvinium and cancer [111]. Thus, PP is an ideal candidate for drug repurposing for CSC targeting and cancer therapy [108].

3.6. Ivermectin

Whereas PP is useful for the pinworm, the next anti-parasitic drug that can target CSCs, Ivermectin (IVM), acts on a multitude of ecto- and endo-parasites. IVM has extensive veterinary applications. It is in the news as applicable to COVID-19 due to its known antiviral activity and *in vitro* inhibition of SARS-Cov-2 [112, 113].

IVM belongs to the group of Avermectins (AVMs), 16-membered macrocyclic lactone compounds. The drug was developed in collaboration between investigators in Japan and the United States. In 1970, Satoshi Omura of Kitasato Institute isolated a bacterium in a soil sample from a golf course and sent the isolate to Merck, where William Campbell and colleagues characterized the anti-parasitic compound AVM. The bacterial species became *Streptomyces avermitis*, and AVM-derived IVM became the wonder drug for parasitology. Omura and Campbell received the Nobel Prize in Physiology or Medicine in 2015 [114]. IVM is listed in the WHO essential medicines for both ecto- and endo-parasites [77]. Merck launched the product in 1981 as a veterinary drug against intestinal nematodes in livestock (cattle and sheep), and as a heartworm medication for dogs. IVM was first registered as a human drug under the brand name Mectizan in 1987. It was first used to treat onchocerciasis (river blindness) in humans in 1988. The current estimate for annual use of IVM involves about 250 million people for parasitic diseases, including lymphatic filariasis, onchocerciasis, strongyloidiasis, scabies and lice infections [115].

Significantly, there is the donation of IVM and other drugs to treat neglected tropical diseases. For IVM, Dr. Roy

Vagelos, then CEO of Merck & Co., declared that the company would donate as much IVM (licensed as Mectizan) "as was needed, for as long as needed, to anyone who needed it." Since 1987, the Mectizan Donation Program has approved 1.4 billion treatments for onchocerciasis and 1.2 billion treatments (administered with albendazole, donated by GlaxoSmithKline) for lymphatic filariasis [116].

The mechanisms of action by which IVM works as an anti-parasitic involves targeting the invertebrate ligand-gated chloride channel of nematodes and arthropods. Extensive use led to IVM resistance in some helminths. Alternative applications of IVM in humans have been suggested, including targeting CSCs [116]. Andy Crump commented "Ivermectin: enigmatic multifaceted 'wonder' drug continues to surprise and exceed expectations" [117]. IVM has antiviral and antibacterial (*Chlamydia trachomatis, Mycobacterium tuberculosis*) activities; it may be useful for asthma and neurological disorders, as well as cancer. New derivatives and new formulations may improve IVM properties [118].

IVM acts on multiple pathways seen in cancer and CSCs. Examples include inhibition of P-glycoprotein, AKT/mTOR and Wnt pathways [119]. For breast CSCs, IVM inhibited STAT 3 activation [120]. IVM reduced spheroid formation *in vitro* and decreased tumor volume *in vivo* (in mice) [121]. These findings indicate the potential of IVM to target CSC; and NCT04447235 titled "Early treatment with ivermectin and losartan for cancer patients with COVID-19 infection (TITAN)" will be a clinical trial in Brazil to "evaluate the efficacy of the early use of ivermectin plus losartan in cancer patients who present with a recent diagnosis of COVID-19."

3.7. Chloroquine

A fever-reducing molecule, quinine, was isolated from the bark of the Peruvian *Cinchona* tree. Chloroquine (CQ) is another anti-parasitic drug that targets CSCs. Actually, CQ acts on parasitic protozoan species that cause malaria, such as *Plasmodium falciparum*. FDA approved CQ on October 31, 1949. CQ is listed in the WHO essential medicines for malaria and afflictions of the joints (as Disease-Modifying Agent used in Rheumatoid Disorders, DMARD) [77]. CQ also acts on the parasitic protozoan species *Entamoeba histolytica* (agent for amebic dysentery) and has been used as an anti-inflammatory agent to treat Rheumatoid Arthritis (RA) [122]. CQ and hydroxychloroquine have been found to be controversial with respect to potential COVID-19 treatments. The FDA initially allowed Emergency Use Authorization (EUA) on March 28 but revoked it later on June 15, 2020.

CQ is a synthetic relative of quinine. This 4-aminoquinoline anti-malarial drug was first discovered in 1936 by Hans Andersag at Bayer but was initially thought to be toxic and was ignored until its rediscovery by the US Army during World War II. CQ remains the drug of choice for malaria chemotherapy; it is highly effective and well-tolerated [123]. However, widespread use has led to the development of drug resistance by the malarial parasite *Plasmodium* species.

Various thoughts on CQ mechanisms of action are available. The lysosomotropic CQ accumulates in the lysosome and raises lysosomal pH, resulting in inhibition of autophagy in mammalian cells (and *Plasmodium*). CQ inhibits specific enzymes, such as the *Plasmodium* heme polymerase and proteinases. CQ is known to bind DNA and other molecules [124]. Furthermore, for CQ resistance in malaria, redox and glutathione system may be involved [125].

As for CQ's anticancer effects, it can act in synergy with ionizing radiation and chemotherapeutic agents [123]. CQ inhibits autophagy, and autophagy is important for cancer cells to generate energy. However, there are concerns regarding CQ as a "double-edged sword" because autophagy plays a protective role against acute kidney injury [126].

Chloroquine has been found to act on CSCs [54, 127]. Our previous review on CSC targeting included both metformin and CQ [18]; there is a paper titled "Repositioning chloroquine and metformin to eliminate cancer stem cell traits in pre-malignant lesions" [57]. Autophagy is an important characteristic as it may enable cancer cells to make an epithelial-to-mesenchymal transition (EMT) to acquire CSC traits. Moreover, CQ may affect tissue metabolic activity and modulate key functions of the immune system [127]. There are many clinical trials on CQ and cancer [127] and multiple investigations have been carried out on CQ and CSCs. As an example, CQ sensitized breast CSCs to paclitaxel *in vitro*, *via* the inhibition of autophagy, STAT3 and DNMT1 [128]. In ovarian CSCs, CQ and carboplatin showed synergistic effects in spheroids and in xenografts [129]. In $CD133^+$ lung CSCs, CQ inhibited autophagy and reduced spheroids *in vitro*. Furthermore, for lung CSC xenografts in NOD/SCID mice, the combination of CQ and cisplatin treatment dramatically suppressed tumor growth as compared to individual agents, indicating autophagy inhibition of CSCs can promote the efficacy of cisplatin [130]. These findings demonstrate that CQ targets CSCs and produces synergistic effects with conventional therapy. With respect to patents, WO2016196614 involves CQ and cancer [131]. There is also a 2019 South Korean patent, KR20190094765, related to the topic.

