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CDA Formulations as Superb and Excellent Cancer Drugs to Save Cancer Patients

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ABSTRACT

The objective of this article is to develop effective cancer drugs to save cancer patients. There are three categories of cancer drugs: the superb cancer drugs are those that can prevent cancer from taking place, the excellent cancer drugs are those to target on the causes of cancer, and ordinary cancer drugs are those to focus on the elimination of symptoms. Cancer therapy had a bad to rely on toxic chemicals to kill cancer cells (CCs), the most outstanding symptom of cancer, which was a mistake committed at a time we did not have a complete knowledge of cancer. Cytotoxic agents were the choice of cancer establishment to combat cancer when President Nixon declared war on cancer during 1971-1976, which was not successful. Despite failure, cytotoxic agents continued to dominate cancer therapy because cancer establishments could not find drugs better than failed cytotoxic agents to kill CCs. The consequence is as expected that cancer mortality keeps on escalating. Cancer stem cells (CSCs) became known in 1997. The discovery of CSCs unraveled an important issue of cancer. It became evident that, although CSCs constituted only a small sub-population, these cells were responsible for the initiation of tumor growth and the treatment failure. Therefore, the elimination of CSCs is essential to the success of cancer therapy. Our studies of abnormal methylation enzymes (MEs), chemo-surveillance, and wound healing were closely related to the issue of CSCs. Thus, we are in a unique position to offer the best solution of CSCs to save cancer patients.

Wound healing is an important health issue. The nature creates chemo-surveillance to ensure perfection of wound healing to avoid disastrous consequences of wound unhealing, cancer being the worst. Chemo-surveillance is specifically destroyed in cancer patients to result in wound unhealing, which forces progenitor stem cells (PSCs) to evolve into cancer stem cells (CSCs), and then to progress to faster growing CCs. PSCs are the most primitive stem cells to initiate the development of organ or tissue during embryonic development of the fetus. These cells are also the cells involved in wound healing. MEs of PSCs are abnormal due to association with telomerase, which are an important cause of cancer to promote perpetual proliferation by blocking differentiation. Chemo-surveillance is the nature's creation of allosteric regulation on abnormal MEs to prevent the buildup of cells with abnormal MEs to become clinical problems. Human body produces metabolites active as differentiation inducers (DIs) and differentiation helper inducers (DHIs), which are wound healing metabolites and also the active components of chemo-surveillance. Protection of the functionality of chemo-surveillance is important to ensure perfection of wound healing to avoid cancer. Pathological conditions inducing the production of tumor necrosis factor (TNF) are particularly damaging to chemo-surveillance. Anti-cachexia chemical phenylacetylglutamine can effectively antagonize the effect of TNF to protect chemo-surveillance. Phenylacetylglutamine is, therefore, a superb cancer drug that can prevent cancer from taking place.

Cell differentiation agent-2 (CDA-2) is a preparation of wound healing metabolites purified from urine, which has been approved by the Chinese FDA for the therapy of cancer and myelodysplastic syndromes (MDSs). MDSs are diseases attributable entirely to CSCs. CDA-2 is demonstrably the best drug for the therapy of MDSs, showing superior therapeutic efficacy without adverse effects. Phenylacetylglutamine is a major chemical component, and DIs and DHIs are the active anti-cancer components effective to destabilize abnormal MEs and to eliminate CSCs, both of which are critical causes of cancer. CDA-2 fit the description as superb and excellent cancer drugs. We have carried extensive studies on natural and non-natural DIs and DHIs to manufacture CDA formulations. Cancer establishments stand in the way to block the development of CDA formulations, which is a difficult hurdle.

