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INHIBITORS OF CANCER STEM CELL

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ABSTRACT

These stem cells have ability of self-renewal, and intrinsic survival mechanisms which helps to maintains growth of tumour cells. Now they are considered auspicious therapeutic targets in the treatment of the cancer. These cancer stem cells also have resistance to the chemotherapy. They contribute to multiple tumour malignancies, such as repetition, metastasis, heterogeneity, resistance to many drugs, and also resistance to various radiations. Targeted therapies are directly related to suppressing or eliminating cancer stem cells may synergize with well-known therapies and increase efficacy. Enhanced understanding of CSC markers, such as CD133, CD44, and epithelial cell adhesion molecule (EpCAM), may facilitate development of therapies that target them. These gives review on information about CSC, its inhibitors, and its working on cancer cells.

KEYWORDS: Adenocarcinoma, Chemotherapy, Malignant, Immunosuppressive, CD133, CD44, Hedgehog, Wnt, Verteporfin, Curcumin.

INTRODUCTION

Cancer stem cells (CSCs) were first recognized in leukaemia in year 1994 by John. E. Dick.

A single cancerous cell having an ability to forming a new cancer cell and create heterogeneous posterity which provides an origin for cancer stem cells. In the first probability, if a normal stem cell turns into CSC, it indicates that it having a stem-cell package. Formation of cancer cell from stem cell is started when a stem cell has "gone bad" and therefore the essential stem-cell properties of a cancer cell are commonly inbred. The second possibility is CSCs developed from any cell which gains the characteristic properties of stem cell which is stimulated with a partial stem-cell package.[1]

Eventually, it gets malicious behaviour. So, by acquiring the wrong ways of a stem cell by a good cell resulting into a cancer formation. Hypothetically, when discriminated cell gains components of stem cells it turns differentiated and cancerous. And in last, the third possibility, when cancer involves normal SCs gets a separate package. And the attachment of bad cell with a good SC turns into cancer formation. In this phenomenon, CSCs are attracted by normal stem cells thus which ultimately plays the vital role in establishing and improvement of the malignancy. A very common interrogation about the theory of a stem-cell origin of cancers is whether cancer results from stem cells or it is determined by cells that have stem cell–like property.[22]

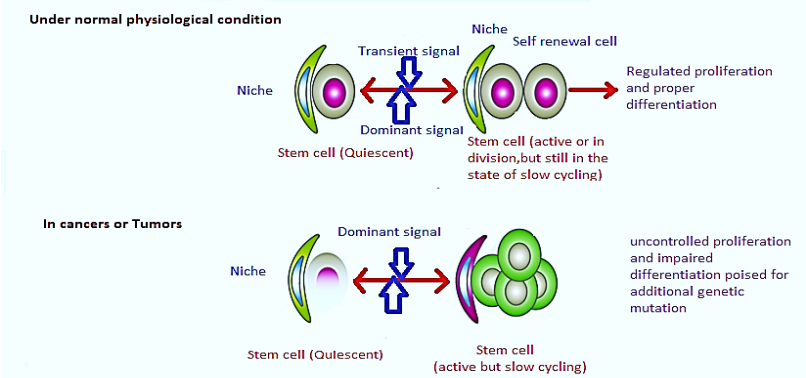


Figure 1: Niche are attached to normal stem cell which is self-renewable called as active or in division state which forms a new stem cell by this renewable cycle. But in cancer cell, stem cells are uncontrolled proliferation and impaired differentiation poised for additional genetic mutation.

Cancer stem cell (CSCs) inhibitors can also be known as novel drug delivery system. In conventional therapy anti-tumour/cancer cells directly attacks in aggressively to the targeted cancerous cells which results into a rupturing of normal cells, this drawback is overcomes in the cancer stem cell inhibiting therapy. In CSCs inhibitor therapy drug attached to the targeted cell and differentiates the cancer cell and progenitor cell after the separation of these cell inhibitors suppresses the cancer cell without harming a normal cell.

There are many strategies and therapies available for the cancer treatment which includes chemotherapy, radiotherapy, surgery and targeted therapy.

Cancer stem cells (CSC) are found in the small subpopulation in the bulky heterogenous solid and liquid tumours.