3.8. Auranofin

Whereas CQ, discussed above, is primarily an anti-malarial drug but also useful to treat Rheumatoid Arthritis (RA), Auranofin (ANF) is specific for RA. Treatment of RA patients with monovalent gold drugs possessing anti-inflammatory and other properties is known as chrysotherapy. Gold has a medicinal history that can be traced through the writings of every culture and far into pre-history by means of archaeological records [132]. ANF was developed by Smith Kline and French laboratories as a novel oral gold-containing drug for RA in 1976. It was approved by FDA for RA in 1985. Recently, auranofin has been investigated as a potential therapeutic agent for many human diseases, including neurodegenerative disorders such as Parkinson's

and Alzheimer's disease, HIV and acquired immunodeficiency syndrome, bacterial and parasitic infections, as well as some cancers. Repurposing ANF is reaching a "Golden New Age" when ANF itself is no longer be the drug of choice for RA [133, 134]. ANF is effective against parasitic protozoa such as *Entamoeba histolytica* and *Giardia lamblia* [135]. It is active against a variety of pathogenic bacteria [136]. ANF has been reported to inhibit the replication of SARS-CoV-2 of the COVID-19 pandemic [137].

ANF is a gold-containing triethylphosphine. Its IUPAC name is [(2R,3R,4S,5R,6S)-3,4,5-tris(acetyloxy)-6-{[(triethyl-lambda5-phosphanylidene)aurio]sulfanyl}oxan-2-yl] methyl acetate. Its mechanism of action as an anti-arthritic gold drug remains controversial. ANF is a strong inhibitor of Thioredoxin Reductase (TrxRs). Such inhibition leads to alterations in the intracellular redox state, and oxidative stress may induce apoptosis. Takefumi Onodera and colleagues discussed the association of TrxR overexpression and aggressive tumor progression and poor survival in patients with breast, ovarian, and lung cancers, and ANF is an ideal candidate for drug repurposing with respect to CSC targeting and cancer therapy [133].

The capacity of ANF to target CSCs has been reported. In ovarian CSCs, ANF inhibited spheroid formation *in vitro* and reduced tumor size *in vivo* [138]. The mechanism causing these effects is thought to be the inhibition of the PKC kinase signaling pathway [138]. In lung CSCs, ANF showed the same effect, but the mechanism has switched to inhibition of TrxR and hexokinase, yielding an increase in Reactive Oxygen Species (ROS) and a decrease in glycolysis. Furthermore, ANF worked together with adriamycin in mouse xenografts [139]. With respect to patents, WO2012142615 involves ANF and cancer [140].

3.9. NSAIDs

Similar to ANF, Non-Steroidal Anti-Inflammatory Drugs (NSAIDs) have a long history. Chewing the leaves of the willow tree to alleviate pain (including joint pain) was known to ancient civilizations of Sumerians, Egyptians, and Greeks. This is due to the glycoside salicyline. In 1897, Felix Hoffmann at Bayer synthesized Acetylsalicylic Acid (ASA), a more palatable form of salicylate which was named aspirin. Aspirin is currently the most widely used drug worldwide [141]. Many drugs having similar actions to aspirin were discovered, and the group was termed "aspirin-like drugs" (now known as NSAIDs). Among these are acetaminophen (N-acetyl-para-aminophenol or paracetamol) and celecoxib. Both ASA and acetaminophen are listed in the WHO essential medicines for treatments, including migraine pain [77]. Acetaminophen was synthesized by Harmon Northrop Morse in 1877. In 1955 it was marketed as Tylenol by McNeill. Available without a prescription, it is the most commonly used medication for pain and fever in the United States and Europe.

The NSAIDs have antiseptic, antipyretic, and anti-rheumatic activities. Mechanisms of action by NSAIDs involve the inhibition of prostaglandin synthesis. In 1971, John Vane and colleagues proposed the dose-dependent inhibition of prostaglandin biosynthesis as the mechanism of action of aspirin and all NSAIDs [141, 142]. NSAIDs inhibit the target enzyme Cyclooxygenase (COX). COX has two main forms, COX1 and COX2 (constitutive and inducible, respectively). It is believed the anti-inflammatory effects that need to be targeted are due to COX2. COX2 selective inhibitors, such as celecoxib, are sought after.

One major concern is NSAID adverse effects. There exists a danger of an acetaminophen overdose. Side effects include acute liver toxicity and risk of gastrointestinal bleeding [143]. Indeed, there were COX2 inhibitor recalls. Rofecoxib (brand name Vioxx), originally approved by FDA for osteoarthritis in 1999, was voluntarily withdrawn by Merck in 2004. Valdecoxib (brand name Bextra), originally approved for arthritis and menstrual cramps, was recalled by FDA in 2005 due to potential cardiovascular adverse effects. Celecoxib (Celebrex) by Pfizer, approved by FDA in 1998, is still available.

It is well known that low-dose aspirin is chemopreventive for colorectal cancer [144]. Hence, NSAIDs may be potentially useful for cancer therapy and CSC targeting. COX2 is released to the tumor niche by cancer cells, fibroblasts, and immune cells within the tumor. COX2 induces the CSC phenotype [145]. There are clinical trials on celecoxib and cancer, with findings demonstrating promising results of the role of celecoxib in cancer prevention and treatment [146].

Instances of NSAIDs targeting CSCs are known. For lung CSCs, aspirin inhibited the $ALDH^+$ cells and their exosome production; aspirin was synergistic with cisplatin in triggering apoptosis in target cells *in vitro* [147]. In breast CSCs, acetaminophen inhibited EMT-related microRNA expression [148], induced breast CSC differentiation *via* the Wnt pathway, and reduced tumor size in xenografts together with doxorubicin [149]. Celecoxib also targeted the Wnt pathway of breast CSCs and inhibited the synthesis of Prostaglandin E_2 (PGE2) [150]. In medulloblastoma brain CSCs expressing CD133, celecoxib inhibited spheroid formation *in vitro via* the STAT3 pathway, and reduced tumor size in xenografts together with irradiation [151]. These findings suggest the potential to use NSAIDs together with conventional chemotherapeutics for cancer therapy. With respect to patents, US20190307780 involves NSAID and cancer [152], as well as a Taiwan patent: TW201934143.

3.10. Tranilast

In our previous review on the combination of dietary phytochemicals and repurposed drugs to target CSCs, we briefly mentioned "anti-allergy drug tranilast, cholesterol-lowering statins (simvastatin and lovastatin), and anti-alcoholism drug disulfiram" [18]. In the following sections, we discuss these drugs in detail, starting with tranilast.

