

MINI-REVIEW

Repurposing existing drugs for cancer stem cell-directed therapy

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(This article belongs to the *Special Issue: Novel findings in cancer stem cells research and therapy*)

Abstract

Cancer stem cells (CSCs) pose a significant challenge in tumor treatment due to their ability to remain quiescent during therapy and thus evade chemo- and radio-therapy. In addition, their ability to initiate tumor formation from a single cell is another essential factor to consider when developing a strategy to eradicate CSCs. Given that developing novel drugs is a time-consuming and costly process, drug repurposing has become an increasingly utilized and appealing alternative in recent research. Drug repurposing involves testing existing medications that have already completed substantial portions of drug development for the treatment of new medical conditions. Artificial intelligence tools can assist in this process. This review presents a series of compounds, initially developed for a wide range of conditions, including antidiabetic, antipsychotic, anti-inflammatory, cholesterol-lowering, and antiparasitic drugs, that can be repurposed as targeted therapies for CSCs. Metformin and doxycycline have also been evaluated in clinical studies targeting CSCs. Furthermore, novel artificial intelligence tools will be vital for predicting the potential of repurposed drugs before *in vitro* and *in vivo* testing.

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Citation: Glavan TM. Repurposing existing drugs for cancer stem cell-directed therapy. *Cancer Plus*. 2026;8(1):025450073.
doi: 10.36922/CP025450073

Received: November 7, 2025

Revised: December 1, 2025

Accepted: January 22, 2026

Published online: February 12, 2026

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Keywords: Cancer stem cells; Therapy; Chemoresistance; Radioresistance; Drug repurposing

1. Introduction

Cancer is a group of diseases characterized by the uncontrolled growth and spread of abnormal cells in the body. While conventional treatments effectively reduce the primary tumor mass, a critical need exists for therapies that specifically target cancer stem cells (CSCs), as these highly resilient cells drive both metastasis and disease relapse.¹ CSCs are a subpopulation of cancer cells that share key characteristics with normal stem cells, including self-renewal, differentiation, tumorigenicity, and quiescence.² Specifically, CSCs can divide to produce more CSCs, sustaining their population. CSCs can differentiate into more specialized, non-stem cancer cells that constitute the bulk of a tumor and can also dedifferentiate under certain conditions. CSCs are the only cells within a tumor that are capable of initiating new tumor growth when transplanted into a host, and may divide more slowly than other cancer cells, allowing them to escape conventional cancer therapies that primarily target rapidly dividing cells.

The existence of CSCs poses several challenges in cancer treatment. The CSC hypothesis suggests that tumors are not a homogeneous mass of cells but are instead driven by a

small population of CSCs. These cells are responsible for the initial formation and growth of the tumor. Conventional cancer treatments, such as chemotherapy and radiation, usually target rapidly proliferating cells. However, as CSCs are often slow-growing or quiescent, they can survive these treatments. The surviving CSCs can then repopulate the tumor, leading to relapse. CSCs are also believed to contribute to metastasis because they can survive in new microenvironments, self-renewal, and generate diverse tumor cell populations, and they often exhibit features associated with epithelial-mesenchymal transition.

