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Perfection of Wound Healing to Win the War on Cancer

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ABSTRACT

The objective of this article is to find a right approach to win the war on cancer. To win the war on cancer, it is necessary to establish a valid concept of cancer to confront cancer successfully. Cancer evolves due to wound unhealing, which was a valid concept introduced by Virchow in 1858. Cancer establishments pursued cancer therapies by a commanding principle of creating wound to kill cancer cells (CCs) exactly opposite to the Virchow's advice, resulting in the failure to win the war on cancer. We have unknowingly pursued cancer therapy following the guidance of Virchow's wound healing through employment of wound healing metabolites purified from urine which we named cell differentiation agnet-2 (CDA-2) to produce excellent cancer therapy. CDA-2 is the only drug best to handle the issue of cancer stem cells (CSCs). CSCs became known in 1997. The discovery of CSCs unraveled CSCs as the most important issue of cancer to reveal CSCs as the cells to initiate tumor growth and the cells to contribute to the most fatal effects of cancer. Fatal effects of cancer such as metastasis, drug resistance, anti-apoptosis, angiogenesis, unresponsiveness and recurrence are all attributable to CSCs. The nature creates chemo-surveillance as a defense mechanism to guard the pathological build-up of CSCs and CCs by destabilizing abnormal methylation enzymes (MEs) which are the driving cause of CSCs and CCs. CDA formulations are the right drugs to turn off abnormal MEs to win the war on cancer.

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Introduction

Solution of top killing diseases is a national interest to every country. Cardiovascular diseases are a top killer of many countries including USA. Cancer is also a top killer of many countries, noticeably Asia [1]. Cardiovascular diseases are very difficult to solve. Cancer is not as difficult to solve as cardiovascular diseases. President Nixon declared War on Cancer in 1971, intended to solve cancer as a presidential project to ensure success in 5 years following the successful precedents of Manhattan Project of President Roosevelt and Moonshot Project of President Kennedy, but ended up in failure [2]. Realizing health profession was not able to accomplish a presidential project on cancer in 5 years, President Bilen declared Cancer Moonshot Initiative in 2022 requesting a modest saving of 50% cancer patients in 25 years. Thus far, the cancer mortality in the US is still increasing at a rate of 0.2% annually [1]. It should decrease at a rate of 2% annually to meet the modest request of President Biden.

Cancer therapy had a bad start to rely on toxic chemicals to kill CCs. Cytotoxic chemotherapy was an unfortunate byproduct of World War II. During the war, toxic sulfur mustard gas 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. Indeed, toxic chemicals were very effective to wipe out leukemia cells to achieve elimination of the symptom of the proliferation of leukemia cells. Cytotoxic chemotherapy thus became the standard care of cancer, and the reduction of tumor became a standard criterion as a cancer drug, which were set up at a time we did not have a complete knowledge of cancer. Both were wrong based on the present knowledge of cancer. The mistakes were excusable made at a time we did not have a complete knowledge of cancer. But to carry on the use of drugs unable to cure advanced cancer patients was inexcusable. Health profession is an authoritarian profession. When the mistake is made at the very top, the mistake carries on to damage the reputation of health profession and to hurt cancer patients.

CSCs became known in 1997 [3]. The discovery of CSCs unraveled an important issue of cancer to reveal CSCs as the cells to initiate tumor growth and the cells to cause fatal effects of cancer. Fatal effects of cancer such as metastasis, drug resistance, anti-apoptosis, angiogenesis, unresponsiveness and recurrence are all attributable to CSCs [4-8]. Thus, CSCs are the most critical battlefield to dictate the success of cancer therapy [9-11]. Our studies of abnormal MEs [12-14], chemo-surveillance [15-17], wound healing [18-21], and CDA formulations [2,9,22-24] are closely related to the issue of CSCs. So, we are in a unique position to offer solution of CSCs. We have predicted that the winner of the contest to eradicate CSCs won the contest of cancer therapies [10]. We are clearly the winner of the contest of cancer therapies. Our winner's status was denied by the cancer establishments who put up a rule of tumor shrinkage as a condition to qualify as cancer drugs. That rule denies the winning status of CDA formulations, but also defeats their mission to win the war on cancer as CDA formulations are the only drugs to solve the issue of CSCs.

