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RESEARCH ARTICLE

Decoding Cancer Stem Cells: A Game Change in Oncology Therapeutics

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Abstract

The objective of this article is to identify cancer stem cells (CSCs) as a more critical target than cancer cells (CCs) to achieve cancer therapy. To effectively solve cancer, it is essential to identify the most critical issue and to use the right medicine to solve the problem. The inability to solve cancer is due to inadequacies in existing oncology approaches, resulting in a global mortality exceeding 10 million annually. Cancer stem cells became known in 1997. The discovery of cancer stem cells identified these cells as the most critical issue of cancer to initiate tumor growth and to cause fatal effects of cancer. Thus, the elimination of CSCs is very critical to the success of cancer therapy. Cancer establishments recognized the importance of CSCs, but they used wrong drugs to result in failure to solve this critical issue. Cancer evolves due to wound unhealing. Wound healing requires the proliferation and the terminal differentiation of progenitor stem cells (PSCs). Wound unhealing is attributable to the collapse of chemo-surveillance which is the nature's creation to ensure perfection of wound healing to avoid disastrous consequences of wound unhealing, with cancer representing the most severe pathological consequence. Wound unhealing forces PSCs to evolve into CSCs. Thus, the appearance of CSCs is critically linked to wound unhealing. Therefore, induction of terminal differentiation is the only option to solve CSCs. Myelodysplastic syndromes (MDSs) are diseases attributable entirely to CSCs, which are a model to test the effectiveness of drugs against CSCs. Cell differentiation agent-2 (CDA-2), which is a drug of wound healing metabolites purified from urine we produced, is the best drug for the therapy of MDSs. CDA formulations patterned after CDA-2 are perfect cancer drugs to achieve life-long survivor of cancer patients through elimination of CSCs and CCs by induction of terminal differentiation and restoration of chemo-surveillance.

Keywords: Cancer Stem Cells, Cell Differentiation Agents, Chemo-Surveillance, Terminal Differentiation, Wound Healing.

1. Introduction

Cancer therapy had a bad start to rely on toxic chemicals to kill cancer cells (CCs). Perpetual proliferation of CCs is the most outstanding symptom of cancer. Naturally, killing of CCs is a legitimate choice. But the selection of toxic chemicals as the killing method is wrong, because proliferation is not limited to CCs. It is also needed for the turnover and growth of normal stem cells which are mostly unipotent stem cells. Selection of DNA interacting chemicals is particularly bad. DNA modifications can turn cells if not killed into monstrous cells nobody can handle. Cytotoxic agents and radiation are very effective to kill CCs, which were the drugs used to combat cancer when President Nixon declared War on Cancer during 1971-1976, which was not successful [1]. If a cancer drug is employed as a presidential project to receive unlimited support from national resources but fails to achieve its goal, it is fair to conclude that the drug employed is not good for cancer therapy and should

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be removed. Cancer establishments realized that chemotherapy and radiotherapy were unable to solve cancer. They did not have other choice. So, they kept using those failed drugs to treat cancer patients while searching for the replacements. They held on to the principle of cell killing to search for the replacements, focusing on gene therapy during 1976-1996, on anti-angiogenesis therapy during 1996-2016, and now on immunotherapy from 2016 onward until may be 2036 [2]. They did not find drugs that were better than the failed cytotoxic agents and radiation to kill CCs and to cause tumor to disappear. The kept on using failed cancer drugs to treat cancer patients and the outcome was as expected that cancer mortality kept on escalating. It has reached 10 million record annually worldwide [3]. Health profession is an authoritarian profession. When the mistake is made at the very top. There is no mechanism to rectify the mistake. The mistake carries on to hurt cancer patients.

CSCs became known in 1997 [4]. The discovery of CSCs unraveled CSCs as the cells responsible for the initiation of cancer growth and to cause the fatal effects of cancer [5-9]. Thus, CSCs are the most critical battle field to decide the outcome of cancer therapy [10-13]. Our studies of abnormal MEs [14-16], chemo-surveillance [17-19], wound healing [20-23] and CDA formulations [24-28] are closely related to the issue of CSCs, thus, we are in a unique position to offer the solution of CSCs to save cancer patients [3, 29-33]. We have developed a solution that can easily put cancer away. This solution is actually the creation of the nature for the perfection of wound healing. Wound healing comes naturally if the protection mechanisms on CSCs and their precursors PSCs are functioning well. Collapse of protection mechanisms results in the evolution of cancer. Restoring the protection mechanisms of wound healing is thus the right and the easiest strategy of cancer therapy [34].