The discovery of CSCs has opened a new paradigm for cancer research and treatment, with the primary goal of developing therapies that specifically target and eliminate CSCs.^{2,3} To develop therapies that specifically target CSCs, several strategies have been investigated. Identifying specific biomarkers (cluster of differentiation [CD] 44, CD133, and aldehyde dehydrogenase [ALDH]) to isolate and study CSCs may aid in targeting CSCs in various cancer types. Another approach is to develop drugs that target the self-renewal pathways specific to CSCs, such as Wnt/ β -catenin, Notch, Sonic hedgehog, Hippo, and Janus kinase-signal transduction and activation of transcription. Combination therapies that simultaneously target both the bulk tumor cells and the resistant CSCs may be the best strategy; however, it is also crucial to investigate the tumor microenvironment (TME) and its role in supporting the “stemness” properties of CSCs. This is especially important as plasticity is not only a CSC-exclusive feature; non-CSCs can spontaneously acquire a CSC-like phenotype *in vitro* and *in vivo*, regulated by zinc finger E-box-binding homeobox 1.⁴ In addition, well-known CSC markers, such as CD133, A2B5, stage-specific embryonic antigens, and CD15, are not uniformly expressed among glioblastoma cells; however, the majority of cancer cells adopt a plastic state in response to stimuli from the TME.⁵ These interactions create a specialized environment, often called the CSC niche, which is essential for CSC survival, self-renewal, dormancy, and resistance to therapy. The cells contributing to the CSC niche include cancer-associated fibroblasts, immune cells (tumor-associated macrophages and myeloid-derived suppressor cells), endothelial cells, and mesenchymal stromal cells. Cancer-associated fibroblasts, a predominant component of the TME, drive tumor remodeling to enhance proliferative capacity, plasticity, and drug resistance. Recruitment and polarization of immunosuppressive cells (tumor-associated macrophages, myeloid-derived suppressor cells) allow CSCs to escape surveillance and destruction by the immune system.^{6,7}

2. CSCs markers

CSC markers are specific molecules that are used to identify and isolate the CSC population within a tumor.

There is no single universal marker for all CSCs. Instead, a variety of markers have been identified, with specific markers often linked to different types of cancer. The use of surface proteins to isolate CSCs is challenging, as these markers are not exclusive to CSCs; they also appear on normal stem cells and non-tumorigenic cancer cells. Furthermore, their expression is highly variable across different tumor types, depending on the tissue of origin and the microenvironment. Such widespread heterogeneity indicates that the nature of CSCs is shaped by a combination of intrinsic (genetic) and extrinsic (microenvironmental) factors.⁸

2.1. Cell surface markers

Cell surface markers are proteins located on the cell membrane and are commonly used to isolate CSCs (e.g., by flow cytometry). One of the most researched markers is CD44, a cell surface glycoprotein involved in cell adhesion, migration, and interaction with the extracellular matrix, notably acting as a receptor for hyaluronic acid. CD44 is one of the most widely reported markers for CSCs across different cancers, including breast, pancreatic, prostate, and head and neck cancers. It is often used in combination with other markers to define the CSC population (e.g., CD44⁺/CD24⁻ or CD44⁺/ALDH1⁺).⁹ Another cell surface marker, CD133 (Prominin-1), is a transmembrane glycoprotein and a well-known marker for CSCs in various solid tumors, such as brain, colon, lung, liver, and prostate cancers. The CD133⁺ cell population is highly tumorigenic.¹⁰ Epithelial cell adhesion molecule, also known as CD326, is a transmembrane glycoprotein that is widely recognized as a marker for CSCs, particularly in solid tumors of epithelial origin. It plays a significant role in cancer biology, promoting cell growth and survival and contributing to metastasis and drug resistance.¹¹

2.2. Pluripotency-associated transcription factors

Proteins that regulate gene expression and are crucial for maintaining the “stem-like” state of normal stem cells and CSCs are referred to as pluripotency-associated transcription factors. Core transcription factors that are essential for maintaining the pluripotency of embryonic stem cells include octamer-binding transcription factor 4, sex-determining region Y-box 2, and NANOG. They are re-expressed in cancer cells through dedifferentiation, serving as strong indicators of a stem-like phenotype.¹² c-MYC is an oncogene and a transcription factor involved in the regulation of cell cycle progression and proliferation. It also plays a key role in maintaining stem cell self-renewal properties.¹³

2.3. Other markers and signaling pathways

The evolutionarily conserved signaling pathways that are crucial for regulating cell development and stem cell fate include Wnt/ β -catenin, Hedgehog, and Notch.¹⁴ Their dysregulation is frequently observed in CSCs and contributes to their self-renewal and proliferation. ALDH1 is a cytosolic enzyme associated with self-protection and detoxification mechanisms in many cancers.¹⁵ Drug efflux pumps (adenosine triphosphate-binding cassette [ABC] transporters) are highly expressed in CSCs, where they act as efflux pumps that export chemotherapeutic agents, contributing to the high level of drug resistance seen in CSCs. These include ABC superfamily G member 2, ABC subfamily B member 1, and ABC subfamily C member 1, also known as multidrug resistance-associated protein 1, which is the most prominent.¹⁶