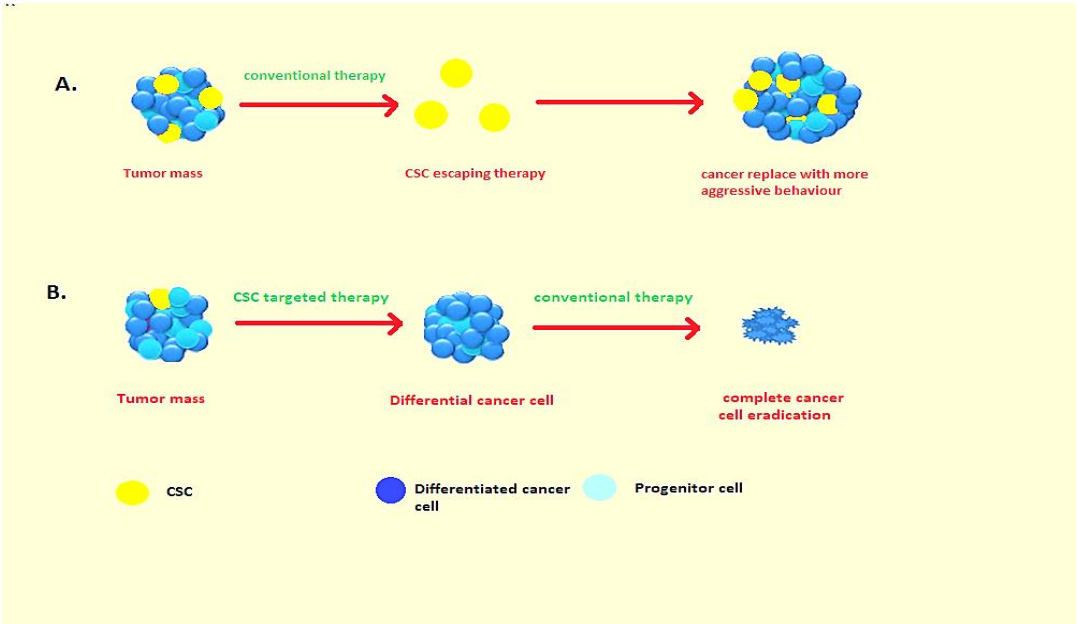


Figure 2: Renewal and differentiation properties which leads to intra tumoral and inter tumoral heterogeneity.

Where chemotherapy usually eliminates or destroys the non-CSC tumour cells bulk population, but CSCs are relatively chemo resistant and become enriched after chemotherapy also they enter a transient dormant state which may result in tumour metastasis.

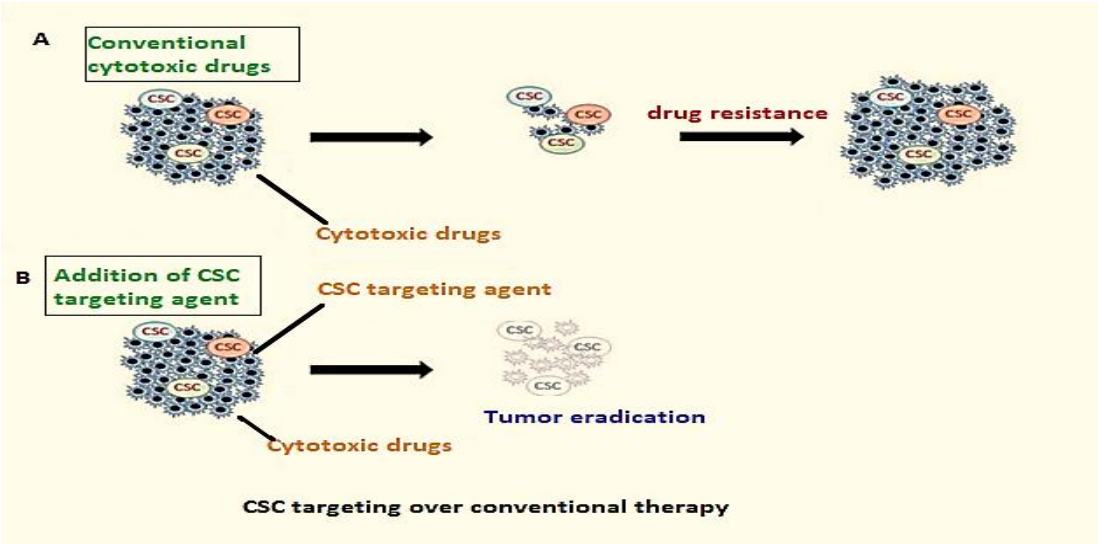


Figure 3: Combining conventional cytotoxic drugs with cancer stem cell (CSC)-targeting agents. (a) Although chemotherapeutic and molecular-targeted drugs can attack most cancer cells, CSCs can evade these agents, leading to tumour regrowth. (b) Combination therapy with CSC-targeting agents and conventional drugs is predicted to be more effective because it eliminates both CSCs and non-CSC tumour cells.