2. Commentaries and Discussion

2.1 Cancer Evolves due to Wound Unhealing

Establishing a valid concept of cancer is very important to the solution of cancer. Cancer evolving due to wound unhealing was a concept introduced by the great German pathologist Virchow in 1858 [35]. Virchow was a very well respected pioneer on cancer, but his view of cancer evolving due to wound unhealing was not well accepted by the cancer establishments, had his view accepted by the cancer establishments. Cytotoxic chemotherapy would not come into practice to stir up cancer as a giant killer of cancer patients. Cytotoxic chemotherapy creates wound, definitely is contraindication to his concept. Virchow's concept of cancer due to wound unhealing was brought up once 128 years later by Dvorak [36]. Again, it was ignored by the cancer establishments. We pursued cancer therapy unknowingly following Virchow's guidance of wound healing. Our studies of abnormal MEs [14-16], chemo-surveillance [17-19], and wound healing [20-23] provided experimental data to support the validity of cancer evolving due to wound unhealing. Evidently, wound healing is a very important issue of health, so that the nature creates chemo-surveillance and immuno-surveillance to ensure perfection of wound healing, chemo-surveillance to heal wounds caused by toxic chemicals or physical means, and immuno-surveillance to heal wounds caused by infectious agents. Chemo-surveillance and immuno-surveillance can act synergistically on wound healing to prevent disastrous consequences of wound unhealing. Chemo-surveillance was a terminology we created to describe an observation that healthy people were able to maintain a steady level of metabolites active as differentiation inducers (DIs) and differentiation helper inducers (DHIs). DIs are metabolites capable of eliminating telomerase from abnormal MEs and DHIs are metabolites active as inhibitors of MEs which can greatly potentiate the activity of DIs. DIs and DHIs are most likely degradative products of erythrocytes that contribute active DIs as acidic peptides, membrane fragments containing phosphatidylinositol designated as pigment peptide-0 (PP-0), arachidonic acid (AA) or dicycloprostaglandins as liposomal complexes with pregnenolone designated as organic acid-0.79 (OA-0.79) [25, 37, 38] and active DHI as uroerythrin [39]. Active DHIs as steroid metabolites must come from organs actively involved in steroid hormone metabolism, whereas DHIs as amino acid derivatives are most likely coming from liver. The production of DIs and DHIs is constant except pregnenolone which depends on ages. According to Morley, the production of pregnenolone is bell shape with a peak production of around 50 mg daily at the ages of 20 to 25 [40]. It appears that chemo-surveillance is always operating at the maximum capacity. The functionality of chemo-surveillance is dictated by renal excretion that can be influenced by pharmacologically active metabolites such as tumor necrosis factor (TNF) which can increase hyperpermeability of blood vessel to promote excessive excretion of low molecular weight metabolites [41, 42]. Therefore, pathological

