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CDA Formulations as the Best Drugs to Turn Around Cancer Mortality from Escalation to Deceleration

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ABSTRACT

The objective of this article is to rectify cancer therapies to turn around cancer mortality from escalation to deceleration. Cancer therapy had a bad start to rely on toxic chemicals to kill cancer cells (CCs). That was an unintentional mistake made by cancer establishments at a time we did not have complete knowledge of cancer. The incidence of cancer keeps on increasing as the world becomes more industrialized. The escalation of cancer incidence and the mishandling of cancer therapies stir up cancer as a giant killer to claim 10 million casualty worldwide a year. Now we have better knowledge of cancer. We know better ways to put out cancer. Unfortunately, the health profession is an authoritarian profession. When the mistake is made at the very top, there is no mechanism to rectify the mistake. Cancer patients continue to suffer.

Cancer stem cells (CSCs) became known in 1997. The discovery of CSCs unraveled a very important issue of cancer. It became evident that, although CSCs constituted only a very small side population, these cells were responsible for the initiation of tumor growth, and the treatment failure. Thus, elimination of CSCs is essential to the success of cancer therapy. Our studies of abnormal methylation enzymes (MEs), chemo-surveillance, wound healing and cell differentiation agent (CDA) formulations are closely related to CSCs. Therefore, we are in a unique position to offer CDA formulations as the best solution of CSCs and CCs to put out cancer to turn around cancer mortality from escalation to deceleration. The therapeutic endpoint of CDA formulations is terminal differentiation of CSCs and CCs that cannot make tumor to disappear. The tumor residue is harmless. If it is a concern, it can be safely removed by surgery.

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Introduction

Cancer therapy had a bad start to rely on toxic chemicals to kill CCs to eliminate the most outstanding symptom of cancer, the perpetual proliferation of CCs. Cytotoxic chemotherapy was actually a tragic byproduct of World War II. During the war, toxic sulfur mustard bombs were used. Victims of toxic gas all displayed depletion of leukocytes in their blood specimens, which inspired oncologists to employ toxic chemicals to treat leukemia patients. Toxic chemicals were indeed very effective to eliminate leukemia cells to achieve therapy of leukemia. Cytotoxic chemotherapy, thus, became a standard care of cancer, and the disappearance of CCs in the case of hematological cancers and the disappearance of tumor in the case of solid cancers became the standard criteria for the evaluation of cancer therapy. Both were wrong, because cancer evolved due to wound unhealing [1, 2]. Killing CCs to create wound was contraindication of cancer therapy. The mistakes were made at a time we did not have complete knowledge of cancer. The mistakes were excusable. Cytotoxic chemotherapy and radiotherapy were the major therapies employed in the combat of cancer when President Nixon declared War on Cancer during 1971-1976, which was not successful [3]. If a cancer treatment is employed as a presidential project to receive unlimited support from national resources, but fails to achieve the goal to put out cancer. It is fair to conclude that this treatment is not good for cancer therapy which should be dismissed. Apparently, cancer establishments agreed to the conclusion that cytotoxic agents could not solve cancer and started to search for other cancer drugs to replace failed cytotoxic agents [4]. They did not find cancer drugs that could kill CCs to cause the shrinkage of tumor better than the failed cytotoxic agents to win the War on Cancer, and kept using the failed cytotoxic drugs to treat cancer patients, that was inexcusable to result in ever escalation of cancer mortality to reach 10 million mark around the world in 2019 with an annual increment of 5% according to the experts of NCI [5].

CSCs became known in 1997 [6]. The discovery of CSCs unraveled a very important issue of cancer. It became evident that, although CSCs constituted only a very small side population, these cells were responsible for the initiation of tumor growth and the treatment failure [7-10]. Therefore, the success of cancer therapy is critically dependent on the elimination of CSCs [11]. Our studies of abnormal MEs [12-14], chemo-surveillance [15-17], wound healing [18-22] and CDA formulations [23-26] are very closely related to the issue of CSCs. Thus, we are in a unique position to offer best solution of CSCs that were a major factor to contribute to the failure of cancer therapies. We have to convince cancer establishments that saving cancer patients can be as easy as healing wounds that come naturally without having to put up

any efforts. To save cancer patients, we have to approve CDA formulations to restore the functionality of chemo-surveillance that was specifically destroyed in cancer patients [27-37]. A switch of cancer therapy from cytotoxic agents that create wounds to CDA formulations that heal wounds can make a dramatical reversal of cancer mortality from escalation to deceleration.