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Introduction

Cancer therapy had a bad start to rely on toxic chemicals to kill CCs, the most outstanding symptom of cancer. 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 use toxic chemicals to treat leukemia patients. Cytotoxic chemotherapy, thus, became a standard care of cancer, and the disappearance of cancer cells in the case of hematological cancers and the disappearance of tumor in the case of solid tumors became standard criteria for the evaluation of cancer therapy. Both were wrong [1,2]. The mistake was made at a time when we did not have a complete knowledge of cancer. The mistake was excusable. Cytotoxic chemotherapy and radiotherapy were the major treatment modalities employed in the combat of cancer when President Nixon declared War on Cancer during 1971-1976,

which was not successful [3]. When a treatment modality is drilled through as a presidential project to receive unlimited support of national resources and fails to achieve its goal, it is fair to conclude that the treatment modality is not good for cancer therapy which should be dismissed. Cancer establishments knew cytotoxic chemotherapy and radiotherapy were unable to solve cancer, but kept using the failed drugs because they could not find drugs better than the failed cytotoxic drugs to kill CCs. That was inexcusable. The consequence is as expected that cancer mortality keeps on escalating. The latest cancer statistics of the world compiled by NCI were those of the year 2019 which showed cancer incidence of 19 million and cancer mortality of 10 million, which were 5.0% and 5.3% increment over the previous year [4]. Cancer statistics of USA look better. The latest statistics compiled by ACS were those of the year 2024 which showed cancer incidence of 2.0 million and cancer mortality of 0.61 million, which were 2.1% and 0.2% increment over the previous year. Evidently, cancer establishments are unable to turn around cancer mortality from escalation to deceleration, a clear indication of the failure of cancer therapy. Actually, there are better cancer drugs overlooked by the cancer establishments. Superb cancer drugs are those that can prevent cancer from taking place such as phenylacetylglutamine that can protect chemo-surveillance to ward off carcinogens and vaccines of infectious agents that can cause cancer. Excellent cancer drugs are those to target on the causes of cancer such as CDA formulations to target abnormal MEs and CSCs, gene therapeutic agents to target chromosomal abnormalities, and signal transduction inhibitors to target oncogene products. Unfortunately, cancer establishments are trapped in belief that killing CCs is the best approach of cancer therapy.

CSCs became known in 1997 [5]. The discovery of CSCs unraveled a very important issue of cancer. It became evident that, although CSCs constituted only a very small subpopulation, these cells were responsible for the initiation of tumor growth and the treatment failure [6-9]. Thus, the elimination of CSCs is essential to the success of cancer therapy [10,11]. Of course, cancer establishments knew the importance 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 did not materialize, because killing of CSCs was not an option for the solution of CSCs. Again, they took a wrong approach to solve an important cancer issue. Our studies on abnormal methylation enzymes (MEs) [12-14]; Chemo-surveillance[15-17]; andwound healing [18-21] are closely related to the issue of CSCs. Thus, we are in a unique position to offer the best solution of CSCs to save cancer patients [22-31].

Wound healing is an important health issue, so that the nature creates chemo-surveillance and immuno-surveillance to ensure perfection of wound healing to avoid disastrous consequences of wound unhealing. Agents that offer protection of chemo-surveillance and immuno-surveillance are effective to prevent cancer evolution. These agents are regarded superb cancer drugs. Superb cancer drugs are neglected because they do not produce noticeable effects to attract attention. Excellent cancer drugs are those to target on the causes of cancer, which are a better choice than ordinary cancer drugs to focus on the elimination of symptoms. Unfortunately, health profession is an authoritarian profession. When the mistake is made by the cancer establishments, there is no mechanism to rectify the mistake. The mistake carries on to hurt cancer patients. A drastic change of cancer leaderships is obviously needed to save cancer patients [32,33].

Commentaries and Discussion

Chemo-surveillance Specifically Destroyed in Cancer Patients

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. DIs are metabolites capable of eliminating telomerase from abnormal MEs, and DHIs are inhibitors of MEs capable of potentiating the activity of Dis. Dls and DHIs are hydrophobic metabolites that can be retained by C18 in aqueous solution and recovered by organic solvent. Peptides share physical chemical properties similar to DIs and DHIs, thus, can be used as surrogate molecules to represent DIs and DHIs. As a matter of fact, acidic peptides are major DIs of Antineoplaston A5, which is an Antineoplaston preparation purified from urine using C18 as the adsorbant. Peptides were initially purified from plasma after deproteinization with sulfosalicylic acid or urine without deproteinization treatment with cartridge of C18. Unadsorbed metabolites were washed away by water, and retained metabolites were recovered by 80% methanol. Methanol solution was removed by lyophilization, the residue was then dissolved in a small volume of water for HPLC resolution of peptide profiles on a column of sulfonated polystyrene and quantitative assay of peptides by Ninhydrin reaction. Peptide analyses of 108 cancer patients are presented in Table 1, which is reproduced from the reference [15]. Data presented in Table 1 clearly show that chemo-