3. Therapies targeting CSCs

The main strategies for targeting CSCs include: (i) Targeting cell surface markers, such as CD44 and CD133; (ii) targeting signaling pathways critical for CSC maintenance, including Wnt/ β -catenin, Hedgehog, Notch, and phosphatidylinositol 3-kinase; and (iii) targeting drug transporters responsible for chemoresistance, such as ABC superfamily G member 2 and ABC subfamily B member 1. Other recent strategies include inducing CSC differentiation, overcoming CSC immune evasion, and targeting DNA repair in CSCs.⁸ Another approach is to target quiescent CSCs, which remain a significant challenge in CSC therapy. Quiescent CSCs resist conventional therapies, such as chemotherapy and radiation, as these treatments primarily target rapidly dividing cells. The primary strategy to overcome this resistance is to induce CSCs to exit dormancy, making them susceptible to treatment. This can be accomplished through several mechanisms: (i) inhibiting dormancy regulators (such as p21 and p27) to force cell cycle entry, (ii) combining cyclin-dependent kinase 4/6 inhibitors (e.g., palbociclib) with chemotherapy, (iii) disrupting the Notch and transforming growth factor beta pathways to interrupt dormancy, and (iv) using Wnt agonists to stimulate CSC division, which also enhances their sensitivity to chemotherapy. Forcing CSCs into an active, dividing state reduces their ability to evade therapy and drive tumor relapse.¹⁷ However, dormancy-inhibiting strategies must be combined with a cytotoxic agent to prevent tumor progression. For the “wake-up and kill” approach to succeed, the cytotoxic agent must be administered at the right time after CSCs exit dormancy, ensuring that vulnerable, newly dividing CSCs are promptly eliminated so as not to fuel tumor progression.

4. Repurposing existing drugs for CSC therapy

Drug repurposing, also known as drug repositioning, is the process of finding new therapeutic uses for existing drugs that have already been approved or are in development for a different medical condition. The advantage of drug repurposing is that, rather than starting from scratch, it explores new applications for drugs that have already undergone a substantial portion of the development process.¹⁸ A significant advantage of drug repurposing is that it circumvents the most time-consuming and expensive stages of traditional drug development (early-stage discovery and pre-clinical testing). Consequently, the safety, toxicity, and pharmacokinetic profile of the drug in humans are already known, so it often proceeds directly to phase II/III clinical trials for the new indication (Figure 1). Traditional drug development is expensive and has a high failure rate. Drug repurposing mitigates these risks using drugs with established safety records, significantly lowering costs and increasing the chances of success. In the past, many successful cases of drug repurposing have been the result of unexpected observations. A drug's side effect in a clinical trial might be recognized as a potential treatment for another disease. In addition, in recent years, computational methods, bioinformatics, and artificial intelligence have been applied to analyze vast amounts of data, including genomic data, protein structures, and clinical trial results, to predict new indications for existing drugs. Furthermore, drug repurposing is especially useful for rare diseases. For these conditions, the small number of patients makes it financially unfeasible to develop a new drug. By repurposing an existing, often generic drug, a faster and more affordable treatment option can be provided. However, it is essential to emphasize that there are significant challenges in translating pre-clinical findings, particularly regarding the pharmacokinetics and dosing schedules required for anti-CSC efficacy. Assumptions that doses and formulations can be directly applied from the original indication to a new condition may be incorrect and should be avoided.¹⁹

Drugs originally developed for other diseases have been investigated for their potential to specifically target CSCs (Figure 2). These compounds span multiple drug categories. For example, disulfiram is a drug for chronic alcoholism, which works by producing an acute sensitivity to ethanol through the inhibition of the enzyme ALDH. Disulfiram's anticancer mechanisms involve a copper-dependent pathway that targets cancer cells by generating reactive oxygen species and inhibiting the proteasome, leading to