Commentaries and Discussion

Commanding Principle of Killing CCs to Direct Cancer Therapies is Basically Wrong

Cytotoxic chemotherapy was a tragic byproduct of World War II. At that time we did not have complete knowledge of cancer. The perpetual proliferation of CCs was the most outstanding symptom of cancer. Naturally, employing toxic chemicals to eliminate the most outstanding symptom of cancer was a popular choice of cancer therapy. Eventually, it became the commanding principle to lock the entire health profession to the wrong direction to result in cancer as a giant killer of cancer patients. Now we have better knowledge of cancer. We know CDA formulations are better cancer drugs. But cancer establishments stand in the way to block CDA formulations that can come to the rescue of cancer patients desperately in need of help [1,2,11, 26-37]. Cytotoxic approach of cancer therapy and CDA approach of cancer therapy are vastly different approaches of cancer therapies. Cytotoxic therapy is focusing on the elimination of cancer symptom, whereas CDA therapy is targeting on the cause of cancer. Cytotoxic cancer therapy is the choice of cancer establishments, which has failed to win the War on Cancer during 1971-1976 [3], has failed to develop anti-angiogenesis therapy during 1996 - 2016, and now is in a questionable attempt to develop immunotherapy from 2016 onward [4]. The development of anti-angiogenesis was a success, but the success of blocking angiogenesis ended up causing the death of cancer patients due to internal bleeding. It echoes the failure of cytotoxic therapies. The success of reaching complete remission results in the death of cancer patients due to adverse toxic effects or recurrence. The inability to eliminate CSCs and the contribution to the destruction of chemo-surveillance are the reasons to cause the failure of cytotoxic cancer therapies. Immunotherapy has the same problem of cytotoxic cancer therapies to show ineffectiveness against CSCs and to trigger the production of tumor necrosis factor (TNF) to destroy chemo-surveillance. Immunotherapy is definitely a better choice to kill CCs to spare adverse effects on normal stem cells. But it may not be able to save advanced cancer patients like cytotoxic agents [26-37].

The attempt to develop gene therapy during 1976-1996 right after the failure to win the War on Cancer was a right approach of cancer therapy. But it was really difficult to correct chromosomal abnormalities, the cancer establishments did not succeed in developing any gene therapeutic agent. They wasted 20 years to learn the difficult of gene therapy. They did succeed in developing several excellent targeted cancer drugs such as Her-2 Neu, ATRA, and Gleebec and related signal transduction inhibitors (STIs) during this period. These drugs cannot make tumor to disappear and, therefore, are not their favored cancer drugs. Cancer establishments are very keen on the issue of CSCs. Approximately 18 years ago, the 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. Cancer evolves from CSCs due to wound unhealing [38,39]. CSCs are critically linked to wound unhealing. Induction of terminal differentiation is the critical mechanism of wound healing [18]. Which is also the only viable option to handle the issue of wound unhealing involving undifferentiated. PSCs and CSCs [40]. Cancer establishments should accept CDA formulations as valuable drugs to solve CSCs.