CSC-Targeting therapies

Recently, several attempts have been made to combine CSC targeting agents with conventional drugs, which are seen to be effective in treating cancer.[1,2] The high plasticity and heterogeneity of the CSC as well as non-CSC makes a challenge in finding the targeting molecule in different cancers.[3] This plasticity of the non-CSC allows them to transdifferentiate, this may resist the CSC targeting therapies.[4]

The malignant state and the effects differ from different cancer. The malignant state also differs patient by patient for the patients having same cancer. In all these the CSC's have the same ability to drive tumorigenesis, metastasis, drug resistance, and immunosuppressive microenvironment.[1] These features make CSCs attractive targets for the development of more effective treatments for cancer. Till the date attempts have been made to target stemness markers, such as STAT3 and NANOG,[1] as well as pathways that regulate malignant stemness, most notably the β-catenin, Notch, hedgehog, and JAK-STAT pathways, which promote stemness features in various cancers.[5]

No.	Type of cancer/tumor CSC markers	Phenotype of CSCs markers
1	colon cancer	CD133þ, CD44þ, CD166þ, EpCAMþ, CD24þ, CXCRþ, CK20þ, CEAþ, LGR5þ
2	Pancreatic	CD133þ, CD44þ, EpCAMþ, CD24þ, ABCG2high
3	Lung cancer	CD133þ, ABCG2high
4	Leukaemia	CD34þ, CD38-, HLA-DR-, CD71-, CD90-, CD117-, CD123þ
5	Breast cancer	ESAþ, CD44þ, CD24-/LOW, LINEAGE-ALDH1high
6	Multiple myeloma	CD138-
7	Brain cancer	CD133þ, BCRP1þ, A2B5þ, SSEA1þ
8	Liver cancer	CD133þ, CD49þ, CD90þ
9	Prostate cancer	CD44þ, α2β1high, CD133þ
10	Head and neck cancer	CD44þ, ALDHþ, YAP1þ, BMI1þ

Targeting CSCs by Inhibiting YAP1

We have to focus on YAP1, In terms of targeting of CSCs to regulating effector molecules as it is a main effector of Hippo signalling pathway which regulates the normal organ tissue growth. YAP 1 has a assorted roles in tumorigenesis and drug resistance. and it has been reported to encourage malignant features (e.g., cell proliferation, invasion, migration, and anti-apoptosis).[6,7,8,9,10] and drug resistance in several cancers. Recently investigated that YAP1 pays in the founding of an immune-suppressive tumour microenvironment [fig 3]. Furthermore, there is extensive evidence is that YAP1 also regulates malignant cell stemness.[27] YAP1 is capable of regenerating non-CSCs into cells that have CSC-like characteristics and helps cancer cells to maintain their stemness by promoting autophagy. In case of NSCLC, YAP1 directly get interacts with OCT4 afterward SOX2 upregulation to enable self-renewal and gaining of endothelial-like properties of CSCs.[13,14,15,16] YAP1 regulates pluripotency and chemoresistance in case of overian cancer.[17] YAP1 induction synchronously persuades two potential stemness markers viz; EPCAM and keratin 19 in hepatocellular carcinoma.[18] Recently, YAP1 has been reported to activate SOX9 to deliberate CSC-like features in oesophageal squamous tissue cell carcinoma. Additionally, YAP1 signalling is activated by long noncoding RNAs in liver cancer, leading to the induction of self-renewal by CSCs. Prominently, YAP1 interacts with numerous oncogenic signalling pathways, including MAPK, PI3K/mTOR, and Hippo, which augment tumorigenesis.[19,20,21]

The interaction between YAP1 and the Wnt/β-catenin pathway is known to be important for the maintenance and expansion of CSCs. Cancerous tissue is made up of not only cancer cells but also mesenchymal cells, endothelial cells, and immune cells.[144, 20] Fascinatingly, YAP1 in these cells also pays to cancer progression. In immature T-cell, YAP1 promotes polarization to regulatory T-cell through inducing TGFBR2 for immune-suppressive tumor microenvironment. From these studies, YAP1 is considered as an attractive therapeutic target.