Table 1: Chemo-Surveillance Specifically Destroyed in Cancer Patients

Plasma/Urine Peptide 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	16.5
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; Urine Peptides: nmoles/mg creatinine

surveillance is specifically destroyed in cancer patients. Chemo-surveillance is the nature's creation of allosteric regulation on abnormal MEs. Human body produces metabolites active as DIs and DHIs to keep a check on the buildup of cells with abnormal MEs. PSCs are the cells involved in wound healing. MEs of PSCs are abnormal, so are most cancer cells which are derived from PSCs. When wounds are unable to heal because of the collapse of chemo-surveillance, PSCs will be forced to evolve into CSCs to escape contact inhibition which limits the extent of the growth of PSCs. Pathological conditions triggering the production of TNF are particularly damaging to chemo-surveillance. TNF can cause blood vessel hyperpermeability to trigger excessive excretion of low molecular weight metabolites [34,35]. Dls and DHIs are among low molecular weight metabolites excreted, resulting in the collapse of chemo-surveillance. The progression of cancer also produces TNF to aggravate the damage of chemo-surveillance. Treatment with cytotoxic agents also produces TNF to further

aggravate the damage of chemo-surveillance. CDA level of 2.5 is very likely a critical threshold to determine the responsiveness to cytotoxic therapies. Above CDA 2,5, cancer patients will respond to the therapy, relying on the restoration of chemo-surveillance to subdue surviving CSCs which are resistant to cytotoxic agents. Below CDA 2.5, damaged chemo-surveillance has no chance of recovery to subdue CSCs. Patients become unresponsive to the treatment, or even still responsive to reach complete remission, these patients are eventually succumbed to recurrence. Therefore, ineffectiveness against CSCs and the contribution to the damage of chemo-surveillance are responsible for the failure of cytotoxic therapies to put cancer away. CDA formulations are the best hope to the rescue of advanced cancer patients whose chemo-surveillance have been fatally damaged .

Our carcinogenesis studies are indicative of the importance of chemo-surveillance to dictate the outcome of carcinogenesis. When animals were challenged with hepatocarcinogens, we noticed the appearance of numerous tiny hyperplastic nodules which displayed abnormal MEs [36]. These hyperplastic nodules must represent the active proliferation of PSCs in the process of wound healing. Most of these tiny hyperplastic nodules disappeared shortly, indicating the completion of wound healing. Only a few large size carcinomas appeared later from unhealed nodules. If phenylacetylglutamine was provided during the challenge of animals with potent hepato-carcinogen aflatoxin B1, the appearance of carcinomas could be effectively prevented as shown in the Figure 1, which is reproduced from the reference [37]. Phenylacetylglutamine is

Figure 1: Phenylacetylglutamine as A Superb Cancer Drug for the Prevention of Cancer

a major chemical composition of the urinary preparations of wound healing metabolites as CDA-2 or Antineoplastons [38]. Phenylacetylglutamine is biologically inactive. However, it is very effective to protect chemo-surveillance. By the protection of chemo-surveillance, phenylacetylglutamine can function as an effective chemo-preventive agent, namely a superb cancer drug.