Cancer Evolves Due to Wound Unhealing

The concept that cancer evolves due to wound unhealing was introduced by the great German pathologist Virchow in the 19th century [38]. It was again brought up by Dvorak in 1986 [39]. The close relationship between cancer and wound healing was noticed by MacCarthy-Morrough and Martin [41]. We provided the most important details on this subject that included abnormal MEs to promote the exceptional growth needed for the development of fetus, wound healing and malignant cells [12-14, 36]; chemo-surveillance as the nature's creation of allosteric regulation on abnormal MEs for the perfection of wound healing to avoid disastrous consequences of wound unhealing [15-17,29]; DIs and DHIs as wound healing metabolites and the active players of chemo-surveillance [4,15-17,29]; hypomethylation as a critical mechanism of terminal differentiation [42]; mechanism of wound healing and the evolution of cancer due to wound unhealing [4,18-22,25-37]. These studies very convincingly establish the validity of cancer evolving due to wound unhealing. Our carcinogenesis studies also strongly support the validity of this concept. During the challenges of animals with hepatocarcinogens, we noticed the appearance of numerous tiny hyperplastic nodules displaying abnormal MES soon after the application of carcinogens, which must represent the active proliferation of PSCs in the process of healing wounds created by carcinogens [43]. Most of these tiny hyperplastic nodules disappeared soon, indicating the completion of wound healing, and only a few large size hepatocarcinomas appeared later from unhealed tiny hyperplastic nodules. If during the challenge of animals with potent hepatocarcinogens, Antineoplaston A10 was provided to protect the functionality of chemo-surveillance, the appearance of hepatocarcinomas could be prevented as shown in Figure 1, which is reproduced from the reference [44]. Thus, we have provided two very critical experimental data to support the concept of cancer evolution due to wound unhealing.

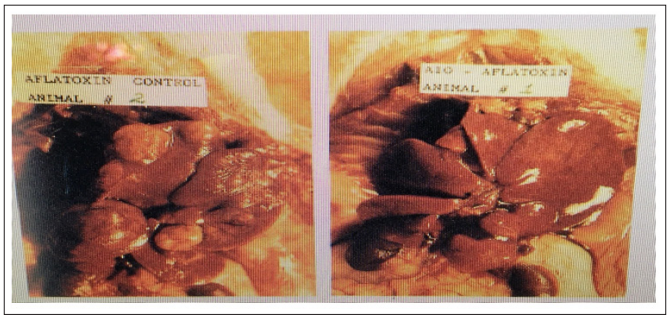

Figure 1: Effective Chemoprevention of Hepato-Carcinogenesis by Phenylacetylglutaime

One experimental datum is the effective prevention of hepatocarcinogenesis by phenylacetylglutamine, namely Antineoplaston A10, induced by potent carcinogen aflatoxin B1, and another experimental datum in the selective destruction of chemo-surveillance in cancer patients as shown in Table 1, which is reproduced from the reference [15]. 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), whereas cancer patients tended to show deficiency of such metabolites [15]. DIs are metabolites capable of eliminating telomerase, which is a specific tumor factor [14], from abnormal MEs, and DHIs are inhibitors of MEs that can strongly promote the activity DIs [15-17]. DIs and DHIs are hydrophobic metabolites

that can be purified from urine by reverse phase chromatography, namely retention by C18 from aqueous solution and recovery by organic solvent. Since peptides share physical chemical properties similar to DIs and DHIs, peptides can be used as surrogate molecules to represent DIs and DHIs [45]. Quantitative assay of plasma and urinary peptides of 108 cancer patients shown in Table 1 indicates that chemo-surveillance is selectively destroyed in cancer patients. Obviously, wound healing is an important health issue, so that the nature creates chemo-surveillance and immuno-surveillance as the protection mechanisms, chemo-surveillance to heal wounds caused by toxic chemicals and physical means [18,19,46], and immuno-surveillance to heal wounds caused by infectious agents. Immuno-surveillance can act synergistically with chemo-surveillance to heal wounds. But immuno-surveillance can also act antagonistically against chemo-surveillance. Immunological responses tend to trigger the production of TNF to induce cachexia symptom, which is very damaging to chemo-surveillance. TNF can cause hyperpermeability of blood vessel to result in excessive excretion of low molecular weight metabolites [47, 48]. DIs and DHIs are among low molecular weight metabolites excreted to result in the collapse of chemo-surveillance. Pathological conditions boosting the production of TNF are detrimental to chemo-surveillance. Inflammation, progression of cancer, cytotoxic chemotherapy and immunotherapy are very damaging to chemo-surveillance to aggravate cancer therapy. Destruction of chemo-surveillance is a major factor to contribute to the failure of cytotoxic cancer therapies and immunotherapy. Since cytotoxic cancer therapies and immunotherapy are ineffective on CSCs, the success of these therapies must rely on the recovery of chemo-surveillance. CDA level of 2.5 may be a critical fatal threshold. Above this level, CDA level may have a chance to recover to subdue surviving CSCs which resist cytotoxic cancer therapies and immunotherapy. Below this level, cancer patients become either unresponsive, or still responsive to reach complete remission, these patients are eventually succumbed to recurrence. Thus, cytotoxic cancer therapies and immunotherapy can only benefit a small number of cancer patients in the early stage. These therapies are responsible for the fatality of advanced cancer patients whose chemo-surveillance have been fatally damaged [33,35-37].