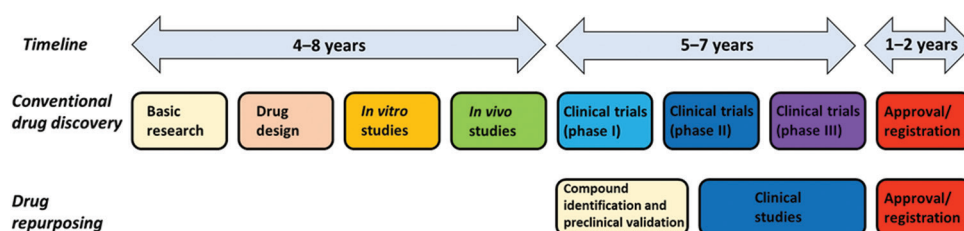


Figure 1. Timeline for conventional drug discovery compared to drug repurposing. Drug repurposing can shorten drug development by ~15–20 years, allowing compounds to enter phase II/III clinical trials after a relatively short period of identification and pre-clinical validation.

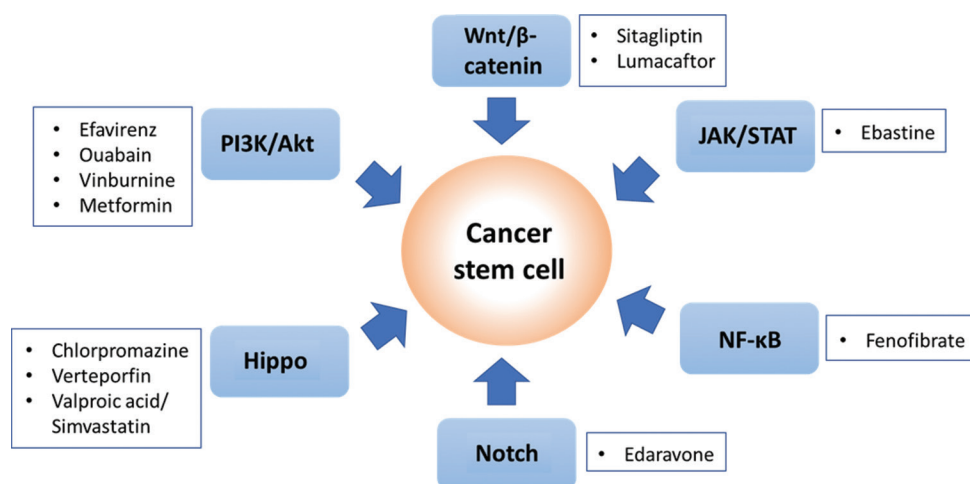


Figure 2. Signaling pathways critical for cancer stem cells and the drugs under investigation for their targeting. Data from Table 1 on repurposed drugs currently being evaluated for cancer stem cell therapy are presented, along with the signaling pathways they affect.

Abbreviations: JAK: Janus kinase 2; NF-κB: Nuclear factor kappa B; STAT: Signal transduction and activation of transcription.

the accumulation of misfolded proteins, promoting cell death, and suppressing CSCs. Different antidiabetic drugs, such as metformin, have been studied extensively for CSC-targeted therapy. Metformin's antitumorigenic potential includes activation of the energy sensor 5' adenosine monophosphate-activated protein kinase, which inhibits the mechanistic target of rapamycin pathway to suppress cell growth. It also directly targets cancer cell metabolism, induces cell cycle arrest, and can reduce circulating insulin levels that promote tumor growth. Metformin selectively kills CSCs, inhibits their self-renewal, and also acts synergistically with chemotherapy.²¹ Interestingly, several drugs developed for the treatment of mental illnesses, along with other commonly used drugs, such as anti-inflammatory medications, cholesterol-lowering agents, medications used to lower blood pressure, and different antiparasitic drugs, have been effective in CSC targeting. Moreover, molecular docking suggested that lumacaftor, a cystic fibrosis treatment drug, may be a candidate drug for targeting breast CSCs via β-catenin.²² These repurposed drugs have been shown to target different signaling pathways essential for cancer survival,