conditions triggering the production of TNF is very damaging to chemo-surveillance. TNF is also named cachectin after its notorious effect to cause cachexia symptoms. A manifestation of cachexia symptoms is the excessive urinary excretion of low molecular weight metabolites. DIs and DHIs are among low molecular weight metabolites excreted. Pathological conditions triggering the production of TNF often can lead to cancer evolution. On the other hand, chemicals that can antagonize the action of TNF are effective chemo-preventive agents of cancer. Myelodysplastic syndromes (MDSs) are a classical case to demonstrate the evolution of cancer due to wound unhealing. MDSs often start with a display of immunological disorder or wound which prompts the production of inflammatory cytokines [43]. TNF among such cytokines is the critical factor related to the development of MDSs, because antibody of TNF can effectively prevent the progression of MDSs [44]. TNF causes excessive apoptosis of bone marrow stem cells, thus severely affecting the ability of the patient to produce hematopoietic cells such as erythrocytes, platelets or neutrophils. TNF also causes cachexia symptoms to result in the collapse of chemo-surveillance to disrupt wound healing. Antibody of TNF can stop the damaging effect of TNF. Phenylacetylglutamine can also effectively antagonize TNF to prevent excessive excretion of DIs and DHIs [17]. By the protection of the functionality of chemo-surveillance, we have shown that phenylacetyl-glutamine was very effective chemo-preventive agent against potent hepatocarcinogen aflatoxin B1 [45]. It was also a good therapeutic agent against early stage cancer patients [17, 46]. This is a clear indication that wound healing if proceeds perfectly under effective protection of chemo-surveillance, cancer can be avoided even challenged with potent carcinogen. If chemo-surveillance is destroyed, wound may not heal to result in the evolution of cancer. Wound unhealing in most case is due to the collapse of chemo-surveillance to achieve completion of terminal differentiation of PSCs. PSCs are the most primitive stem cells to initiate the development of organs or tissues during fetal stage, which are also the cells involved in wound healing [20]. Wound healing requires the proliferation and the terminal differentiation of PSCs. Proliferation is under the control of prostaglandins (PGs) and terminal differentiation is achieved by chemo-surveillance. Wound unhealing will force PSCs to evolve into CSCs to escape the limitation of contact inhibition which control the extent of proliferation of PSCs. It takes a single hit to silence ten-eleven translocator-1 enzyme, which is the enzyme to direct lineage transitions, to achieve the conversion. This is very easy for PSCs to accomplish, since these cells are equipped with exceptionally active MEs [33]. The appearance of CSCs is critically linked to wound unhealing. The proliferation of CSCs still cannot heal the wound, since the problem of wound unhealing is the collapse of chemo-surveillance. By the same reason, CSCs are forced to progress to faster growing CCs through chromosomal alterations such as translocations to activate oncogenes or deletions to inactivate suppressor genes. So, the evolution of cancer starts from PSCs to CSCs, and then from CSCs to CCs. CSCs are PSCs minus TET-1 enzyme. CSCs are very similar to PSCs on cell feature, antigenicity and biological mission. CCs have multiple chromosomal alterations to behave vastly different from PSCs. CSCs, CCs, chemo-surveillance and immuno-surveillance are all significantly involved in the evolution of cancer. A perfect cancer therapy must be able to take care of all contributing factors of cancer. Focusing on a specific issue is insufficient. Cancer establishments have been fighting cancer solely on CCs, and totally ignored other issues. That is why they are unable to put cancer away. Cytotoxic therapies focusing on the killing of CCs can only benefit a quarter of cancer patients in the early stage whose chemo-surveillance have not yet been fatally damaged, relying on the recovery of chemo-surveillance to subdue surviving CSCs which are not responsive to cytotoxic therapies [3, 12, 33, 34, 46]. The elimination of CSCs by chemo-surveillance plays a decisive role on the success of cytotoxic therapies. Cytotoxic therapies are ineffective to save three quarter of cancer patients in advanced stage whose chemo-surveillance have been fatally damaged. The ineffectiveness against CSCs and the contribution to the damage of chemo-surveillance are the reasons cytotoxic cancer therapies fail to accomplish cancer therapy.

2.2 CSCs as the Most Critical Battle Field to Decide the Outcome of Cancer Therapy

Identification of the critical battle field and the employment of the right medicine are essential to the success of cancer therapy. Targeting CCs so far is not successful, because CCs are not a critical battle field. CCs are the most abundant cells contributing the biggest battle field. But these cells are not that fatal. The critical battle field is CSCs, contributing the most fatal effects of cancer such as metastasis,