To Win the War on Cancer and Discussion

Establishing A Valid Concept of Cancer

To effectively solve cancer, we must establish a valid concept of cancer. Thus far, we have been relying on the elimination of

piecemeal displays of symptoms to conduct cancer therapies, which were not successful. We have to get to the very fundamental to establish a valid concept of cancer. Cancer evolved due to wound unhealing, which was a valid concept introduced by the great German pathologist Virchow in 1858 [25]. Virchow was well respected as a pioneer on cancer. But his concept of cancer evolving due to wound unhealing was not accepted by the cancer establishments. Had his concept accepted by the cancer establishments, cytotoxic chemotherapy would not come into practice, which created wounds clearly in violation of his concept to heal wounds. Virchow's concept of cancer evolving due to wound unhealing was brought up once 126 years later in 1986 by Dvorak [26]. Again, it was ignored by the cancer establishments. We unknowingly pursued cancer therapy following the guidance of Virchow to heal wound to show MEs were abnormal in cancer cells [12-14]. The finding of abnormal MEs during the early stage of hepatocarcinogenesis as tiny hyperplastic nodules was apparently due to the wound healing requiring the proliferation of progenitor stem cells (PSCs), which express abnormal MEs [27]. Most of tiny hyperplastic nodules disappeared shortly, indicating the completion of wound healing created by hepatocarcinogens. Only a few large size carcinomas appeared later from unhealed wounds. This was our first experimental datum to support the validity of cancer evolving due to wound unhealing. We have produced two additional data to support the validity of cancer evolving due to wound unhealing. One datum was the effective prevention of aflatoxin B1 induced hepatocarcinogenesis by Antineoplaston A10, which is a code name of phenylacetylglutamine by Burzynski, as shown in Fig. 1, which is reproduced from the reference [28].

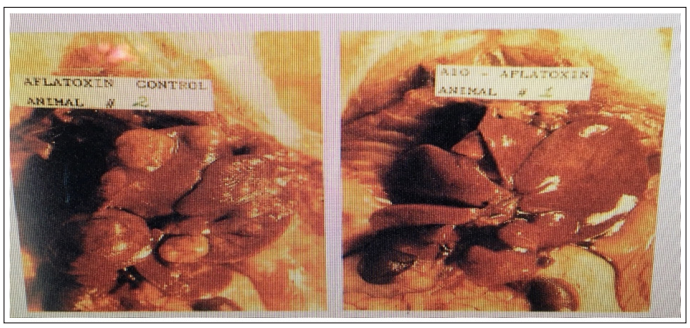


Figure 1: Phenylacetylglutamine as An Effective Chemo-Preventive Agent

The figure on the left is the control liver receiving aflatoxin B1 only, and the figure on the right is the liver receiving aflatoxin B1 followed by the administration of phenylacetylglutamine, namely A10. A10 is biologically inactive, but it can antagonize the effect of tumor necrosis factor (TNF) to prevent excessive excretion of low molecular weight metabolites to protect the functionality of chemo-surveillance [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 as shown in Table 1, which was our another experimental datum to support the validity of cancer evolving due to wound unhealing. Table 1 is reproduced from the reference [15].

Table 1: Chemo-Surveillance Selectively Destroyed in Cancer Patients

Plasma/Urine Peptide Ratios	CDA Levels	Number of Patients	% 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