Table 1: Chemo-Surveillance Selectively Destroyed in Cancer Patients

Plasma/Urine Ratios	CDA Level	Patient Number	% Distribution
0.83 - 0.80 (Normal)	5.0	2	1.8
0.80 - 0.60	4.3	7	6.5
0.60 - 0.40 (Responsive)	3.1	18	16.7
0.40 - 0.20	1.8	38	35.2
0.20 - 0.10	0.9	24	22.2
0.10 - 0.02 (Unresponsive)	0.37	19	17.6

Plasma Peptides: nmoles/ml; Urinary Peptides: nmoles/mg Creatinine

Antineoplastons were preparations of wound healing metabolites purified from urine by reverse phase chromatography on C18 as the adsorbant, which were the right indication of cancer therapy. The therapy with Antineoplastons was effective and without adverse effects. Patients responded favorably to the therapy would show CDA levels increasing to the healthy level of CDA-5 [15, 45]. If not, CDA levels would continue to decline. Evidently, not all cancer patients responded favorably to Antineoplaston therapy. Fast growing CCs are known to express a high level of degradative enzymes to salvage substrates for macro-molecular syntheses to support their fast growth. Natural DIs and DHIs may be degraded in fast growing CCs to lose activity. We recommend two sets of CDA formulations: one set CDA-CSC made up by natural DIs and DHIs to access CSCs, and another set CDA-CC made up by non-natural DIs and DHIs to resist enzymatic degradation of fast growing CCs.

Antineoplastons were excellent cancer drugs that could also help terminal cancer patients often refused by conventional oncologists as hopeless patients. The therapy was so different from the cytotoxic therapy, which was banned by the cancer establishments around 1990. The therapy of Antineoplastons was based on the destabilization of abnormal MEs we discovered [12-15,45]. We were convinced that wound healing metabolites were excellent cancer drugs, which are very much like Chinese herbal medicines. Chinese herbal medicines are therapeutic efficacy oriented medicines, while chemical compositions can be largely unknown. We went to China in 1993 to develop CDA-2, which was also a preparation of wound healing metabolites purified from urine. We used XAD-16 instead of C18 as the adsorbant of DIs and DHIs. C18 was a privileged method of Dr. Burzynski we could not use. CDA-2 was a preparation with XAD-16 as the adsorbant and Antineoplaston A5 was a preparation with C18 as the adsorbant. Both preparations had comparable activities to induce terminal differentiation of HL-60 cells, although chemical compositions were different. Peptides were major chemical constituents of Antineoplaston A5, and acidic peptides were major active DIs of Antineoplaston A5. Peptides could not be retained by XAD-16. PP-0, which were membrane fragments containing phosphatidylinositol, were the major DIs of CDA-2, which were only a minor active DIs of Antineoplaston A5. Other active components such as OA-0.79, which was a liposomal complex containing organic acids, most likely arachidonic acid (AA) or dicycloprostaglandin E2 [49, 50], and pregnenolone. Uroerythrin, riboflavin and steroid metabolites [51-53] were present in both CDA-2 and Antineoplaston A5. CDA-2 was approved by the Chinese FDA for cancer therapy in 2004 as an adjuvant to supplement cytotoxic chemotherapy based on its remarkable effects to improve quality of life of cancer patients. Since the therapeutic endpoint of CDA-2 was induction of terminal differentiation, the effect to reduce tumor size was not obvious. The development of CDA-2 as a cancer drug was abandoned in 2007, because it was difficult to promote the acceptance of a cancer drug that could not cause the tumor to shrink. The remarkable effect of CDA-2 against CSCs was found later. The eradication of CSCs is essential to the success of cancer therapy. Thus, CDA-2 is potentially the drug for the standard care of breast, lung and liver cancers [26,54].