Tranilast is an anti-allergic drug developed by Kissei and approved in 1982 in Japan and South Korea for the management of bronchial asthma. Indications for keloid and hypertrophic scar were added in 1993. It has been used for the treatment of allergic disorders such as asthma, allergic rhini-

tis, and atopic dermatitis. Tranilast is currently used in China, Japan, and Korea. In 2016, in the "List of Bulk Drug Substances that can be used to Compound Drug Products," FDA ruled tranilast as a substance not proposed for inclusion on the 503A bulks list, although noting: "Of the four bulk drug substances evaluated and not proposed for inclusion on the 503A Bulks List, tranilast appears to be the most widely compounded" [153].

Tranilast's IUPAC name is 2-[(2E)-3-(3,4-dimethoxyphenyl)prop-2-enamido] benzoic acid. It is an analog of a metabolite of tryptophan. It was originally developed as an anti-allergy drug due to its ability to inhibit the release of inflammatory mediators, such as histamine, from mast cells and basophils. In addition, tranilast seems to benefit many other diseases, including fibrosis, proliferative disorders, cardiovascular problems, autoimmune disorders, ocular diseases, diabetes, renal disease, and cancer [154]. Mechanisms of action of tranilast have been found. It inhibits TGFβ, NF-κB and MAPK signaling pathways. Tranilast is an agonist of the Aryl Hydrocarbon Receptor (AHR), as well as an inhibitor of the transient receptor potential channel vanilloid 2 (TRPV2), a calcium channel [154].

Tranilast's capacity to target CSCs has been linked to its effect on AHR and TRPV2. Gerald Prud'homme and colleagues found that tranilast inhibited $ALDH^+$ breast CSCs by inhibiting spheroid formation *in vitro* and reduced metastasis in xenografts. The role of AHR was shown using AHR specific and scrambled siRNA [155]. There was also inhibition of breast CSC NF-κB [156]. Similar inhibition was reported for esophageal CSCs. These CSCs expressed TRPV2 and were inhibited by tranilast [157]. However, a different picture emerged for liver CSCs. TRPV2 was still important but showed the opposite effect. Its inhibition by tranilast led to an increase in spheroids and tumor formation in xenografts, whereas its activation by probenecid led to decreased spheroids and tumors in xenografts [158]. Thus, the potential use of tranilast to target CSCs may be cancer type-dependent.

3.11. Statins

Statins are cholesterol-lowering drugs. In 1972 Akira Endo at Sankyo isolated the first compound that would inhibit cholesterol biosynthesis: mevastatin (alias compactin) from *Penicillium citrinum*, a mold infecting the Japanese Mikan orange. Collaboration between Sankyo and Merck led to the isolation of a second statin, called lovastatin, from *Aspergillus terreus* in 1979 by Alfred Alberts at Merck. FDA approved lovastatin (brand name Mecavor) in 1987 to treat hypercholesterolemia [159, 160]. Other statins followed: simvastatin (Zocor) in 1988, pravastatin (Pravachol) in 1991, fluvastatin (Lescol) in 1994, atorvastatin (Lipitor) in 1997, cerivastatin (Baycol) in 1997, rosuvastatin (Crestor) in 2003, and pitavastatin (Livalo) in 2009. Among all statins, only simvastatin is listed in the list of WHO essential medicines for high-risk patients [77]. Bayer voluntarily withdrew Baycol from the market in 2001 due to the fatal side effect, rhabdomyolysis. On a related note, FDA approved Nexletol in 2020 (to Esperion) as a combination pill of bempedoic acid (new medication) plus ezetimibe (a non-statin previously approved by FDA in 2002).

In 2010, Akira Endo presented this comment: "Sales for this one class of drugs in 2005 were $25 billion. Today, an estimated 30 million people worldwide are taking statins. It is said that the lives of millions of people have been extended through statin therapy" [160]. Indeed, millions of patients around the world are receiving statin therapy. Once statin therapy is initiated, in general, it is continued for life [161]. Statin adverse effects include myopathy and hepatotoxicity [161]. Furthermore, there are concerns that the benefits have been exaggerated and the risks have been underplayed. Despite these negative views, revenue for statins is expected to rise, with total sales on track to reach an estimated US $1 trillion by 2020 [162].

For statins, the main mechanism of action is acting as a competitive inhibitor of the enzyme 3-Hydroxy-3-Methylglutaryl-Coenzyme A (HMG-CoA) reductase [163]. Statin is experiencing drug repurposing. Besides its inhibition of cholesterol biosynthesis, statin also inhibits the synthesis of essential isoprenoid intermediates such as farnesyl pyrophosphate, geranylgeranyl pyrophosphate, isopentanyl adenosine, dolichols and polyisoprenoid side chains of ubiquinone, heme A, and nuclear lamins [164, 165]. As these molecules are essential in many signaling pathways, statins have anti-inflammatory, anti-proliferative, anti-oxidative and immunomodulatory effects. For anti-proliferative activity, statins may have a role in cancer therapy and CSC targeting. Anti-cancer capacity of statins may be due to induction of cell cycle arrest and apoptosis, the reversal of multidrug resistance, and inhibition of cancer metastasis [166]. Statins may also target cancer-related inflammation [167]. Statins' inhibition of the cholesterol synthesis pathway (alias mevalonate pathway) may inhibit CSCs by regulating the Hippo pathway [168, 169].

Examples of lipophilic statins on CSCs have been shown. For brain CSCs, simvastatin inhibited spheroid formation *in vitro via* Myc, Ras and the mevalonate pathway [170]. Simvastatin also inhibited ovarian CSCs in the spheroid formation and metastasis in xenografts *via* the Hippo pathway [171]. For nasopharyngeal carcinoma CSCs, lovastatin inhibited spheroid formation and the expression of stemness genes such as CD44, Myc and Snail (for EMT) [172]. With respect to patents, US20130131088 involves statins and cancer [173]. For potential future applications, the focus should be on the combined use of statins and other chemotherapeutics for targeting both bulk cancer cells and CSCs [166].

3.12. Disulfiram

Anti-alcoholism drug Disulfiram (DSF) has been repurposed to target CSCs. Alcoholism is a significant contributor to annual deaths. In the US, 9.8% of all annual deaths (about 88,000 individuals) are attributable to alcohol use (data from 2006 to 2010), with the majority due to binge drinking, a habit that can lead to Alcohol Use Disorder (AUD). World-

wide, the number is 5.9%, but more for males than females (7.6% versus 4.0%) [174].

The effect of DSF on alcohol was discovered by accident. The intended focus of Erik Jacobsen and Jens Hald's research, conducted at Medicinalco in Copenhagen, Denmark, was DSF's anti-parasitic capacity against intestinal worms and scabies. In 1948, the pair published their findings that DSF and alcohol would yield mild sickness (nausea), as first noted by Jacobson (by self-administration with both agents). A new form of DSF, with increased purity due to the removal of copper contaminants, reached the Danish Market in 1949 under the brand name Antabuse. FDA approved DSF in 1951 [175]. FDA later approved other drugs to treat AUD: naltrexone (opiate antagonist) in 1994, and acamprosate (calcium acetylhomotaurinate) in 2004 [176]. Today, DSF is used as a second-line treatment, as current treatment preferences are naltrexone and off-label use of baclofen (γ-aminobutyric acid-B receptor agonist with FDA approval to reduce spasticity associated with neurologic disorders) [177]. Hence, there is a prior history of drug repurposing of DSF.