Preparations of wound healing metabolites are excellent cancer drugs to target on the causes of cancer. Antineoplastons were initiated by Burzynski in 1976 and CDA-2 was initiated by Liau in 1993 [39,40]. 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 most critical causes of cancer to promote perpetual proliferation of CCs, abnormal MEs by blocking differentiation and chromosomal abnormalities to accelerate cell replication. Destabilization of abnormal MEs is the critical mechanism of wound healing, which is also the critical mechanism of cancer therapy to eliminate CSCs and CCs . Both Antineoplastons and CDA-2 demonstrated excellent therapeutic efficacy with negligible adverse effects. Patients responding favorably to Antineoplastons all showed elevation of CDA levels to reach the healthy level of 5, whereas patients not responding to Antineoplastons continued to show the decline of CDA levels [41]. Obviously not all cancer patients respond favorably to Antineoplaston therapy. Cancer cells are known to express a high level of degradative enzymes to salvage substrates for macromolecular syntheses to support their fast growth. antineoplaston and remove the gap are natural metabolites which may be quickly degraded to lose activity. It is advisable to provide two sets of CDA formulations: one set CDA-CSC made by natural DIs and DHIs to access CSCs and another set CDA-CC made by non-natural DIs and DHIs to resist degradation by fast growing CCs. Antineoplastons were blocked by cancer establishments around 1990. Antineoplastons are very much like Chinese herbal medicines which are therapeutic efficacy oriented medicines while chemical compositions can be largely unknown. We were convinced that Antineoplastons could be accepted in China. So, we went to China in 1993 to develop CDA-2. We used XAD-16 instead of C18 as the adsorbant to purify DIs and DHIs. Chemical compositions of CDA-2 and Antineoplaston A5 are not exactly the same, but both preparations have comparable activities to induce terminal differentiation of CCs. CDA-2 has been approved by the Chinese FAD for the therapy of cancer and myelodysplastic syndromes [42,43]. CDA-2 is a persuasive excellent cancer drug effective to eradicate CSCs and to destabilize abnormal MEs, both are critical causes of cancer.

CDA-2 as the Best Drug for the Therapy of MDSs and CSCs

MDSs often start with a display of an immunological disorder to trigger the production of inflammatory cytokines [44]. Among such cytokines, TNF is the critical factor related to the development of MDSs [45]. It causes excess apoptosis of bone marrow stem cells, thus severely affecting the ability of the patient to produce hematopoietic cells such as erythrocytes, platelets and neutrophils. TNF is also named cachectin after its effect to cause cachexia symptom. A characteristic disorder of cachexia symptom is the excessive excretion of low molecular weight metabolites, resulting in the collapse of chemo-surveillance as above described. During the course of MDSs progression, ten eleven translocator-1 enzyme (TET-1) is silenced to force the evolution of PSCs to become CSCs to escape contact inhibition thus allowing CSCs to buildup in order to replenish unipotent stem cells wiped out by TNF [46,47]. The propagating pathological cells have been identified as human CSCs [48]. MDSs are diseases attributable entirely to the propagation of CSCs.

Vidaza, Decitabine and CDA-2 are the three drugs approved for the therapy of MDSs by the Chinese FDA. Vidaza and Decitabine are also approved for the therapy of MDSs by the US FDA.

Professor Ma, the Director of Harbin Institute of Hematology and Oncology, was instrumental in conducting clinical trials of all three MDSs drugs. According to his assessments, 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, meaning to become independent on blood transfusion to stay alive, as shown in Figure 2, which is reproduced from the reference [43].

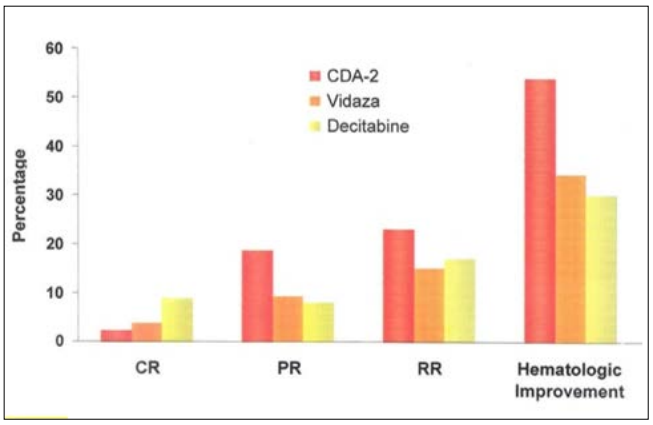

Figure 2: CDA-2 as the Best Drug for the Therapy of MDSs

Therapy of MDSs requires inactivation of abnormal MEs to achieve differentiation of CSCs to become functional erythrocytes, platelets and neutrophils. Killing of CSCs is not an option. CDA-2 achieves inactivation of abnormal MEs by targeting on the elimination of telomerase, which is a selective tumor factor , whereas Vidaza and Decitabine inactivate abnormal methylation. enzymes by covalent bond formation between methyltransferase and 5-azacytosine incorporated into DNA, which is non-selective on CCs [49]. CDA-2 is without adverse effects, whereas Vidaza and Decitasbine are proven carcinogens and very toxic to DNA [50-54]. The difference is very persuasive that CDA-2 is the drug of choice for the therapy of MDSs. Solution of CSCs is very critical to the success of cancer therapy. We have predicted that the winner of the contest to eradicate CSCs wins the contest of cancer therapy [55]. Clearly, the winner is CDA formulations.