Abnormal MEs as the Most Important Cause of Cancer

Cancer is basically a problem of growth regulation going awry. Abnormal MEs and chromosomal abnormalities to activate oncogenes or to inactivate suppressor genes are the two major causes to mess up growth regulation. Chromosomal abnormalities attract most attention. The cancer establishments even designated 20 years between 1976 to 1996 to develop gene therapy. They gave up because it was really very difficult to correct chromosomal translocations or deletions. Actually, abnormal MEs are more important than chromosomal abnormalities to contribute to the evolution of cancer, which happens at the very beginning of

life and shared by all cancers [13,14], whereas chromosomal abnormalities take place after the establishment of CSCs, and show different abnormalities among different cancers. Correction of abnormal MEs can activate terminal differentiation to exit cell cycle to also put to rest chromosomal abnormalities. Afterall, oncogenes and suppressor genes are cell cycle regulatory genes which have important roles to play when cells are in cell cycle replicating. But if replicating cells exit cell cycle to undergo terminal differentiation, these genes have no roles to play. So, destabilization of abnormal MEs can also put to rest the issue of chromosomal abnormalities. Solution of chromosomal abnormalities cannot put away the issue of abnormal MEs. It is obvious that abnormal MEs are more important than chromosomal abnormalities. Chromosomal abnormalities receive a lot of attention. We are the only one to work on abnormal MEs with our own very limited resources. Of course, killing of CCs can also put to rest the issues of abnormal MEs and chromosomal abnormalities. That has been tried, but failed.

MEs are a ternary enzyme complex consisting of methionine adenosyltransferase (MAT)-methyltransferase (MT)-S-adenosylhomosysteine hydrolase (SAHH). SAHH has the smallest mass and is the most unstable enzyme of the three MEs. It requires the association with steroid hormone, or comparable factor to assume a configuration to form a dimer complex with MT to become stable. This MT-SAHH dimer has a mass similar to MAT to form a ternary MEs which is the most stable and active form of MEs. On the individual enzymes, steroid hormone is an allosteric factor to regulate the stability and the activity of MEs [46,55]. In telomerase expressing cells, MEs become associated with MEs [14]. The association of MEs with telomerase changes kinetic properties of MAT-SAHH isozyme pair and the regulation of MEs greatly in favor of cell growth. The telomerase associated isozyme pair, MATLT-SAHHLT display Km values 7-fold higher than the normal isozyme pair [12-14,46,55]. The increased Km values indicate that cells expressing telomerase have a larger pool sizes of S-adenosylmethionine (AdoMet) and S-adenosylhomocysteine (AdoHcy) which are important to promote the growth of cells expressing telomerase. The study of Prudova [56] indicates that the association with AdoMet can greatly increase the stability of protein against protease digestion, and the study of Chiba [57] indicates that when HL-60 cells are induced to undergo terminal differentiation, the pool sizes of AdoMet and AdoHcy shrank greatly. Therefore, the larger pool sizes of AdoMet and AdoHcy are essential to promote the growth of cells expressing telomerase. Obviously, abnormal MEs are needed to promote the exceptional growth of normal stem cells and malignant cells expressing telomerase. The exceptional growth of normal stem cells is well guarded by contact inhibition, TET-1 enzyme to direct lineage transitions and chemo-surveillance to prevent exceptional growth of normal stem cells from becoming clinical problems. If the function of abnormal MEs is disrupted during the embryonic stage by thalidomide, it can lead to malformation of the fetus, noticeably limbs. Inability to heal wound is primarily due to the collapse of chemo-surveillance. The nature does not have a mechanism to correct the collapse of chemo-surveillance. Instead, the pressure will build up to force the evolution of PSCs to become CSCs in order to escape contact inhibition which limits the extent that PSCs can proliferate. It takes a single hit to silence TET-1 enzyme to convert PSCs to become CSCs [58,59]. This is a task very easy for PSCs to accomplish, since these cells are equipped with abnormally active MEs. The proliferation of CSCs still cannot heal the wound. The pressure is set in to force the progression of CSCs to become faster growing CCs by translocations to activate oncogenes or deletions to inactivate suppressor genes. It appears that the seed of cancer is sawed at the very beginning of life, namely the fertilization of the egg with a sperm to activate the totipotent stem cell which expresses telomerase. The expression of telomerase spreads through pluripotent stem cells, but secedes when pluripotent stem cells undergoing lineage transitions to reach unipotent stem cells. Stem cells expressing telomerase are well guarded to avoid mishaps. Placenta barrier may play an important role to block maternal DIs and DHIs from getting into fetus to influence fetal development. Thus far, fetal development and wound healing are taking place perfectly, safety mechanisms appear to operate just right.