Obviously, wound healing is an important health issue, so that the nature creates chemo-surveillance and immuno-surveillance to ensure perfection of wound healing, chemo-surveillance to heal wounds created by toxic chemicals or physical means, whereas immuno-surveillance to heal wounds created by infectious agents. On wound healing, chemo-surveillance and immuno-surveillance appear to act synergistically to heal wounds to prevent disastrous consequences of wound unhealing that can be tissue fibrosis, organ failure, dementia or cancer [18-21]. Wound healing requires the proliferation and the terminal differentiation of PSCs [18]. PSCs are the most primitive pluripotent stem cells to initiate the development of organs or tissues during the embryonic development of the fetus. A small number of these cells, usually less than 2% of the organ or tissue mass, are reserved in the organs or tissues for future expansion or repair purposes. MEs of cells expressing telomerase are abnormal due to association with telomerase [14]. MEs are a ternary enzyme complex consisting of methionine adenosyltransferase (MAT)-methyltransferase (MT)-S-adenosyl-homosysteine hydrolase (SAHH) [29]. The association of MEs with telomerase changes the kinetic properties of MEs and the regulation greatly in favor of cell growth, which is necessary for the development of the fetus and wound healing. The operation of abnormal MEs during the embryonic development of the fetus or wound healing is guarded by safety mechanisms such as contact inhibition, ten-eleven translocator -1 enzyme (TET-1) which carries out lineage transitions and chemo-surveillance. When such safety mechanisms become dysfunctional, clinical symptoms arises [18-21]. Thus, Virchow's concept of cancer evolving due to wound unhealing was a valid concept strongly supported by experimental data we have produced unknowingly. Virchow was extremely talented to comprehend the logic of wound healing to cancer at a time neither wound healing nor cancer were completely known, and we were also extremely talented to decode the logic of wound healing to cancer by the discoveries of abnormal MEs [12-14], chemo-surveillance [15-17], and the mechanism of wound healing [18-21].

DIs and DHIs are wound healing metabolites. DIs are metabolites capable of eliminating telomerase from abnormal MEs, and DHIs are inhibitors of MEs that can strongly potentiate the activity of DIs. The association of telomerase with MEs increases Km values of MAT-SAHH isozyme pair 7-fold higher, thus, greatly expands pool sizes of S-adenosylmethionine (AdoMet) and S-adenosylhomocyteine (AdoHcy) needed to support the growth of cells with abnormal MEs, which include embryonic pluripotent stem cells and malignant cells derived from PSCs

[12-14]. Evidently, larger pool sizes of AdoMet and AdoHcy favors cell growth as the study of Prudova et al. showed that AdoMet could protect proteins from protease digestion [30], and the study of Chiva et al. showed that when HL-60 cells were induced to undergo terminal differentiation, the pool sizes of AdoMet and AdoHcy shrank greatly [31]. So, the seed of cancer is sown 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 through TET-1 enzyme to reach unipotent stem cells as shown in Chart-1.

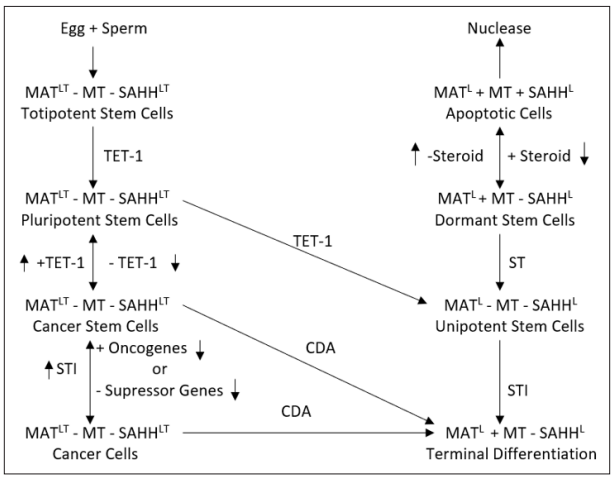


Chart 1: Regulation of Cell Growth by MEs

MAT^{L} and SAHH^{L} are low K_m isozyme pair of normal MEs, and MAT^{LT} and SAHH^{LT} are telomerase associated isozyme pair. TET-1 is the enzyme to carry out lineage transitions. ST is signal transduction and STI is inhibitor of signal transduction. CDA is cell differentiation agent to induce terminal differentiation of cells expressing abnormal MEs.