Verteporfin, derivative of porphyrin, is a photosensitizer used in the photodynamic therapy of macular erosion.[6] Among various drugs, such as dasatinib and statins, that are capable of blocking activity of YAP1, verteporfin is known as the most effective suppressor of YAP1 activity and is widely used in preclinical studies.[23,6] Combination of verteporfin and erlotinib blocked the tumorigenic properties of erlotinib-resistant NSCLC and bladder cancer cells.[25,26] Furthermore, the addition of verteporfin to gefitinib minimises the capability of gefitinib-resistant NSCLC and bladder cancer cells. Though several ongoing clinical trials are now assessing the effectiveness of verteporfin as a photosensitizer in different various cancers, none have declared to evaluate YAP1-inhibitory actions.

Recently showed that, YAP1 is overexpressed in basal type of bladder cancer cell, which are rich in stem cell phenotype.[27,28] In this study, high expression of YAP1 was associated with increased levels of mesenchymal markers, and YAP1 induced CSC properties, such as

sphere-forming and self-renewal abilities, invasiveness and drug resistance through induction of SOX2.

We also demonstrated that COX2/PGE2 signalling upregulates SOX2 and that a feedback mechanism regulates SOX2 through these pathways. Additionally, combination treatment with verteporfin and a COX2 inhibiter increase chemotherapeutic effectiveness through the suppression of CSC properties. Further work will be necessary to determine the potential clinical utility of this combination therapy.[27]

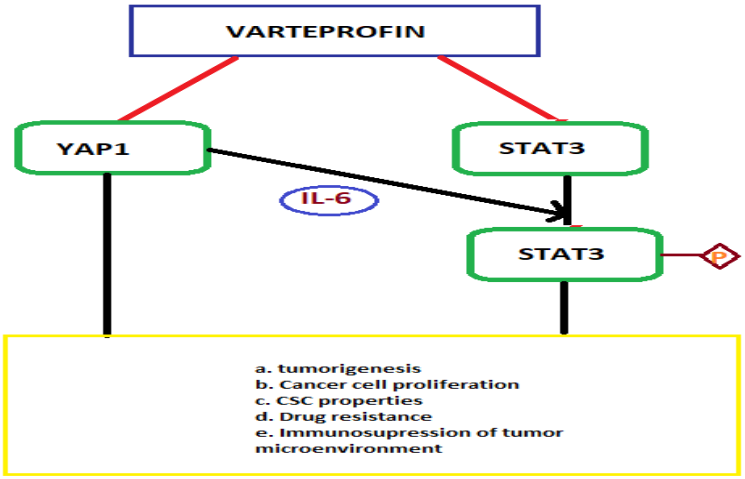


Figure 4: YAP1 and STAT3 are two oncogenic pathways that encourage cancer stemness. YAP1 and STAT3 are independently involved in oncogenic signalling to promote CSCs properties. Though, YAP1 also promotes IL-6-induced STAT3 phosphorylation and activation. Derivative of porphyrin verteporfin inhibits both the YAP1 and STAT3 pathways and may thus be an efficient suppressor of CSC properties.

Inhibitors targeting CSC

A) Curcumin

Curcumin is a natural CSC's inhibitor. Curcumin is derived from the spice turmeric and it is known for its anticancer activities, which also includes suppression of metastasis, proliferation, invasion and induction of apoptosis in cancer cells.[29] It has reported that curcumin alone or together with routine chemotherapies could effectively eliminate colon and lung CSCs.[34,35] Recently the studies found that curcumin is also effective in various cancers treatements, e.g., head and neck, breast, pancreatic, colon, prostate, ovarian, and bladder cancers.[30,31] Curcumin possess an inhibitory effects on CSCs.[32,33] the curcumin suppresses hedgehog (Hh) pathway by declining the level of Gli1 mRNA as well as Gli receptor activity in prostate cancer cell lines.[20]