MEs play a pivotal role of growth regulation by virtue of the fact that DNA MEs control the expression of tissue specific genes [60] and pre-rRNA MEs control the production of ribosome, which in turn controls the initiation of cell replication [61,62]. If enhanced production of ribosome is locked in place, it becomes a driving force to promote carcinogenesis [63]. Therefore, MEs are really very important on the regulation of cell replication, differentiation and apoptosis. Because of such pivotal role on the regulation of cell growth, MEs are subjected to exceptional allosteric regulation [46]. Abnormal MEs are the most important cause of cancer. Thus, destabilization of abnormal MEs is the most appropriate approach for cancer therapy [27-37]. In fact, it is the nature's choice of cancer therapy. The nature creates Chemo-surveillance as the last defense mechanism to prevent the buildup of cells with abnormal MEs. When this mechanism breaks down, the clinical symptom of cancer shows up. Protection of the functionality of chemo-surveillance by phenylacetylglutamine was very effective to prevent cancer from taking place as shown in Figure 1 [15,44] And the restoration of chemo-surveillance by the administration of Antineoplastons or CDA-2 was very effective for cancer therapy [15,23,25,45]. Cancer therapy by CDA formulations displays features as chemo-preventive that can prevent cancer from taking place and as targeted therapy on the most important cancer target of abnormal MEs [36]. The wisdom of oriental medicine stresses the importance of the drugs that can prevent the disease from taking place and the drugs to target on the cause of diseases. Oriental medicine considers drugs that can prevent diseases from taking place as the best drugs, and the drugs to target on the cause as the drugs next to the best. Cytotoxic agents focusing on the elimination of cancer symptoms are merely ordinary cancer drugs. Since cytotoxic agents are not very effective to reduce cancer mortality, the cancer establishments should not block CDA formulations, which can reduce cancer mortality, although these drugs are unable to make tumor to disappear.

CDA Formulations as the Best Drugs for the Solution of CSCs

CSCs are a Very Important issue of Cancer, Perhaps the Most Important issue of Cancer

Myelodysplastic syndromes (MDSs) are diseases best for the illustration of the evolution of CSCs due to wound unhealing and the development of cancer drugs good for the solution of CSCs. MDSs often start from a display of immunological disorder to trigger the local production of inflammatory cytokines [64]. Among cytokines produced, TNF is the most critical factor related to the development of MDSs [65]. TNF causes excessive apoptosis of bone marrow stem cells, thus severely affecting the ability of patients to produce hematopoietic cells such as erythrocytes, platelets or neutrophils. TNF is also responsible for the collapse of chemo-surveillance to initiate cancer evolution as above described. MDSs are diseases due to wound unhealing because of the collapse of the collapse of chemo-surveillance caused by TNF that forces the evolution of CSCs from PSCs. The propagating pathological cells have been identified as CSCs [66]. The therapy of MDSs