Close Relationship between Cancer and Wound Healing

Cancer evolves due to wound unhealing. Naturally, cancer and wound healing are closely related as noticed by MacCarthy-Morrough and Martin[56]. The concept of cancer evolves due to wound unhealing was introduced by the great German pathologist Virchow in the 19th century [57]. It was again brought up by Dvorak in 1986 [58]. We provided the most important details on this subject that included abnormal methylation enzymes to promote perpetual proliferation of CCs by blocking differentiation; chemo-surveillance as the nature's creation of allosteric regulation on abnormal MEs for the perfection of wound healing to avoid disastrous consequence of wound unhealing, cancer being the worst; DIs and DHIs as wound healing metabolites and as the active players of chemo-surveillance; hypomethylation of nucleic acids as a critical mechanism of terminal differentiation; mechanism of wound healing; and close relationship of cancer and wound healing and the evolution of CSCs from PSCs due to wound unhealing [59-62]. These studies clearly establish the validity of the concept that cancer evolves due to wound unhealing. Our studies above described confirm the validity of this concept.

Wound healing requires the proliferation and the terminal differentiation of PSCs. PSCs are the most primitive stem cells to initiate the development of organ or tissue during embryonic development of the fetus. A small fraction of these cells, usually less than 2% of the organ or tissue mass, is preserved in the organ or tissue for future expansion or repair. PSCs are pluripotent stem cells capable of differentiation into various component cells of the organ or tissue. These cells are protected by drug resistance and anti-apoptosis mechanisms, and have strong capability to repair DNA. These cells express chemokine receptor CXCR4 to respond swiftly to signals for expansion or repair. MEs of PSCs are abnormal due to association with telomerase like most cancer cells , which is the most critical cause of cancer [62]. 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 during embryonic development of the fetus, but secedes when pluripotent stem cells undergoing lineage transitions to reach unipotent stem cells. Abnormal MEs obviously carry out functions important for the development of fetus, as premature interruption of abnormal MEs with thalidomide results in the malformation of limbs. Abnormal MEs are not a problem to normal stem cells expressing telomerase, because there are safety mechanisms such as contact inhibition, TET-1 enzyme to direct lineage transitions and chemo-surveillance to prevent pathological buildup of cells with abnormal MEs. When such safety mechanisms become dysfunctional, then clinical symptoms arise.

Wound triggers the biological and the immunological responses. The biological response involves the release of arachidonic acid (AA) from membrane bound phosphatidylinositol through phospholipase A2 for the synthesis of prostaglandins (PGs) by cyclooxygenases and PG synthases [64, 65]. Although AA and PGs are active DIs the induction of terminal differentiation of PSCs at the initial stage of wound is not the primary objective of AA and PGs. Rather, the localized inflammation caused by PGs Is responsible for the increase of membrane permeability to facilitate the extravasation of plasma proteins and regulatory factors into the wound resulting in edema response that is the primary objective of PGs to orchestrate the healing process[67]. Chemo-surveillance mediated through DIs and DHIs normally functions as a brake to prevent the buildup of PSCs. This brake must be released in order for PSCs to proliferate to produce enough cells for the repair of wound. PGs are metabolically unstable. Their biological effects are most likely brief and confined to the wound area. Thus, the promotion of the proliferation of PSCs is the primary objective of PGs on wound healing, whereas the induction of terminal differentiation of PSCs at the final stage of wound healing is accomplished by wound healing metabolites of chemo-surveillance. The stable end products of PGs, dicycloPGs, may then participate in the final stage of wound healing. DicycloPGs as DIs are not as active as PGs. But their activity can be greatly boosted by DHIs. Pregnenolone is a good DHI to boost the activity of AA and dicycloPGs [65,66].