Natural compound	Sources	Tumor types
Genistein	Soy	Pancreatic CSCs
Genistein	Soy	Breast CSCs
Blueberry Polyphenolic Acids	Blueberry	Breast CSCs
20(*S*)-Ginsenoside Rg3	Panax Ginsen	Colon CSCs
Nv-128	Soy (Isoflavone Derivative)	Ovarian CSCs
Broussoflavonol B	Broussonetia Papyrifera	Breast CSCs
Shikonin	Arnebia Euchroma	Glioma CSCs
Curcumin	Curcuma Longa L.	Rectal CSCs, Breast CSCs
Piperine	Pepper	Breast CSCs
Resveratrol	Grape, Peanut, Polygonum Cuspidatum	Breast CSCs
Morusin	Morus Alba L.	Cervical CSCs

Table 1: Most of the natural inhibitors of csc inhibits by blocking the Hh, Wnt, NOTCH pathway.

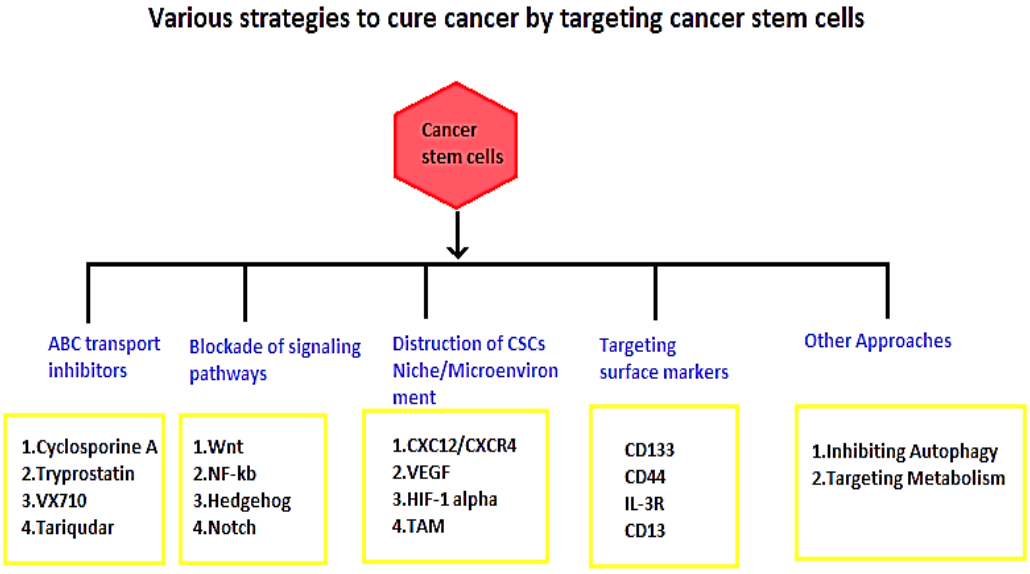
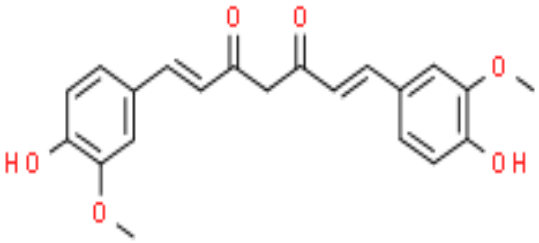


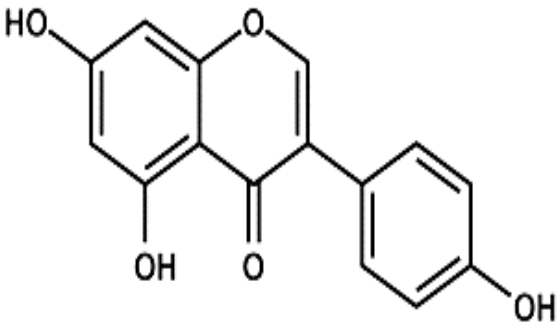
Figure 5: Natural CSC inhibitors.