requires the conversion of pathological CSCs to become functional erythrocytes, platelets or neutrophils. Therefore, inactivation of abnormal MEs to achieve terminal differentiation is the only option for the therapy of MDSs. Vidaza, Decitabine and CDA-2, which is the drug we produced, are the three drugs approved by the Chinese FDA for the therapy of MDSs. 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 to conduct clinical trials of all three MDSs drugs in China. According to his assessments based on two cycles of treatment protocols, each 14 days, CDA-2 had a noticeable better therapeutic efficacy based on the cytological evaluation, although slower to reach complete remission, and a markedly better therapeutic efficacy based on the hematological improvement evaluation, namely becoming independent on blood transfusion to stay alive, as shown in Figure 2, which is reproduced from the reference [67]. CDA-2 inactivates abnormal MEs by eliminating telomerase from abnormal MEs, which is a selective pharmacological action on abnormal MEs [12-14,23-37], whereas Vidaza and Decitabine inactivate abnormal MEs by the elimination of methyltransferase through covalent bond formation between methyltransferase and the aza-cytosine incorporated into DNA [68], which is non-selective against cancer cells. Thus, CDA-2 is free of adverse effects, whereas Vidaza and Decitabine are proven carcinogens [69,70], and very toxic to DNA [71-73]. CDA-2 is obviously the drug of choice for the therapy of MDSs with superior therapeutic efficacy and devoid of adverse effects. CDA-2 is clearly the winner of the contest to eradicate CSCs. We have predicted that the winner of the contest to eradicate CSCs won the contest of cancer therapy [74]. CDA formulations are the clear winner of cancer therapies.

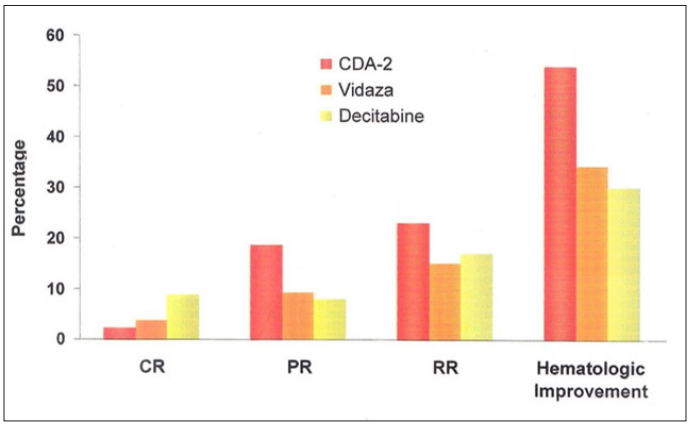

Figure 2: CDA-2 as the Best Drug for the Therapy of MDSs

Development of CDA Formulations to Turn Around Cancer Mortality from Escalation to Deceleration

Abnormal MEs and CSCs are the most critical issues of cancer. These two issues are actually a single issue, because destabilization of abnormal MEs is the only option for the solution of CSCs [40]. Therefore, development of CDA formulations is very important to achieve the mission of cancer moonshot requested by President Biden and to win the War on Cancer requested by President Nixon [75].

We have carried out extensive studies on natural and non-natural DIs and DHIs for the manufacture of CDA formulations [23, 24, 49-53, 76-79], which are summarized in Table 2 and 3. ED25, 50, and 75 of DIs and RI0.5 of DHIs are included for easy manufacturing of CDA formulations. RI0.5 of a DHI is equivalent to ED25 of a DI, which can be determined by the procedure published [79].

DIs and DHIs can be excellent cancer drugs. ATRA is the standard care of acute promyelocytic leukemia. ATRA is an indirect DI. It requires the expression of the receptor of ATRA, namely RAR, for ATRA to be effective [80]. RAR is the repressor of oligoisoadenylate synthetase. The association of ATRA with RAR activate the transcription of oligoisoadenylate synthetase [81].

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	46.5
DicycloPGE2	21.0	43.5	-
AA	21.0	42.0	-
BIBR1532	32.3	43.7	55.1
Boldine	60.1	78.8	94.2