epithelial–mesenchymal transition, and the maintenance of stemness, including protein kinase B, Yes-associated protein/transcriptional coactivator with PDZ-binding motif, Kirsten rat sarcoma viral oncogene homolog, mechanistic target of rapamycin, glycogen synthase kinase-3 beta, Janus kinase–signal transduction and activation of transcription, and mitogen-activated protein kinase kinase/extracellular signal-regulated kinase. Table 1 summarizes recent research on drug repurposing, explicitly focusing on drugs developed for other conditions that show potential for targeting CSCs. Recent studies suggest that aspirin is a promising candidate in targeting CSCs, especially in combination with proton radiation therapy,²³ and that an antineoplastic antibiotic, mithramycin, could also be a valid therapeutic option for effective CSC targeting.²⁴ Table 2 lists all repurposed drugs that have progressed to clinical trials, with doxycycline and metformin being the most frequently studied examples. A phase II clinical trial of metformin as a CSC-targeting agent in ovarian cancer showed promising results and supported the use of metformin in phase III studies.²⁵ Other clinical studies involving repurposed

Table 1. Recent studies on repurposing existing drugs for cancer stem cell targeting

Name of the drug	Category of the drug	Mechanism	Type of CSCs	References
Kinase inhibitors				
Dacomitinib and foretinib	Kinase inhibitors	-	Glioblastoma	26
Dacomitinib and disulfiram/copper	A kinase inhibitor and a chronic alcoholism drug	-	Glioblastoma	26
Foretinib and AZD3759	Kinase and EGFR inhibitor	-	Glioblastoma	26
Bentamapimod (AS602801)	JNK inhibitor, treatment of endometriosis	Reduces survivin expression	Ovarian cancer	27
Antipsychotics and antidepressants				
Penfluridol	Antipsychotic	Targets dopamine receptor D2	Renal cell carcinoma	28
Spiperone	Antipsychotic	Induces ER stress and apoptosis	Colorectal cancer	29
Chlorpromazine	Antipsychotic used to treat schizophrenia, bipolar disorder, and acute psychosis	Suppresses YAP signaling	Breast cancer	30
Sertraline	Antidepressant medication of the selective serotonin reuptake inhibitor class	Induces oxidative stress	Prostate cancer	31
Anti-inflammatory drugs				
Aspirin	Non-steroidal anti-inflammatory drug	-	HNSCC	23
Ketoprofen	Non-steroidal anti-inflammatory drug	Targets PUM1	Colon cancer	32
Sulfasalazine	Anti-inflammatory drug	Targets KRAS/MMP7/CD44 signaling	Colorectal carcinoma	33
β-Escin	Anti-inflammatory drug	Reduces ALDH1 activity	HER2-positive breast cancer	34
Antiparasitic drugs				
Mebendazole	Medicine for treating worms	Reduces integrin β4 expression and cancer stem cell properties	Breast cancer	35
Fenbendazole	An anthelmintic agent commonly used to treat animal parasitic infections	Enforces G2/M blockade	Cervical cancer	36
Niclosamide	Anthelmintic medication used to treat tapeworm infestations	Decreases pregnane X receptor through miR-148a	Colon cancer	37
Cholesterol-lowering drugs				
Lovastatin	Cholesterol-lowering agent	Disrupts the mevalonate pathway	Brain cancer	38
Fenofibrate	Medication for treating abnormal blood lipid levels	Downregulates NF-κB	Oral carcinoma	39
Fluvastatin	Member of the statin drug class, used to treat hypercholesterolemia and to prevent cardiovascular disease	-	Breast cancer	40
Antiviral drugs				
Efavirenz	Antiretroviral	Blocks Akt	TNBC	41
2-thio-6-azauridine	Antiviral	Targets CD151 and ELAVL1	TNBC	42
Other drugs				
Ouabain	Cardiac glycoside	Blocks Akt	TNBC	41
Vinburnine	Vasodilator	Blocks Akt	TNBC	41
Verteporfin	Photosensitizer for photodynamic therapy	YAP/TAZ small molecule inhibitor	Breast cancer	43
Quercetin and luteolin combined with paclitaxel	Flavonoids and chemotherapeutic	Targeting CD73	Breast cancer	44

(Cont'd...)