In addition to its role in alcohol use disorder, DSF acts on ecto- and endo-parasites, as originally studied by Jacobsen and Hald. As an antimicrobial, there is a potential application in the treatment of resistant staph infections [178]. Similarly, DSF works together with antifungal drugs to target species such as *Candida* [179]. DSF may have a role in HIV treatment: targeting the latent virus [180, 181]. For the COVID-19 pandemic, it has been proposed that DSF may inactivate the main protease of SARS-CoV-2 [182].

The most significant drug repurposing of DSF is for cancer and CSCs. DSF, alias tetraethylthiuram disulfide, is a carbamate derivative. Its IUPAC name is diethylcarbamothioylsulfanyl *N*,*N*-diethylcarbamodithioate. It is used as an alcohol deterrent because of its property as an Aldehyde Dehydrogenase (ALDH) inhibitor, altering the intermediary metabolism of alcohol. Normally, ingested alcohol is broken down in the liver by alcohol dehydrogenase to acetaldehyde, and ALDH further converts acetaldehyde to a harmless acetic acid derivative (acetyl CoA). As ALDH is expressed in many CSCs, DSF targets these $ALDH^+$ CSCs. DSF also acts on other CSC pathways, such as NF-κB and MAPK. For cancer, DSF sensitizes resistant tumors to chemotherapeutics, suppresses DNA methylation (epigenetic effects), inhibits metastasis, and induces ROS [179, 183]. DSF binds metal ions; DSF/copper suppresses proteasome activity [184].

Many studies have shown DSF targeting CSCs; some examples are given here. For breast CSCs, DSF inhibited spheroid culture and the NF-κB and MAPK pathways in triple-negative cancer cells [185]. In a screen of 3,185 compounds, DSF was found to inhibit breast CSCs and act synergistically with doxorubicin *in vitro* [186]. DSF effect in breast CSCs was extended to xenografts and its inhibition of STAT3 was noted [187]. Similar DSF effect on ovarian CSCs *in vitro* was found [188]. For pancreatic CSCs in xenografts, DSF acted together with irradiation and fluorouracil [189]. For brain CSCs, DSF would kill GBM (glioblastoma) CSCs [190]. In addition to solid tumors, DSF acted on multiple myeloma CSCs in xenografts *via* inhibition of the Hedgehog pathway [191].

There are multiple patents [192] and clinical trials related to DSF and cancer [184]. Improvements in the delivery system are being made, especially DSF/Cu combination therapy that results in copper diethyldithiocarbamate [Cu(DDC)2] complex showed to be the major active anticancer ingredient [193]. The findings described above confirm DSF as an ideal candidate for drug repurposing with respect to CSC targeting and cancer therapy [193].

3.13. Thioridazine

Thioridazine (THZ) is a phenothiazine antipsychotic (alias neuroleptic) used in the management of psychoses, including schizophrenia. THZ was a first-generation antipsychotic drug manufactured by Sandoz (brand name Mellaril) and approved by FDA in 1962. In 1987, in response to concerns with THZ generics raised by two Rutgers pharmacists (Joseph Barone and John Colaizzi), FDA rejected their assertion that several of the approved generic THZ products were not bioequivalent. FDA stated that phenothiazines were among the most widely used drugs to treat symptoms commonly associated with acute and chronic psychoses, and the commonly prescribed phenothiazine was THZ, available both as a generic and as Mellaril [194]. However, central nervous system and cardiac side effects (severe cardiac arrhythmia) resulted in worldwide voluntarily withdrawn of branded versions by Norvatis, the parent company of Sandoz, in 2005. The generic form is still available in the US.

As a piperidine phenothiazine derivative, THZ's IUPAC name is 10-[2-(1-methylpiperidin-2-yl)ethyl]-2-methylsulfanylphenothiazine. THZ acts as a Dopamine Receptor (DR) antagonist; it blocks postsynaptic mesolimbic dopaminergic D1 and D2 receptors in the brain. Besides its antipsychotic function, THZ reverses drug resistance in microbes and cancer cells. Interestingly, THZ can kill multidrug-resistant *Mycobacterium tuberculosis* [195]. For the protozoan agent of Chagas' disease *Trypanosoma cruzi* in a mouse model, THZ showed beneficial effects [196]. As a group, the phenothiazines have antiviral, antiprotozoal, antifungal, and anti-prion activities. Phenothiazines have been shown to kill cancer cells and sensitize them to chemotherapy [197].

Although there is no association between THZ treatment for schizophrenia and patient cancer risk, THZ has been used in drug repurposing with respect to CSC targeting and cancer therapy [198]. The mechanisms of action by THZ towards cancer include inhibition of multidrug-resistant pump, anti-angiogenesis, apoptosis induction, and CSC targeting (as DRs are expressed in these cells) [199]. With respect to patents, South Korea KR101538264 titled "Pharmaceutical composition for preventing or treating cancer comprising thioridazine and TRAIL" was published in 2015.

Many studies have shown THZ targeting CSCs. In a combined normal and CSC screen of 590 compounds, THZ was shown to target only leukemic CSCs, whereas salinomycin targeted both CSCs and normal stem cells [200].

THZ targeted ovarian CSCs in xenografts in nude mice, *via* inhibition of the mTOR pathway [201]. We have found that THZ acted synergistically with curcumin to inhibit the spheroid formation of ovarian cancer cells *in vitro* when we proposed repurposed drug-dietary phytochemical combinations to target CSCs [18]. In glioblastoma CSCs treated with THZ (selected from 79 drugs), SP was reduced and autophagy was induced, together with a reduction in tumor size in NOD/SCID mice xenografts [202]. In lung CSCs, THZ-treated spheroids showed apoptosis *in vitro*, as well as a reduction in tumor volume of nude mice xenografts [203]. Interesting observations were reported for breast CSCs: THZ targeted the self-renewal of basal-like breast cancer cells; all breast cancer cell lines tested expressed DRD2 mRNA and protein; and, for the first time, dopamine was directly detected in human breast tumors [204]. The DRD2-targeting antipsychotic THZ induces apoptosis in tumor cells from brain, lung, colon, and breast cancer [204]. Just like disulfiram, the activity of THZ can be enhanced by delivery system improvements. An example is the co-delivery of THZ and doxorubicin in mixed polymeric micelles targeting both CSCs and cancer cells in breast cancer cell lines *in vitro* [205]. Summarizing the above findings, THZ is a promising candidate repurposed drug for CSC-targeted therapy.