drug resistance, anti-apoptosis, angiogenesis, unresponsiveness and recurrence [5-9]. Cancer establishment knew CSCs were the most critical battle field to decide the outcome of cancer therapy. Approximately 18 years ago, pharmaceutical giant GSK put up 1.4 billion, the most expensive investment on a cancer drug, to develop monoclonal antibodies against CSCs invented by the scientists of Stanford University, which was not successful because killing of CSCs was not an option to solve CSCs. It was very strange that there was no follow up as if CSCs were no longer a critical issue. The focus of attention shifted to immunotherapy. In fact, CSCs remained a very popular issue in oncological field [47-52]. Cancer establishments are capable of identifying the important issues of cancer, but often pick the wrong medicine or wrong battle field to result in the failure to solve the important issues. The identification of CSCs as the most critical issue of cancer was correct, but the use of monoclonal antibodies to kill CSCs was wrong, because killing CSCs was not an option to solve CSCs. The appearance of CSCs was critically linked to wound unhealing [23, 30, 31], therefore, induction of terminal differentiation of CSCs was the only option to solve CSCs [2, 11, 20, 32]. The identification of perpetual proliferation of CCs as an important issue of cancer was correct, but the selection of CCs as the primary battle field and the use of toxic agents to put out replicating cells were wrong. CSCs and CCs are two competing battle fields to solve perpetual proliferation of CCs. Before CSCs became known in 1997, CCs are the only known battle field. The selection of this less important battle field was excusable. CSCs, although only a tiny battle field, were a far more important battle field than CCs to contribute to the fatality of cancer as above described. The selection of toxic agents to combat cancer was a grave mistake, since creating wounds was contra-indication of cancer therapy. The identification of aberrant tRNA methylation around 1966 and DNA methylation around 1985 was correct, but the emphasis on methylated tRNA and DNA was wrong, because the key issue was abnormal MEs [11, 15, 29, 33]. The promotion of immunotherapy

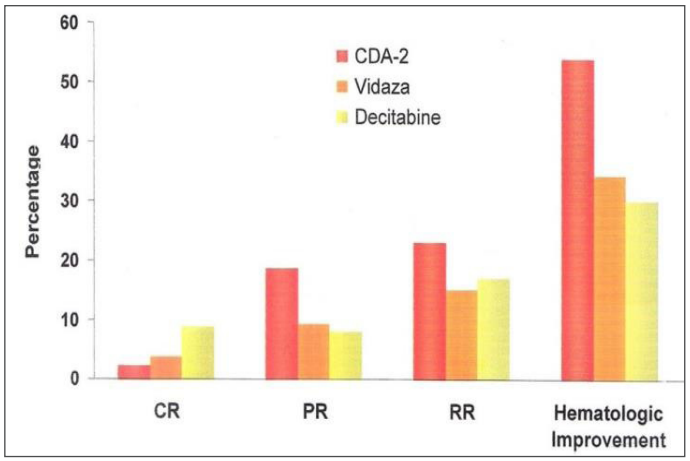

Figure 1. *CDA-2 as the Best Drug for the Therapy of MDSs*

of cancer was questionable, because the problem of cancer was basically a problem of growth regulation going awry [33, 53]. Immunology has nothing to do with growth regulation. Immunology may play certain roles on cancer. For example, immuno-surveillance is a very important mechanism to ward off cancer, and to eliminate pathological cells marked by program death antigen. Elimination of CSCs is most critical issue to the success of cancer therapy [3, 10, 12, 33]. Can immunotherapy eliminate CSCs? Put those promising immunotherapeutic agents on MDSs to get the answer. If immunotherapy cannot eliminate CSCs, it is not helpful to reduce cancer mortality. Cancer establishments are hopelessly trapped in belief that killing of CCs is the best strategy to achieve cancer therapy. The solution of CSCs is far more important than the solution of CCs, although CSCs constitute only a very small minority of side population of cancer. The mean CSC count for malignant astrocytoma is less than 1%, but for glioblastoma it can increase to 3-5% [54]. Astrocytoma is responsive to chemotherapy and radiotherapy, but glioblastoma is unresponsive to chemotherapy and radiotherapy. Thus, a primary cancer with CSCs less than 1% can be cured by cytotoxic therapy, but if a primary cancer with CSCs more than 3% becomes unresponsive to cytotoxic therapy. This is the basis of our arguments that the winner of the contest to eradicate CSCs wins the contest of cancer therapy [10]. It is also the definitive judgement that cytotoxic therapies are bound to fail if chemo-surveillance cannot be recovered to subdue the surviving CSCs [2, 12, 34, 46]. Cytotoxic agents

create wounds to promote the proliferation of CSCs to repair the wound, thus contributing to the increase of CSCs population [55]. If chemo-surveillance is destroyed beyond recovery to functional state to subdue surviving CSCs, the patient is going to become like glioblastoma patients unresponsive to further treatments. This is the reason why such a tiny battle field of CSCs can dictate the success of cancer therapy.