Table 1. (Continued)

Name of the drug	Category of the drug	Mechanism	Type of CSCs	References
Disulfiram/Cu	Chronic alcoholism drug	Inhibits ALDH	Breast, oral, cervical, ovarian cancer, glioblastoma, medulloblastoma, chondrosarcoma, multiple myeloma	20
Dolasetron	Serotonin 5-HT 3 receptor antagonist	Targets PUM1	Colon cancer	32
Venetoclax	γ -secretase inhibitor	-	Breast cancer	45
IRMOF3-DSF-FA	Nanoparticles with folic acid and disulfiram	-	Oral cancer	46
Aloe-emodin	Anthraquinone	-	Lung cancer	47
Digoxin	Cardiac glycoside used in the treatment of mild-to-moderate heart failure	-	Lung cancer	47
Valproic acid/simvastatin combination	Anticonvulsant/lipid-lowering medication	Sensitizes cells to docetaxel and reverses docetaxel resistance (via YAP inhibition)	Metastatic castration-resistant prostate cancer	48
Metformin	Type 2 diabetes medication	Inhibits inflammation, activates AMPK, and disrupts pathways PTEN/PI3K/Akt/mTOR and PKA/GSK3 β /KLF5	Breast cancer	49
Deferiprone	Iron chelating medication	Inhibits mitochondrial metabolism and induces ROS production	Breast cancer	50
Pranlukast	Leukotriene receptor-1 antagonist	Antagonizes CD49f	Breast cancer	51
AM404	Metabolite of acetaminophen with antibacterial activity	Suppresses the expression of FBXL5	Colorectal cancer	52
Edaravone	Treatment of stroke and amyotrophic lateral sclerosis	Impairs Notch signaling pathways	Glioblastoma	53
Abemaciclib	Medication for the treatment of advanced or metastatic breast cancers	Targeting GSK3 β	Glioblastoma	54
Lumacaftor	Prescription medicine used for the treatment of cystic fibrosis with F508del/F508del mutations	Targets β -catenin	Breast cancer	22
Sitagliptin	Antidiabetic	Targets CD24/CTNNB1/SOX4	Colorectal cancer	55
Ebastine	Second-generation antihistamine	Targets Janus kinase 2–signal transduction and activation of transcription 3 and MEK/ERK	Breast cancer	56
Renin-angiotensin system (RAS) inhibitors	Medications used to lower blood pressure and treat conditions such as hypertension, heart failure, and chronic kidney disease	Acts on the molecules of the RAS, which CSCs express, and RAS is involved in CSC maintenance, self-renewal, and tumor growth	Many different types of cancer	57

Abbreviations: Akt: Protein kinase B; CSC: Cancer stem cell; CTNNB1: Catenin B1; EGFR: Epidermal growth factor receptor; ELAVL1; ELAV-like RNA-binding protein 1; ER: Endoplasmic reticulum; FBXL5: F-box and leucine-rich repeat protein 5; GSK3 β : Glycogen synthase kinase 3 beta; HNSCC: Head and neck squamous cell carcinoma; JNK: c-Jun N-terminal kinase; KLF5: Kruppel-like factor 5; MEK/ERK: Mitogen-activated protein kinase/extracellular signal-regulated kinase pathway; mTOR: Mechanistic target of rapamycin; NF- κ B: Nuclear factor kappa B; PKA: Protein kinase A; PI3K: Phosphoinositide 3-kinase; PTEN: Phosphatase and tensin homolog; PUM1: Pumilio RNA-binding family member 1; ROS: Reactive oxygen species; SOX4: Sex-determining region Y-box 4; TNBC: Triple-negative breast cancer; YAP/TAZ: Yes-associated protein/transcriptional coactivator with PDZ-binding motif.

drugs to treat CSCs had no published results. Given that the mechanism of action for numerous repurposed drugs targeting CSCs has not been fully elucidated, there is a

clear requirement for direct experimental validation of these mechanisms, particularly within well-characterized CSC subpopulations.