3.14. Antipsychotics

Thioridazine (THZ) that targets CSCs is an antipsychotic. There are many others. Antipsychotic drugs are involved in multiple intracellular functions, including metabolism, cell stress, cell cycle regulation, survival, and apoptosis. The drugs can modulate cellular signaling pathways such as PI3K/AKT/GSK-3β, STAT3 and wingless (Wnt)-related intracellular signaling. Some may stimulate the cellular immune system and natural killer cells that target cancer cells. The lipophilicity of antipsychotics can play a role in the inhibition of P-glycoprotein pumps, resulting in intracellular accumulation of chemotherapy drugs [206]. In this discussion on antipsychotic drugs targeting CSCs, it is noted that drugs such as phenothiazines may result in a tolerance problem in patients and efforts at improvements are urgently needed [207]. One example is to generate better versions to target CSCs [208].

Besides THZ, another phenothiazine antipsychotic that targets CSCs is Trifluoperazine (TFP). It shows antipsychotic and antiemetic activities. Mechanisms of action include TFP's anti-adrenergic and anti-dopaminergic effects. By blocking the dopamine D2 receptor, there can be a decrease in symptoms of schizophrenia, such as hallucination and delusion. The brand name version, Stelazine, has been discontinued by GlaxoSmithKline in 2004, but generics are currently available. With respect to CSC targeting, TFP inhibited the $ALDH^+$ lung CSCs' spheroid culture *in vitro*, and decreased tumor size by itself, or together with the drug gefitinib in murine xenografts *in vivo* [209].

Another group of antipsychotics belongs to the Diphenylbutylpiperidine (DPBP) class. Both fluspirilene and pimozide belong to this group of CSC targeting drugs. Fluspirilene, discovered at Janssen in 1963, is a long-acting injectable antipsychotic agent used for chronic schizophrenia. As for its mechanism of action, it also inhibits the dopamine D2 receptor and sedates the positive symptoms of schizophrenia. With respect to CSC targeting, fluspirilene was selected from a 1,301 compound screen for glioma stem cells. Fluspirilene inhibited the STAT3 pathway and extended mouse survival in the xenograft animal model. Repurposing fluspirilene has potential clinical application to treat GBM [210].

Besides fluspirilene, another DPBP that targets CSCs is pimozide. Approved by FDA in 2011 under the brand name Orap (by Teva), pimozide has been used to suppress vocal and motor tics in patients with Tourette syndrome. It also acts on the dopamine D2 receptor. With regard to CSC targeting, in cell culture, pimozide inhibited SP and $CD133^+$ liver CSCs *via* inhibition of the STAT3 pathway [211]. Researchers have determined that pimozide targets multiple features and pathways of CSCs, including Wnt, EMT, proteasome and others [212].

Sulpiride, a dopamine D2 receptor antagonist, also targets CSCs. Approved by FDA in 1993, sulpiride (brand name Dogmatil) belongs to the benzamide class and has been used therapeutically for psychosis associated with schizophrenia and major depressive disorder, as well as a digestive aid. As for its CSC targeting ability, sulpiride inhibited breast CSC spheroid formation *in vitro*, and enhanced the drug dexamethasone's effect on tumor growth (reduction of tumor size) and metastasis (inhibition of lung metastasis) in xenografts in mice [213].

Clomipramine is a dibenzazepine-derivative Tricyclic Antidepressant (TCA). TCAs are structurally similar to phenothiazines. First discovered at Ciba-Geigy in 1964, clomipramine (brand name Anafranil) is the only TCA that has been shown to be effective in the treatment of Obsessive-Compulsive Disorder (OCD). It was approved by FDA for the treatment of OCD in 1989; it is also used for the treatment of panic disorder, major depressive disorder, and chronic pain. Clomipramine is on the essential medicines list of the World Health Organization [77]. For mechanisms of action, clomipramine is a strong, but not completely selective Serotonin Reuptake Inhibitor (SRI), and its metabolite desmethyclomipramine also acts as an inhibitor of noradrenaline reuptake. With respect to CSC targeting, desmethyclomipramine showed an effect on lung CSCs in aiding their killing by conventional therapeutics *via* the Itch pathway. Clomipramine is an inhibitor of Itch, an E3 ubiquitin ligase; it has potential clinical application to treat lung cancer [214].

We end this section on CSC targeting by antipsychotic drugs with Valproic Acid (VPA). VPA is a branched short-chain fatty acid derived from valeric acid. As an anticonvulsant, it is used to treat epilepsy and bipolar disorder and prevent migraine headaches. VPA (brand name Depakene), approved by FDA in 1978, is on the list of essential medicines of the World Health Organization [77]. It has multiple proposed mechanisms of action: affecting GABA levels, blocking voltage-gated sodium channels, and inhibiting histone

deacetylases. VPA is a molecule that can interfere with multiple regulatory pathways, including PI3K, OXPHOS, AKT, GSK, and tricarboxylic acid cycle; it is emerging as a potential anticancer drug [215]. With respect to CSC targeting, VPA inhibited breast CSC spheroid formation, induced apoptosis, and increased histone acetylation [216]. Summarizing the above findings, the discussed antipsychotics can be promising candidate repurposed drugs for CSC-targeted therapy.

3.15. Antibiotics

In 2005, Michael Lisanti and colleagues proposed treating cancer as an infectious disease by identifying a conserved phenotypic weak point of CSCs, namely a strict dependence on mitochondrial biogenesis for the clonal expansion and survival of CSCs [217]. Using 12 different cancer cell lines, they demonstrated antibiotics can eradicate CSCs; they also noted positive effects in clinical trials using doxycycline and azithromycin. These investigators later proposed "the term MITO-ONC-RX," to describe this anti-mitochondrial platform for targeting CSCs [218]. As an example, they reported doxycycline, azithromycin and vitamin C as a potent combination targeting mitochondria and leading to eradicating of breast CSCs [219].

Antibiotics doxycycline and azithromycin are FDA-approved drugs for infectious diseases (including bacterial pneumonia, acne, chlamydia infections). Doxycycline is a second-generation tetracycline and a broad-spectrum antibiotic for a wide range of bacterial infections (based on results of antibiotic susceptibility testing). Approved by FDA in 1967, doxycycline is on the essential medicines list of the World Health Organization [77]. Approved by FDA in 1991 (branded as Zithromax, by Pfizer) and on the World Health Organization list, azithromycin is a broad-spectrum macrolide antibiotic possessing a long half-life and a high degree of tissue penetration. It has been used for middle ear infections, strep throat, pneumonia, and gonorrhea. For the COVID-19 pandemic, a small clinical study in France, with only 20 cases, showed positive clinical effect using a combination of azithromycin and Chloroquine (CQ) [220]. Another study with 2,541 patients in Detroit, Michigan, concluded: "treatment with hydroxychloroquine alone and in combination with azithromycin was associated with a reduction in COVID-19 associated mortality" [221]. However, a third study with 1,438 hospitalized patients in metropolitan New York with COVID-19, "treatment with hydroxychloroquine, azithromycin, or both, compared with neither treatment, was not significantly associated with differences in in-hospital mortality" [222].