The product of this enzyme oligoisoadenylate is the actual DI. The rest of DIs listed in Table 2 are direct DIs. AA and PG derivatives are natural DIs involved in chemo-surveillance. BIBR1532 and boldine are non-natural DIs, which have been approved as telomerase inhibitors for cancer therapy. PG derivatives are approved drugs for the delivery. Drugs requested to change indication do not require clinical trial as long as 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. The association with telomerase in telomerase expressing cells further increases its stability. It takes a large amount of inhibitor to shake loose of this enzyme. Thus, SAHH and MT inhibitors are better DHIs. Pregnenolone is a major DHI of CDA-2. Apparently, pregnenolone is an important player of chemo-surveillance. It is the master substrate of all biologically active steroids. Therefore, it has a profound influence on the growth regulation. According to Morley [82], the production of pregnenolone is bell shape in relation to ages with a peak daily production of approximately 50 mg at 20-25 years old. The youngest and the oldest people produce relatively the least amount of pregnenolone, and these are the two age groups most vulnerable to develop cancer. It is our choice of natural DHI to make CDA-CSC formulations, although it is not the most active natural DHI. The finding of STIs as excellenct DHIs is expected, since the activation of signal transduction always results in the production of factors to promote the activity MEs. STIs are excellent cancer drugs. Gleebec is the standard care of chromic myeloid leukemia [83]. The finding of polyphenols as effective DHIs is a surprise, but is a pleasant surprise. Since polyphenols are generally regarded as health foods, the finding of polyphenols as excellenct DHIs increases their credibility as health foods.

Table 3: Active DHIs

SAHH Inhibitors	**RI0.5 (μM)**
Pyrivinium Pamoate	0.012
Vitamin D3	0.61
Dexamethasone	0.75
Beta-Sitosterol	1.72
Dihydroepiandrosterone	1.79
Prenisolone	2.22
Hydrocortisone	4.59
Pregnenolone	7.16
MT Inhibitors	**RIo.5 (μM)**
Uroerythrin	1.9
Hycanthone	2.1
Riboflavin	2.9
MAT Inhibitors	**RI0.5 (μM)**
Indol Acetic Acid	220
Phenylacetylvaline	500
Phenylacetylleucine	780
Butyric Acid	850
Phenylbutyric Acid	970
STIs	**RI0.5 (μM)**
Sutent	0.28
Berberine	1.62
Vorient	10.1
Gleevec	11.9
Selenite	19.7
Polyphenols	**RI0.5 (μM)**
Tannic Acid	0.37
EGCG	0.62
Resveratrol	1.16
Curcumin	1.24
Kuromanin	1.43
Coumestrol	1.95
Genisteine	2.19
Pyrogallol	3.18
Silibinine	3.80
Caffeic Acid	3.87
Ellagic Acid	4.45
Gallic Acid	5.35
Ferulic Acid	7.41
Phloroglucinol	38.82

Effective CDA formulations can be the plasma concentrations of ED_{25} of a DI + 3x$RI_{0.5}$ of a DHI, or ED_{50} of a DI + 2x$RI_{0.5}$ of a DHI, or ED_{75} of a DI + $RI_{0.5}$ of a DHI [24]. DIs are more important active components. But the inclusion of DHIs in necessary, because DIs alone tend to result in the dissociation ternary MEs to become individual enzymes. MT as monomeric enzyme has a tendency to be modified to become nuclease to disrupt differentiation process to result in incompletion of terminal differentiation. The damaged cells may resume malignant growth if the damage is repaired. The inclusion of DHI can prevent incompletion of terminal differentiation and 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 factor of melanoma, and collagen envelop of pancreatic cancer.

Disappearance of tumor is an important issue of cancer. The therapeutic endpoint of CDA formulations is the terminal differentiation of CSCs and CCs that cannot make tumor to disappear. The tumor residue is made up by terminally differentiated CSCs and CCs which are unable to replicate, and, therefore is harmless. If it becomes a concern, it can be safely removed by surgery.

Conclusion

CSCS evolve from PSCs due to the collapse of chemo-surveillance, which is the nature's creation for the perfection of terminal differentiation of PSCs to heal wound. The appearance of CSCs is critically linked to wound unhealing. Induction of terminal differentiation of PSCs and CSCs is the only option to solve wound unhealing. Induction of terminal differentiation of PSCs and CSCs is best accomplished by CDA formulations to destabilize abnormal MEs. Thus, CDA formulations are the best drugs for the solution of abnormal MEs and CSCs, the two very critical issues of cancer to accomplish the therapy of cancer to turn around cancer mortality from escalation to deceleration. Induction of terminal differentiation can also solve the issue of CCs, but cannot make the tumor to go away. Residual tumor is harmless, which can be safely removed by surgery.

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Conflicts of Interest

The authors declare no conflicts of interest

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