Table 2. Clinical studies of repurposed drugs for cancer stem cell therapy

Name of the drug	Category of the drug	Mechanism	Type of CSCs	ClinicalTrials.gov ID	Status	References
Doxycycline	Antibiotic	Suppresses EMT and stem cell markers such as OCT4, SOX2, and CD44	Breast cancer	NCT06452394	Recruiting	-
Doxycycline	Antibiotic	Inhibits key pathways like PAR1/FAK/PI3K/Akt, and enhances chemosensitivity	Resectable pancreatic cancer	NCT02775695	Completed	-
Metformin	Medication for the treatment of type 2 diabetes, particularly in people who are overweight	Prevents EMT	Gynecological cancers	NCT01579812	Completed (with cited publication)	25
Metformin	Medication for the treatment of type 2 diabetes, particularly in people who are overweight	Activates the AMPK pathway, suppresses the Wnt/ β -catenin signaling pathway	Colon cancer	NCT01440127	Terminated	-
Fursultiamine	Medication and vitamin used to treat thiamine deficiency	Suppresses OCT4, SOX2, NANOG expression	Esophageal squamous cell carcinoma	NCT02423811	Completed	-
Broccoli sprouts are rich in sulforaphane and quercetin	Dietary phytochemicals found in vegetables such as broccoli and onions	Inhibits self-renewal capacity	Advanced pancreatic cancer	NCT01879878	Unknown status	58

Abbreviations: AMPK: Adenosine monophosphate-activated protein kinase; CD44: Cluster of differentiation 44; CSC: Cancer stem cell; EMT: Epithelial-mesenchymal transition; FAK: Focal adhesion kinase; OCT4: Octamer-binding transcription factor 4; PAR1: Protease-activated receptor 1; PI3K: Phosphoinositide 3-kinase; SOX2: Sex-determining region Y-box 2; Wnt: Wingless-type signaling pathway.

5. Conclusion

The primary challenge in eliminating CSCs is their heterogeneity, which prevents the development of a single, effective treatment. To move forward, a precision approach is needed to characterize CSC complexity, using tools such as single-cell sequencing to decode the differences between CSCs and pinpoint therapy-resistant subtypes. A multi-omics approach would allow a more comprehensive study of CSCs, including insights into chemo- and radio-resistance, providing novel strategies for developing therapies that target specific genes, proteins, or signaling pathways. Moreover, as CSC survival depends significantly on the TME, effective treatment strategies must combine therapies that target CSCs, the TME, and the tumor bulk to ensure complete eradication. This review has highlighted potential therapies available for using repurposed drugs to target CSCs. This could quickly lead to improved and new therapies, as repurposed drugs do not require lengthy and costly assessment.

Furthermore, novel approaches based on the application of artificial intelligence tools to predict the potential of repurposed drugs before testing them *in vitro* and *in vivo* will be of great assistance. Robust experimental models (e.g., patient-derived organoids and sophisticated *in vivo* models) are essential to validate these computational predictions and to recapitulate CSC heterogeneity and therapy resistance. In addition, it is important to establish clinical trial designs that incorporate biomarker-based

endpoints to precisely select the patient population expected to derive the maximum benefit from these novel, repurposed therapeutic approaches. Finally, future oncology should move toward therapies that are highly tailored to the individual patient, including identification of patient-specific CSC markers, novel combination therapy strategies, and predictive diagnostics.

Acknowledgments

None.

Funding

This work was supported by the Croatian Science Foundation (project number: IP-2020-02-4225) for the project: Toll-like receptor 3 in the development and treatment of human head and neck cancer: The role of endogenous ligands.

Conflict of interest

Tanja Matijevic Glavan is the Guest Editor of this special issue, but was not in any way involved in the editorial and peer-review process conducted for this paper, directly or indirectly. The author declared that he has no known competing financial interests or any conflict of interest.

Author contributions

This is a single-author article.

Ethics approval and consent to participate

Not applicable.

Consent for publication

Not applicable.

Availability of data

Not applicable.

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