Following Lisanti's lead, a group in Spain targeted CSCs with anti-protozoal and anti-bacterial antibiotics [223]. However, their selected compounds, including puromycin, cycloheximide and emetine (used to treat amoebiasis), may be too toxic for clinical use, but knowledge gained could be applicable in developing second-generation inhibitors of ribosomal translation to eradicate CSCs.

We end this section on CSC targeting by antibiotics with mithramycin A (Mit-A). Approved by FDA in 1970, Mit-A (alias plicamycin, brand name Mithracin), is an antineoplastic antibiotic produced by *Streptomyces plicatus*. It is an RNA synthesis inhibitor. Mit-A has been used in the treatment of testicular cancer and Paget's disease of bone. It is currently unavailable in the US, as the manufacturer discontinued the drug in 2000. Screening of an NCI library of FDA-approved drugs led to the identification of Mit-A as "a potential total cancer therapy drug" because it targeted both the bulk cancer cells and CSCs of colorectal cancer [224]. Once this finding has been confirmed by other investigators, Mit-A may indeed be a very useful antineoplastic antibiotic for destroying both CSCs and bulk cancer cells.

There are multiple patents related to the topic. For example, WO2020131696 involves mitochondrial targeting and CSC killing [225] and US10105357 involves antibiotic drugs and cancer inhibition [226]; there is a Chinese patent: CN111148750.

3.16. Additional Repurposed Drugs Targeting CSCs

We shall briefly mention additional drugs that have shown CSC targeting capability. As CSCs have self-renewal and differentiation properties, we start with differentiation agents. Arsenic trioxide (brand name Trisenox) is a drug for acute promyelocytic leukemia and targets thioredoxin reductase. With respect to CSC targeting, arsenic trioxide induced the differentiation of $CD133^+$ liver CSCs, leading to prolonged survival of treated mice with xenografts *via* down-regulation of GLI1 [227]. Another differentiation agent is all-trans retinoic acid (ATRA, brand name Tretinoin), a derivative of vitamin A. ATRA is a drug for acne and acute promyelocytic leukemia; it is on the essential medicines list of the World Health Organization [77]. ATRA binds retinoic acid receptors. With respect to CSC targeting, ATRA inhibited spheroids *in vitro* and tumor progression of $CD44^+$ and $ALDH^+$ gastric CSC xenografts by down-regulating their stemness genes and inducing differentiation [228].

Antifungal agents can be CSC targeting. The antifungal azoles function by inhibiting cytochrome P-450-dependent enzymes and preventing the synthesis of ergosterol, the fungal equivalent of cholesterol, thereby increasing membrane fluidity and preventing the growth of fungal species. Itraconazole (brand name Sporanox) is a triazole that has been used to treat aspergillosis, histoplasmosis, blastomycosis, cryptococcal meningitis and other fungal infections. With regard to CSCs, itraconazole inhibited spheroid formation and stemness gene expression (CD133, ABCG2) by suppressing the Wnt pathway [229]. Another triazole, posaconazole (brand name Noxafil), has been used to treat invasive infections by *Candida* species and *Aspergillus* species in severely immunocompromised patients. Ketoconazole is an imidazole that acts against a variety of fungal infections. It has been used for fungal skin infections (dandruff, tinea, cutaneous candidiasis). Ketoconazole internally has been replaced by triazoles due to gastrointestinal side effects and dose-related hepatitis. With respect to CSCs, ketoconazole and posaconazole target glioblastoma (GBM) CSCs by inhibiting hexokinase II, an enzyme overexpressed in GBM, to decrease tumor metabolism [230].

An iron chelator is also able to target CSCs. Deferiprone (DFP, brand name Ferriprox) is used to treat iron overload in thalassemia major. DFP, originally approved in 1994 for treating thalassemia major in Europe and Asia, was approved by FDA in 2011. DFP is also used to treat acute iron or aluminum toxicity in certain patients. It is a natural product isolated from *Streptomyces pilosus*, and forms iron complexes. DFP binds trivalent (ferric) iron to form ferrioxamine, a stable complex, which is eliminated *via* the kidneys. DFP has been shown to target CSCs through inhibition of breast CSC spheroid formation *in vitro* by increasing ROS and mitochondrial superoxide production. DFP is a good candidate for drug repurposing with respect to CSC targeting and cancer therapy [231].

4. CONSIDERATIONS ON IMPLEMENTATION OF REPURPOSED DRUGS TARGETING CANCER STEM CELLS

Because CSCs are resistant to conventional chemotherapeutics and radiotherapies, alternative approaches are desired. Treatments designed to eradicate both the bulk tumor cells and CSCs are the most effective way to approach patient care. New strategies could seek to either use a repurposed medication alone or increased efficacy by combining conventional therapy with the repurposed medication. Attempts to identifying CSC vulnerabilities have led to investigations seeking unique mechanisms of action or repurposing drugs effective against specific cancer types.

The mechanism behind CSC drug resistance is an obvious target. It is a CSC's property of Multiple Drug Resistance (MDR) that contributes greatly to the likelihood of cancer recurrence with increased aggression [43]. Drug categories shown to impact MDR of CSCs include ABC transporter inhibitors and non-substrates, ALDH inhibitors, and HDAC inhibitors. Discovering ways to specifically target only CSCs is an issue that persists due to the characteristics CSCs share with Normal Stem Cells (NSCs) [43]. This concern is a complex task worth pondering.

CSCs maintain unique metabolism but retain some degree of variation. Their metabolic profiles differ from those of progeny cells having undergone differentiation. Furthermore, the metabolic phenotype of CSCs may fluctuate [44]. Targeting of CSC metabolism, mitochondria and redox state has been proposed. Consideration of the tumor niche with the presence of multiple cell types could be key to developing better treatments focusing on cancer cell metabolic characteristics [44]. Extrinsic and intrinsic stimuli produced by the tumor niche cause reprogramming from a glycolytic to an oxidative metabolism [232]. The tumor niche/microenvironment may prove to be a means to target CSCs while sparing NSCs.

Another approach is to focus on a specific type of cancer and to search for repurposed drugs targeting CSCs of that cancer type. For Pancreatic Ductal Adenocarcinoma (PDAC), the prognosis is dismal; there is an urgent need to obtain repurposed drugs targeting pancreatic CSCs, and this approach may lead to an accelerated rate of novel therapeutic discoveries [45]. Clinical trials are already underway testing repurposed drugs to combat pancreatic cancer.