MDSs are classical diseases to demonstrate the evolution of cancer due to wound unhealing at the stage of PSCs being forced to become CSCs, and before progressing to acute myelocytic leukemia. The propagating pathological cells of MDSs have been identified as CSCs [56]. MDSs are diseases ideal for the evaluation of drugs against CSCs. So far, Vidaza, Decitabine and CDA-2 are the three drugs approved by the Chinese FDA for the therapy of MDSs. CDA-2 is a drug of wound healing metabolites purified from urine we produced [24]. Vidaza and Decitabine are also the two drugs approved by the US FDA. Professor Ma, the Director of Harbin Institute of Hematology and Oncology, was instrumental in carrying out clinical trials of all three MDSs drugs. According to his assessments based on two cycles of treatment protocols, each 14 days, CDA-2 had a noticeable better therapeutic efficacy based on cytological evaluation, although slower to reach complete response, and a markedly better therapeutic efficacy based on hematological improvement evaluation, namely becoming independent on blood transfusion to stay alive as shown in Figure 1, which is reproduced from the reference [57].

Therapy of MDSs requires the conversion of pathological CSCs to become functional erythrocytes, platelets or neutrophils. Thus, inactivation of abnormal MEs is the only option to achieve therapy of MDSs. CDA-2 achieves inactivation of abnormal MEs through destabilization of abnormal MEs targeting on the tumor factor telomerase of abnormal MEs [16, 33], whereas Vidaza and Decitabine inactivate abnormal MEs through covalent bond formation between methyltransferase (MT) and 5-azacytosine incorporated into DNA [58]. The pharmacological action of CDA-2 is selective toward CSCs to spare adverse effects on normal stem cells, whereas the pharmacological action of Vidaza and Decitabine is non-selective to also affect normal stem cells. CDA-2 is devoid of adverse effects, whereas Vidaza and Decitabine are proven carcinogens [59, 60] and very toxic to DNA [61-63]. CDA-2 is clearly the drug of choice for the therapy of MDSs with superior therapeutic efficacy and devoid of adverse effects. We are the clear winner on the development of cancer drug [10]. Our winner's status, however, is denied by cancer establishments who put up a rule of tumor shrinkage as a criterion of cancer drugs. The therapeutic endpoint of CDA-2 and CDA formulations is terminal differentiation, which cannot make tumor to shrink. The rule of tumor shrinkage is a grave mistake of cancer establishments to cause the failure of cancer therapy.

Effects of cancer therapies currently in practice on the important parameters of cancer such as CSCs, CCs, unipotent stem cells (USCs), chemo-surveillance, immuno-surveillance, tumor shrinkage and life-long survival are summarized in Table 1. CSCs are but a very tiny battle field of cancer, but this battle field is the most critical battle field to determine the outcome of life-long survival of cancer patients. Vidaza and Decitabine can also eliminate CSCs to achieve life-long survival. But these two drugs can have severe adverse effects on USCs to affect patient survival. The damaging effects on chemo-surveillance and immuno-surveillance may also cut down life-long survival. It is always a good advice to stay away from using drugs that can alter DNA structure. Such drugs can cause unpredictable damages. Cancer establishments must remove tumor shrinkage as a requirement of cancer drugs. They have approved Vidaza and Decitabine that cannot cause tumor to shrink. They should also remove the requirement of tumor shrinkage on CDA formulations. Chemotherapy, radiotherapy and immunotherapy target on the largest battle field of CCs. But the decision on life-long survival is not on CCs. The complete elimination of CCs may offer short term survival. Life-long survival depends on the restoration of chemo-surveillance. So, only early stage cancer patients whose chemo-surveillance have not yet been fatally damaged can benefit from these therapies. Majority of cancer patients in advanced stage can only survive for a short period even reached complete remission. This is the reason cancer mortality keep on escalating. Cancer drugs interacting with DNA should be removed, which have failed to achieve the goal of War on Cancer during 1971-1976 [1]. These drugs are responsible to cause the death of 10 million cancer patients around the world annually. Targeted cancer drugs are excellent DHIs. Although these drugs alone cannot induce terminal differentiation of CSCs, these drugs can improve chemo-surveillance to subdue CSCs. CDA and targeted cancer drugs are the only drugs to achieve life-long survival.