Example of natural inhibitors

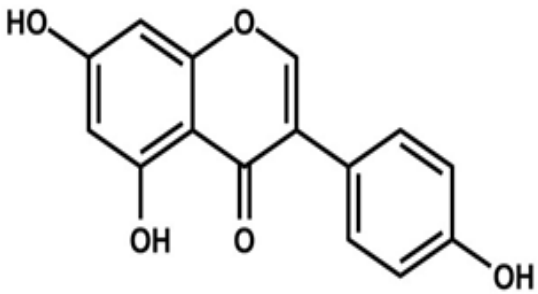
1. Curcumin



2. Genistein



3. Piperine



B) Verteporfin

Verteporfin inhibits activation of the YAP by preventing its binding to TEAD and suppresses tumor growth in independent manner.[37] Verteporfin is new compound as a new target for cancer therapy. The studies shows that vertrporfin has anticancer effects on various malignances which includes esophageal.[39] pancreatic[40] and breast[38] cancers. On the basis of these previous studies found that the, verteporfin-mediated inhibition of YAP expression may result in the regulation of the molecular functions induced by YAP in ICC progression.

Table 2: Some of cancer cell inhibitors.

Target	Cancer Type	Inhibitor	Result	Reference
YAP1	Bladder	Verteporfin	Combination of YAP1 and COX2 inhibitors with chemotherapy attenuated CSC properties and enhanced chemotherapy response.	[21]
	NSCLC Bladder	Verteporfin	Verteporfin attenuated the resistance to EGFR inhibitors.	[21,51,52]
CD44	Breast	Anti CD44 antibody	Nanoparticles with CD44 antibody and gemcitabine specifically targeted CD44+ cells.	[33]
CD133	Ovary	Anti CD133 antibody-toxin conjugate	Cellular growth was inhibited and tumour progression was suppressed in a mouse model.	[34]
Notch2 and Notch3	Various cancers Small-cell lung	Tarextumab	Tumorigenesis and cellular growth were suppressed and chemotherapeutic efficacy was increased.	[39]
			A phase IBM trial showed good tolerability and anti-tumour effect.	[40]
ALDH1	Breast	Histone deacetylase inhibitor	CD44+CD24−/low cell population was decreased and stemness markers were downregulated.	[27,28]
	NSCLC	Disulfiram	Combination of disulfiram and copper downregulated stemness-related genes.	[29]
			When combined with diethylamino-benzaldehyde desensitized resistant cells to cisplatin.	[30]
			A phase II trial showed prolonged survival when disulfiram was combined with cisplatin and vinorelbine.	[31]
	Ovary	Solanum inconnu extract	Notch1 and FoxM1 were downregulated, which resulted in increased chemotherapeutic sensitivities.	[32]
Hedgehog	Bladder	Cyclosporine	Tumour formation was suppressed via inhibition of GALNT1 that mediates SHH signalling.	[35]
	Lung	GDC-0449	Stemness-related features were suppressed in both NSCLC and small-cell lung cancer cells.	[36]
STAT3	Breast	STAT3 inhibitor VII	Combination of STAT3 inhibitor and carboplatin abrogated carboplatin-induced ALDH+ cell enrichment.	[15]
Wnt/β-catenin	Breast	Pyrvinium pamoate	$CD44^{+}CD24^{-/low}$ and $ALDH^{+}$ cells were suppressed by downregulating *NANOG*, *OCT4*, and *SOX2*.	[46]
	Breast	Resveratol	Resveratol, which suppressed Wnt/β-catenin pathway, inhibited CSCs and induced autophagy.	[47]
	Ovary	Imatinib	CSC activity was suppressed when combined with platinum chemotherapy.	[48]
			Phase II clinical trials had only a modest impact on the prognosis of ovarian cancer patients.	[49,50]

Table 3: Patent citation.

Sr. no.	Publication number	Public. Date	Assignee	Title
1	WO2009148623A2	2009-12-10	Stc.Unm	Methods and related compositions for the treatment of cancer
2	US6878688B2	2005-04-12	Celecure As	Method of treatment of malignant neoplasms and complex preparation having antineoplastic activity for use in such treatment
3	US5932243A	1999-08-03	Novartis Ag	Galenical formulations

CONCLUSION

In this review, we have discussed about the CSC and the mechanism for targeting the CSC's. It shows the various therapeutic challenges for different cancers. By observing the complexity of the CSC and non-CSC it is very difficult to eliminate all the cancer cells. Hopefully the addition of the CSC targeting agents with the conventional drugs shows the satisfactory effect against both CSC and non-CSC's. Most of the CSC inhibitors shows their effect by blocking the pathway for CSC which weakens the CSC's or destroys them. Some of the inhibitors are effective alone or in combination. The study indicates that the CSC's can be controlled or destroyed by these inhibitors.

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