The study of brain cancer CSCs and potential repurposed drug options has already begun. Pediatric brain tumors have high mortality rates due to drug resistance and the likelihood of recurrence. Brain cancer medications, like other Central Nervous System (CNS) drugs, have a rather difficult set of obstacles that must be overcome. In the case of pediatric brain cancer, a repurposed drug candidate must be able to cross the Blood Brain Barrier (BBB), gain FDA approval without serious adverse effects that outweigh the benefits conveyed by the medication, pricing should lean on the side of affordability, and the drug should prove to be effective against CSCs [47]. On the other side of the age spectrum is Glioblastoma (GBM), an aggressive form of brain tumor in adults. GBM CSCs from 15 patients were investigated *in vitro* for drug susceptibility. Researchers discovered that CUSP9, named after a mixture of 9 FDA-approved non-oncological drugs comprised of aprepitant, auranofin, captopril, celecoxib, disulfiram, itraconazole, minocycline, quetiapine, and sertraline, disrupts GBM survival mechanisms when used in combination with Temozolomide (TMZ) [46]. The availability of CUSP9 has led to patient use as a combination therapy [46].

The work conducted with CUSP9 and TMZ highlights the importance of repurposed drugs as new treatment options. There are numerous other chemicals that target CSCs, including drugs and dietary phytochemicals [18, 32, 33, 35, 41, 233, 234]. Many CSC targeting agents are undergoing clinical trials [235, 236], and multiple patents have been issued for CSC inhibitors [237]. Novel approaches in clinical trials and patents, such as epigenetic targeting, immunotherapy, and new drugs for signaling pathways involved in CSC maintenance, hold promise for improving patient outcomes but are beyond the scope of this review [42].

By definition, the repurposing of a drug means that it is being applied to a new indication outside of its original intended use. As noted by various investigators, there are concerns in need of being addressed when it comes to the implementation of repurposed drugs against CSCs. If a drug applied to CSC therapy is repurposed from another indication, then off-target effects are a serious issue that needs to be contemplated [37]. The nature of CSCs, particularly their location deep in tumors and under the influence of the tumor niche, may require more concentrated dosing to produce a response [37]. Hypoxic conditions of the inner tumor work antagonistically to drug delivery *via* the circulatory system [234]. As previously discussed, disrupting the niche may be key to ensuring CSCs, not NSCs, are being eradicated through therapy.

One crucial point to consider is evidence for the clinical use of the repurposed drugs that target CSCs. Here we quote the opinion of Fabrizio Marcucci and colleagues [225]: "The first, most important and most difficult point to answer is how to evidence clinical benefit that may derive from anti-CSC compounds. Currently used antitumor drugs target mainly proliferating tumor cells while sparing CSCs and even in-

ducing the generation of new CSCs. On the other hand, anti-CSC compounds are inactive against the bulk of proliferating tumor cells because they target markers or pathways that are overexpressed or selectively expressed on CSCs compared to bulk tumor cells. Consequently, the vast majority of ongoing clinical trials with anti-CSC compounds are performed in combination with other antitumor drugs belonging to different classes of compounds. Therefore, the easiest way to answer the question as to how evidence clinical benefit is to say that anti-CSC compounds should improve the efficacy of anti-cancer therapies that are given in combination, *i.e.*, higher percentages of patients with clinical responses or stable disease for longer periods of time than patients treated with standard-of-care therapies."

Moreover, as with dietary phytochemicals, many CSC targeting repurposed drugs are viewed as "dirty" because of their ability to bind multiple cellular molecules. However, in this case, the characteristic should be regarded as beneficial because a cell's ability to maintain resistance decreases when the probability of multi-site inactivation increases. We have proposed the use of dietary phytochemical-repurposed drugs in combination to target CSCs [18]. It is also advisable to use repurposed drug-conventional anticancer drug combinations to target both CSCs and bulk cancer cells. As cancer is a worldwide affliction and new oncology drugs are expensive, repurposed CSC targeting drugs would be an economical solution. Some repurposed drugs mentioned in this review are listed by clinicians and scientists of "The Halifax Project" under the goal of advancing research in low-toxicity therapeutics that cover a broad spectrum of uses by inhibiting key mechanisms and pathways related to cancer [238].

CONCLUSION

Drug repurposing has many alternative names: drug repositioning, drug reprofiling, drug redirecting, drug rediscovery, and drug rechanneling. This is the process of finding new indications for existing drugs. It may be thought of as an emerging topic, but it is not a new concept. Several successfully rediscovered drugs are generally used in daily practice. As an example, sildenafil was originally intended for the treatment of angina pectoris. However, it was repurposed under the brand name Viagra as a therapy for erectile dysfunction due to the realization of persistent erections as an unexpected adverse event. Drug repurposing follows the principle of poly-pharmacology; it is the idea that medications can have multiple mechanisms of action if it influences numerous targets [239].

Cancer therapies have the lowest clinical trial success rate amongst diseases. Drug repositioning allows for a shorter time, cheaper cost, and higher success rate for product candidates entering clinical trials. This is in part due to the drug safety profile, including maximum tolerated dose, drug-drug interactions, and adverse events, already being known. Knowledge gathered through drug discovery, preclinical and clinical research translates into years of development and millions of dollars in cost. Monetary considerations are also important when it comes to prolonging exclusivity. Just like patents for CSC inhibitors, there are patents issued for repurposed drugs pertaining to cancer [237, 239]. There has even been an increase in the number of patent applications filed by universities, companies, and research institutions involving known compounds being used to potentially treat cancer [240]. We share in the belief that repurposed, FDA-approved drugs lacking patent exclusivity are best used to complement current and future drug discovery by pairing old with new in order to spur innovative therapies [241]. The use of these repositioned drugs in combination, or with conventional therapies, will allow for an enhanced inventory of effective medications for first-line and recurrent patient care.

CURRENT & FUTURE DEVELOPMENTS

Drug repurposing identifies new indications for existing drugs and creates new therapeutic options while bypassing much of the costs and time involved in bringing a new drug to the market. This review has discussed CSC targeting capabilities in off-patent, generic medications. The rediscovery of a generic drug is a challenging pursuit due to the lack of a formal regulatory approach specific to this category and a nearly non-existent economic interest from pharmaceutical companies. These aspects should be recognized by investigators. As an example, we discuss the possibility of developing a safer form of the anticancer medication doxorubicin (Doxo) with less severe side effects on cardiac tissue [242]. Doxo causes DNA damage *via* Double-Strand Breaks (DSBs) by intercalating DNA and inhibiting topoisomerase II (Topo II), referred to as activity 1. Doxo also causes chromatin damage through histone eviction at selected sites in the genome, referred to as activity 2. The drug has adverse effects, especially dose-dependent irreversible cardiotoxicity. Jacques Neefjes and colleagues found that anthracycline-induced cardiotoxicity requires the combination of both activities. Compounds with only one activity fail to induce cardiotoxicity, as seen in Aclarubicin (Acla) and N,N-dimethyldoxorubicin (diMe-Doxo). Thus, Doxo can be detoxified by chemically separating the 2 activities. Through public and private fundraising, these researchers want to produce Acla and diMe-Doxo under rigorous safety conditions to satisfy the clinical trial need of patients. Earlier findings indicated diMe-Doxo with a greater effect on treating solid tumors and Acla with more promise as a blood cancer medication. Although progress is being made outside of the biopharmaceutical industry, an extended effort by pharmaceutical companies and government agencies to combine expertise and financial resources would make the process of drug rediscovery advance much faster.