The biological response triggered by the wound is in general good for wound healing. But the immunological response triggered by the wound is bad for wound healing. Immunological response prompts the patient to produce cytokines to mediate immunological therapeutic effects. TNF among cytokines produced is particularly bad for wound healing as above described. It is the balance of the biological response and the immunological response to determine the outcome of wound healing. If the biological response prevails, wound is healed successfully. If the immunological response prevails, wound cannot be healed to produce clinical symptoms. Thus, immuno-surveillance can act synergistically with chemo-surveillance to prevent wounds caused by infectious agents and toxic chemicals or physical means. But can also act antagonistically to produce TNF to result in the damage of chemo-surveillance. The functionality of chemo-surveillance stands out as the most important factor to dictate the success of wound healing and cancer therapy.

Abnormal MEs as the Most Important Cause of Cancer

Cancer drugs to target on the causes of cancer are much better than those to focus on the elimination of symptoms. There are many causes that can lead to the evolution of cancer. Chromosomal abnormalities resulting in the activation of oncogenes or inactivation of suppressor genes attract the most attention. Cancer establishments put up a great effort to develop gene therapy during 1976-1996 right after the failure to win the war on cancer. They gave up, because it was too difficult to correct chromosomal abnormalities. Chromosomal abnormalities are indeed a very important issue of cancer responsible for the fast growth of CCs. It is very disappointing that the development of gene therapy was not successful. Targeted therapies against oncogene products produced many excellent cancer drugs. The therapeutic endpoint of targeted therapies is terminal differentiation which cannot make tumor to disappear. Cancer establishments are not interested in cancer drugs that cannot make tumor to disappear. Targeted therapies are primarily used in the therapy of hematological cancers.

Actually, abnormal MEs are the most important cause of cancer. MEs are a ternary enzyme complex consisting of methionine adenosyltransferase (MAT)-methyltransferase (MT)-S-adenosylhomocysteine hydrolase (SAHH), which play a pivotal role on the regulation of cell growth [68]. MEs control the expression of tissue specific gene[69]. and the production of ribosome [70]. Ribosome production is a master check point to initiate cell replication [71]. If enhanced production of ribosome is locked in place, it becomes a force to drive carcinogenesis [72]. SAHH is a steroid hormone receptor. In steroid hormone target tissue, MEs are regulated by steroid hormone. In telomerase expressing cells, MEs become associated with telomerase which changes the kinetic properties of MAT-SAHH and the regulation greatly in favor of cell growth. Km values of telomerase associated MAT-SAHH isozymes are 7-fold higher than those of normal isozyme pair. The higher Km values suggest that cells with abnormal MEs have larger pool sizes of S-adenosylmethionine (AdoMet) and S-adenosylhomocysteine (AdoHcy). The larger pool sizes of AdoMet and AdoHcy are important to promote the growth of cells with abnormal MEs such as embryonic stem cells including PSCs and malignant cells as the study of Prudova et al [73]. indicated that AdoMet could protect protein against protease digestion, and the study of Chiba et al [74]. indicated that when cancer cells were induced to undergo terminal differentiation, pool sizes of AdoMet and AdoHcy shrank greatly. Abnormal MEs are indeed an essential factor to promote malignant growth. Destabilization of MEs is, therefore, a very appropriate strategy of cancer therapy [22-31, 38, 62].

Because of the important role on the regulation of cell growth, MEs are subjected to exception allosteric regulation: on the individual enzymes by steroid hormone and on the enzyme complex by telomerase and chemo-surveillance [69-71]. Abnormal MEs start at the very beginning of life and share by all different CCs. When the abnormality of MEs is solved by the induction of terminal differentiation, other cancer causes such as chromosomal abnormalities can also be put to rest. 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 abnormal genes have no roles to play. So, CDA formulations can provide an easy solution of chromosomal abnormalities, which are otherwise very difficult to achieve. Of course, killing of CCs can also put to rest abnormal MEs and chromosomal abnormalities. That has been tried, but failed. Abnormal MEs can be regarded as the bullseye of cancer target [75].