Table 1. *Effects of Cancer Therapies on the Important Parameters of Cancer*

Cancer Therapies	CSCs	CCs	USCs	Chemo-surveillance	Immuno-surveillance	Tumor shrinkage	Life-long Survival
CDA	+	A	-	+	0	-	+
Vidaza & Decitaine	+	A	+	-	-	-	-
Chemo	-	B	+	-	-	+	+ Early - Late
Radio	-	B	+	-	-	+	+ Early - Late
Immuno	-	B	-	-	+	+	+ Early - Late
Targeted	-	A	-	+	0	-	+

Effect on CSCs: + means able to induce terminal differentiation and – means cannot induce terminal differentiation; on CCs: A means induction of terminal differentiation and B means cell killing; on USCs: - means does not have effect and + means can cause damage; on chemo-surveillance: + means can improve and – means can damage; on immuno-surveillance: 0 means does not have effect, + means can improve and - means can damage; on tumor shrinkage: - means cannot induce tumor shrinkage and + means can induce tumor shrinkage; on life-long survival: + means can result in life long survival, the death is unrelated to cancer and CDA treatment and – means cannot result in life long survival, the death can be due to adverse effects of Vidaza and Decitabine. + Early means early stage cancer patients can achieve life-long survival, - Late means late stage cancer patients cannot reach life-survival.

2.3 Development of CDA Formulations to Target CSCs

CDA-2 is the best drug to solve CSCs. CDA formulations patterned after CDA-2 are likely the drugs of choice for the solution of CSCs. We have carried out extensive studies of natural and non-natural DIs and DHIs for the manufacture of CDA formulations [24-28, 37, 64]. Active DIs and DHIs are summarized in Table 2 and 3. $ED_{25,\ 50\ and\ 75}$ of DIs and reductive $index_{0.5}$ ($RI_{0.5}$) are included for easy manufacturing of CDA formulations. $RI_{0.5}$ of a DHI is equivalent to ED_{25} of a DI, which can be determined by the procedure published [64].

Table 2. *Active DIs*

DIs	ED_{25} (μM)	ED_{50} (μM)	ED_{75} (μM)
ATRA	0.18	0.36	0.75
PGJ2	7.9	13.8	20.5
PGE2	20.6	32.0	40.5
DicycloPGE2	21.0	43.5	-
AA	21.0	42.0	-
BIBR1532	32.3	43.7	55.1
Boldine	60.1	78.8	94.2

Active DIs and DHIs can be excellent cancer drugs. ATRA is the standard care of acute promyelocytic leukemia [65], and gleebec is the standard care of chronic myeloid leukemia [66]. ATRA is an indirect DI. It requires the expression of the receptor of ATRA, namely RAR, for ATRA to be effective. RAR is the repressor of oligoisoadenylate synthetase. The association of RAR with ATRA turns on the transcription of oligoisoadenylate synthetase [67] The product of this enzyme, oligoisoadenylate, is the direct DI to destabilize abnormal MEs. The rest of active DIs listed in Table 2 are DIs to act directly on abnormal MEs. BIBR1532 and baldine are approved drugs for cancer therapy as telomerase inhibitors, and PG derivatives are approved drugs for the delivery. Change of indication for the approved drugs does not require clinical trials as long as the drugs requested for new indication.

As shown in Table 3, SAHH and MT inhibitors are much better DHIs than MAT inhibitors. MAT is the largest and the most stable enzyme of the three MEs [68]. The association with telomerase further increases its stability. It takes large amounts of inhibitors to function as active DHIs. Inhibitors of MT and SAHH are better DHIs. Pregnenolone is a major DHI of CDA-2[25].