Investigators interested in further developing CSC-targeting repurposed drugs should take to heart these concerns when considering generics. So, what will be the future of targeting CSCs to improve current therapies? In 2017, Prashant Kharkar made this comment: "The field of anti-CSC therapeutics has a long way to go. We keep our fingers crossed till few of these molecules in advanced phases of clinical trials are available for use in patients" [237]. On the other

hand, in 2019, Amar Desai and colleagues reached a different conclusion: "The volume of preclinical and clinical evidence pointing to the importance of CSCs in cancer progression, relapse, and metastasis suggests that targeted therapies may be the best approach toward a comprehensive treatment regimen; the field is certainly progressing in the right direction and that clinically approved CSC-targeted therapies for the treatment of a number of cancer types are within sight" [42]. We decided to align with the optimists; we look forward to CSC targeting, with repurposed drugs, as a means to improve cancer therapies in a timelier manner. In our assessment, the future is bright, and we predict many more discoveries involving approved drugs with capacities to destroy CSCs.

LIST OF ABBREVIATIONS

ABCG2	=	ATP-Binding Cassette Transporter G2
Acla	=	Aclarubicin
AHR	=	Aryl Hydrocarbon Receptor
AIDS	=	Acquired Immunodeficiency Syndrome
ALDH	=	Aldehyde Dehydrogenase
AML	=	Acute Myeloid Leukemia
AMP	=	Adenosine Monophosphate
AMPK	=	AMP-activated Protein Kinase
ANF	=	Auranofin
ASA	=	Acetylsalicylic Acid
ATP	=	Adenosine Triphosphate
ATRA	=	All-Trans Retinoic Acid
AUD	=	Alcohol Use Disorder
AVM	=	Avermectin
BAAA	=	Biodipy Aminoacetaldehyde
BBB	=	Blood Brain Barrier
BTSC	=	Brain Tumor Stem Cell
BZ	=	Benzimidazole
CD	=	Cluster of Differentiation
CLIC1	=	Inhibiting Chloride Intracellular Channel 1
CML	=	Chronic Myeloid Leukemia
CoA	=	Coenzyme A
COVID-19	=	Coronavirus Disease 2019
COX	=	Cyclooxygenase
CQ	=	Chloroquine
CRC	=	Colorectal Cancer
CSC	=	Cancer Stem Cell
DDC	=	Diethyldithiocarbamate
DFP	=	Deferiprone
diMe-Doxo	=	N,N-Dimethyldoxorubicin
DM	=	Diabetes Mellitus
DMARD	=	Disease-Modifying Agent used in Rheumatoid Disorders
DNMT1	=	DNA (cytosine-5)-Methytransferase 1
DOXO	=	Doxorubicin
DPBP	=	Diphenylbutylpiperidine
DR	=	Dopamine Receptor
DSB	=	Double-Strand Break
DSF	=	Disulfiram
EGF	=	Epidermal Growth Factor
EMT	=	Epithelial-Mesenchymal Transition
EUA	=	Emergency Use Authorization
FDA	=	Food and Drug Administration
FGF	=	Fibroblast Growth Factor
GABA	=	Gamma Aminobutyric Acid
GBM	=	Glioblastoma Multiforme
GDF	=	Growth/Differentiation Factor
GFP	=	Green Fluorescent Protein
GLI1	=	Glioma-Associated Oncogene Homolog Zinc Finger Protein 1
GSK	=	Glycogen Synthase Kinase
HCC	=	Hepatocellular Carcinoma
HIV	=	Human Immunodeficiency Virus
HMG-CoA	=	3-Hydroxy-3-Methylglutaryl-Coenzyme A
$Il2rg^{-/-}$	=	Interleukin-2 receptor gamma chain null
IL-6	=	Interleukin-6
IUPAC	=	International Union of Pure and Applied Chemistry
IVM	=	Ivermectin
JAK-STAT	=	Janus Kinase/Signal Transducer and Activator of Transcription
LOPAC	=	Library Of Pharmacologically Active Compounds
MAPK	=	Mitogen-Activated Protein Kinase
MBZ	=	Mebendazole
MDR	=	Minimal Residual Disease

MDR = Multiple Drug Resistance

Mit-A = Mithramycin A

mTOR = mammalian Target of Rapamycin

NADH = Nicotinamide Adenine Dinucleotide

NCI = National Cancer Institute

NF-κB = Nuclear Factor Kappa B

NOD/SCID = Non-Obese Diabetic/Severe Combined Immunodeficiency

NSAID = Non-Steroidal Anti-Inflammatory Drug

NSC = Normal Stem Cells

OCD = Obsessive-Compulsive Disorder

OXPHOS = Oxidative Phosphorylation

PDAC = Pancreatic Ductal Adenocarcinoma

PI3K = Phosphoinositide 3-Kinase

PKC = Protein Kinase C

PP = Pyrvinium Pamoate

PPAR = Peroxisome Proliferator-Activated Receptor

PPRE = Peroxisome Proliferator Response Elements

RA = Rheumatoid Arthritis

ROI = Reactive Oxygen Intermediates

ROS = Reactive Oxygen Species

RXR = Retinoid X Receptor

SARS-Cov-2 = Severe Acute Respiratory Syndrome Coronavirus-2

SHH = Sonic Hedgehog

siRNA = Small interfering RNA

SP = Side Population

SRI = Serotonin Reuptake Inhibitor

STH = Soil-Transmitted Helminths

T1DM = Type 1 Diabetes Mellitus

T2DM = Type 2 Diabetes Mellitus

TCA = Tricyclic Antidepressant

TFP = Trifluoperazine

TGF = Transforming Growth Factor

THZ = Thioridazine

TME = Tumor Microenvironment

TMZ = Temozolomide

TOPO = Topoisomerase

TRAIL = Tumor Necrosis Factor (TNF)-Related Apoptosis-Inducing Ligand

TRPV2 = Transient Receptor Potential channel Vanilloid 2

TrxR = Thioredoxin Reductase

TZD = Thiazolidinedione

VPA = Valproic Acid

WHO = World Health Organization

CONSENT FOR PUBLICATION

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CONFLICT OF INTEREST

The authors declare no conflict of interest, financial or otherwise.

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