Apparently, there are two systems of growth regulation by MEs, one by normal MEs and the other by abnormal MEs. The importance of MEs in the regulation of cell growth and differentiation is understandable because DNA MEs control the expression of tissue specific genes [32], and 2'O-ribose MEs of pre-rRNA control the production of ribosome [33], which in turn play an important role as the master check point to initiate cell cycle [34]. Enhanced production of ribosome if locked in place becomes a force to drive carcinogenesis [35,36]. Usually, enzymes playing important regulatory roles are often subjected to delicate regulations. Allosteric regulation is the most pervasive biological regulation. Growth regulation is an exceptionally important biological regulation. Thus, MEs are subjected to double allosteric regulations [37]. On the individual enzymes, MEs are under the regulation of steroid hormones or related factors. SAHH is the receptor of steroid hormones, requiring steroid hormones to assume a configuration in order to form dimeric enzyme complex with MT. MT-SAHH dimer has a mass similar to MAT to form ternary enzyme complex with MAT, which is the most stable and the functional unit of MEs [29]. On the enzyme complex, MEs are under the regulation of telomerase and chemo-surveillance [14]. The association with telomerase greatly increases the stability of MEs to promote exceptional growth needed to develop the fetus or to heal wounds, which are two normal functions of abnormal MEs. Interference of the normal functions of abnormal MEs is detrimental, as the interference of abnormal MEs by thalidomide results in malformation of the body parts, noticeably limbs. Maternal DIs and DHIs may also produce interfering effects on the fetal development. That do not happen. Placenta must play a barrier to limit the entrance of maternal DIs and DHIs into fetal blood system. The nature has a perfect design to avoid pathological consequences of abnormal MEs. Following the nature's direction is the best policy to avoid and to correct misfortunes. We are following the nature's direction to pursue cancer therapy, unknowingly of course. The cancer establishments are doing the opposite to fail cancer therapies.

In summary, the valid concept of cancer evolving due to wound unhealing was introduced by Virchow in 1858. Wound unhealing forces PSCs to evolve into CSCs and then to progress to faster growing CCs by the activation of oncogenes or inactivation of suppressor genes. The appearance of CSCs and CCs are due to wound unhealing. CSCs are critically linked to wound unhealing, but CCs are not linked to wound unhealing. Induction of termination differentiation is the only option to solve CSCs because CSCs are critically linked to wound unhealing and the induction of terminal differentiation of PSCs and CSCs is a critical mechanism of wound healing.

Killing is not an option to solve CSCs, besides, CSCs are very tough to kill. CCs can be solved either by induction of terminal differentiation or cell killing with cytotoxic agents, radiation or immunotherapeutic agents. Induction of terminal differentiation is the nature's choice of cancer therapy, but is rejected by the cancer establishment because it cannot eliminate tumor mass. The cancer establishments prefer cell killing to eliminate tumor mass. This is the major strategy of cancer establishments during the last 50 years of unsuccessful cancer therapies. The failure is attributable to the ineffectiveness against CSCs and the contribution to the destruction of chemo-surveillance. The nature creates chemo-surveillance as a safety mechanism to prevent cancer from taking place and to cure cancer [17], which is the approach we are pursuing to win the war on cancer following the guidance of Virchow's wound healing.

Eradication of CSCs is Essential to the Success of Cancer Therapy

Myelodysplastic syndromes (MDSs) are diseases to testify the validity of Virchow's hypothesis. MDSs often start with a display of an immunological disorder or wound unhealing which prompt the local production of inflammatory cytokines [38]. Among such cytokines, tumor necrosis factor (TNF) is the critical factor related to the development of MDSs [39]. It causes excessive apoptosis of bone marrow stem cells, thus severely affecting the ability of the patient to produce hematopoietic sells such as erythrocytes, platelets or neutrophils. TNF is also named cachectin after its notorious effect to induce cachexia symptoms which are commonly shared by inflammatory and cancer patients. A manifestation of cachexia symptoms is excessive urinary excretion of low molecular weight metabolites because of vascular hyperpermeability caused by TNF [40,41]. Wound healing metabolites are among low molecular weight metabolites excreted to result in the collapse of chemo-surveillance. As a consequence, chemo-surveillance normally operating in healthy people to complete terminal differentiation of PSCs becomes dysfunctional forcing PSCs to evolve into CSCs in order to replenish unipotent stem cells wiped out by TNF. The propagating pathological cells of MDSs have been identified as human CSCs [42]. TNF has been described as oncogenic inducing protein [43]. So, MDSs are diseases arising due to wound unhealing according to the advice of Virchow [25].