Apparently, pregnenolone is an important DHI of chemo-surveillance. It is the master substrate of all biologically active steroids. According to Morley [40], the production of pregnenolone is bell shape in relation to ages. The oldest and the youngest produce the least amount of pregnenolone. These are the two age groups most vulnerable to develop cancer. Therefore, pregnenolone is a single metabolite to have profound influence on the evolution of cancer. It is our choice of DHI to make CDA-CSC formulations,

Table 3. *Active DHI*

SAHH Inhibitors	RI0.5 (μ M)	STIs	RI0.5 (μ M)
Pyrvinium Paomoate	0.012	Sutent	0.28
Vitamin D_3	0.61	Berberine	1.62
Dexamethasone	0.75	Vorient	10.1
Beta-Sitosterol	1.72	Gleebec	11.9
Dihydroepiandrosterone	1.79	Selenite	19.7
Prenisolone	2.22		
Hydrocortisone	4.59	Polyphenols	$RI_{0.5}$ (μM)
Pregnenolone	7.16		
		Tannic Acid	0.37
MT Inhibitors	$RI_{0.5}$ (μM)	EGCG	0.62
		Resveratrol	1.16
Uroerythrine	1.9	Curcumin	1.24
Hycanthone	2.1	Kuromanin	1.43
Riboflavin	2.9	Coumestrol	1.95
		Genisteine	2.19
MAT Inhitors	$RI_{0.5}$ (μM)	Pyrogallol	3.18
		Silibinin	3.80
Indol Acetic Acid	220	Caffeic Acid	3.87
Phenylacetylvaline	500	Ellagic Acid	4.45
Phenylacetylleucine	780	Gallic Acid	5.35
Butyric Acid	850	Ferulic Acid	7.41
Phenylbutyric Acid	970	Phlorogllucinol	38.82

although it is not the most active DHI. The finding of signal transduction inhibitors (STIs) as excellent DHIs is expected, since signal transductions (STs) tend to produce factors to promote the activity of MEs. STIs are excellent targeted anticancer drugs. The finding of polyphenols as excellent DHIs is a surprise. EGCG was found a good STI to affect DNA methylation [69]. It is possible that DHIs activities of polyphenols are mediated through STIs. Polyphenols are generally regarded as healthy foods. The finding of polyphenols as excellent DHIs increases their credibility as healthy foods.

Effective CDA formulation can be the plasma concentrations of ED_{25} of a DI + $3xRI_{0.5}$ of a DHI. or ED_{50} of a DI + $2xRI_{0.5}$ of a DHI, or ED_{75} of a DI + $RI_{0.5}$ of a DHI [25]. DIs are more important components of CDA formulations that DHIs. But the inclusion of DHIs is necessary, because DIs alone tend to result in the dissociation of ternary MEs into individual enzymes. Methyltransferase as monomeric enzyme has a tendency to be modified by protease to become nuclease to disrupt differentiation process to result in incompletion of terminal differentiation. The damages created by nuclease can be repaired to resume malignant growth. Therefore, the therapy with ATRA alone can be very excellent, but patients often recur within one year [65]. The inclusion of DHIs can keep MT-SAHH as dimer to prevent modification of MT to become nuclease, so that induction of terminal differentiation can reach completion to avoid recurrence. In the selection of DIs and DHIs, we must also take into consideration non-cancer issues such as blood brain barrier of brain cancer, hypoxia factors of melanoma and collagen envelop of pancreatic cancer to overcome the influence of non-cancer issues.

3. Conclusion

CSCs are only a tiny battle field in comparison to CCs. This tiny battle field is the most critical battle field to decide the outcome of cancer therapy, because CSCs contribute most of fatal effects of cancer. Eradication of CSCs is essential to achieve cancer therapy. The appearance of CSCs in the primary site is critically linked to wound unhealing. Induction of terminal differentiation, a critical mechanism of wound healing, is the only option for the solution of CSCs. Thus, CDA formulations are perfect cancer drugs to achieve life-long survival of cancer patients through elimination of CSCs and CCs by induction of terminal differentiation and restoration of chemo-surveillance.

Concent and Ethical Approval

It is not applicable.

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Competing Intersts

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