Manufacture of CDA Formulations

We have carried out extensive studies on natural and non-natural DIs and DHIs for the manufacture of CDA formulations [77-84]. Active DIs and DHIs are presented in Table 2, and 3. DIs and DHIs can be excellent cancer drugs. All trans-retinoic

Table 2: Active DIs

DIs	ED_{25} (μM)	ED_{25} (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

Acid is the standard care of acute promyelocytic leukemia [84]. It requires the expression of the receptor of ATRA, namely RAR, to activate oligoisoadenylate synthetase to achieve thetherapeutic effect [85]. The product of this enzyme oligoisoadenylate is the actual DI to act on abnormal MEs. PGJ2 is the most active DI of PG derivatives. The half of PGJ2 is very short. It is a good idea to use the more stable AA or dicycloPGE2 as the natural DIs for the manufacture of CDA formulations to target CSCs. BIBR1532 is the only choice of non-natural DI for the manufacture of CDA formulations to target CCs.

For the induction of terminal differentiation, DIs are more important than DHIs, which are able to eliminate telomerase from abnormal MEs. But the inclusion of DHIs is also crucial to achieve effective therapy. DIs alone cannot achieve differentiation to reach 100%, because DIs alone tend to induce dissociation of ternary MEs to become individual enzymes, MT in the monomeric state has a tendency to be modified to become nuclease, which can cause damage to interrupt DNA synthesis. The damaged cells cannot complete differentiation process. These cells, however, can resume replication if repaired. This is the reason, therapy with ATRA has a high rate of recurrence. Addition of DHIs, particularly inhibitors of MT, can prevent modification of MT to become nuclease. So that induction of terminal differentiation can reach completion to avoid recurrence.

The activity of DHIs is expressed as reductive index0.5 (RI0.5), which is equivalent to ED25 of DIs. The procedure for the determination of RI0.5 is published in the reference. The mass of MAT is the same as that of MT-SAHH dimer. It is the most stable enzyme of the three MEs. The association with telomerase further increases its stability. It is very difficult to destabilize this enzyme. It requires a very high concentration of inhibitor to display DHI activity. Inhibitors of

Table 3: Active DHIs

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

SAHH and MT are better choices of DHIs. Although pregnenolone is not a very active DHI, this metabolite deserves special attention. It is the master substrate of all active steroids. This metabolite has a profound influence on the evolution of cancer. According to Morley [86]. The production of pregnenolone is bell shape with a peak production of approximately 50 mg daily at 20-25 ages. The youngest and the oldest people produces relatively smallest amounts, and these are the two age groups most vulnerable to develop cancer. Pregnenolone is our top choice of natural DHI for CDA-CSC.

The finding of signal transduction inhibitors (STI) as excellent DHIs is expected, since ST tend to produce factors to enhance the activity of MEs. Gleevec is an excellent cancer drug. It is the standard care of chronic myeloid leukemia [87]. The finding that polyphenols are excellent DHIs is a surprise, but is a pleasant surprise. Polyphenols have been regarded as healthy foods. The finding of polyphenols as excellent DHIs increases their credibility as healthy foods.

CDA formulations can be ED25 of a DI + 3x RI0.5 of a DHI, or ED50 of a DI + 2x RI0.5 of a DHI, or ED75 of a DI + RI0.5 of a DHI. There are non-tumor factors to be considered in the selection of DIs and DHIs. Non-tumor factors such as blood brain barrier of brain tumors, hypoxia factors of melanoma, and collagen envelop of pancreatic cancer. A lot of work needs to be done. Therapeutic endpoint is also a very important issue to be solved.

Conclusion

Cancer evolves due to wound unhealing. Drugs healing the wound are the right indication, whereas drugs creating wounds are contra-indication. CDA formulations are a better choice that can heal wounds. Cytotoxic agents that create wounds are a bad choice to result in ever escalation of cancer mortality. The best cancer drugs are those that can prevent cancer from taking place, the second best cancer drugs are those to target on the causes. The ordinary cancer drugs are those to focus on the elimination of symptoms. CDA formulations fit the descriptions as the best and the second best cancer drugs to show the ability to prevent cancer and to target on abnormal MEs and CSCs, the two most important causes of cancer. Cytotoxic agents can make tumor to disappear, but cannot take care of CSCs. Ineffectiveness on CSCs and the contribution to the damage of chemo-surveillance are the reasons cytotoxic agents are unable to put cancer away.

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Conflicts of Interest

The authors declare no conflicts of interest.

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