The best solution of MDSs is to follow the wound healing process to induce terminal differentiation of PSCs and CSCs critically linked to wound unhealing. So far, Vidaza, Decitabine and CDA-2 were the three drugs approved by the Chinese FDA for the therapy of MDSs. CDA-2 was a preparation of wound healing metabolites purified from urine we produced [22]. Vidaza and Decitabine were also approved by the US FDA for the therapy of MDSs. Professor Ma, the Director of Harbin Institute of Hematology and Oncology, was instrumental in conducting the clinical trials of all three MDSs drugs. According to his assessments based on two cycles of treatment protocols, each 14 days, he has found a noticeably better therapeutic efficacy of CDA-2 based on cytological evaluation, although slower to reach complete remission., and a markedly better therapeutic efficacy of CDA-2 based on the hematological improvement evaluation, namely becoming independent on blood transfusion to stay healthy, as shown in Figure. 2, which is reproduced from the reference [44]. Evidently, inactivation of abnormal MEs is the only approach for the therapy of MDSs. CDA-2 destabilizes abnormal MEs by targeting telomerase the tumor factor of abnormal MEs [12-14] that is a selective pharmacological action against abnormal MEs, whereas Vidaza and Decitabine inactivate MEs by covalent bond formation of MT with 5-azacytosine incorporated into DNA, which is not a selective pharmacological action against cancer cells [45]. CDA-2 is devoid of adverse effects, whereas Vidaza and Decitagine are proven carcinogens [46, 47], and very toxic to DNA [48-50]. CDA-2 is convincingly the drug of choice for the therapy of MDSs, the diseases attributable entirely to CSCs. We are the clear winner on the eradication of CSCs, and therefore, the winner of the contest of cancer therapies [10]. Our winner's status was stripped by the cancer establishments because CDA-2 could not make tumor to disappear.

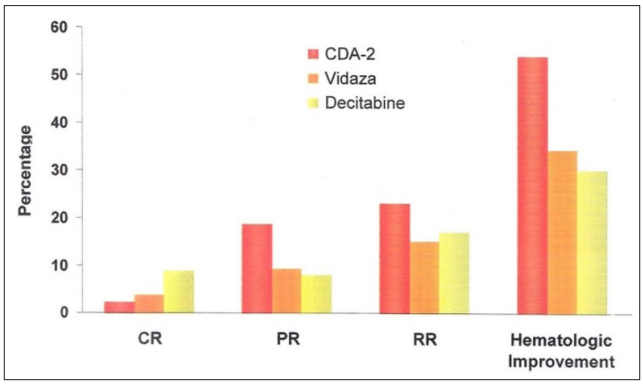


Figure 2: CDA-2 as the Best Drug for the Therapy of MDSs

The solution of CSCs is very critical to the success of cancer therapy. Of course, cancer establishments knew that. About 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 scientists of Stanford University, which was not successful, because the killing of CSCs was not an option to solve CSCs. It was very strange that there was no mention of the failure of monoclonal antibodies against CSCs, neither follow-up of potential drugs to target CSCs, as if CSCs were no longer a critical issue of cancer. Now, the focus of attention is on the immunotherapy. When there was a slime sign of promising success, the cancer establishments would raise up voice on the promising attempts. But if the promising attempts failed, they turned silent. So now, immunotherapy is the only promising attempt of cancer therapy. Cancer establishments have failed to develop cytotoxic chemotherapy and radiotherapy during the war on cancer declared by President Nixon during 1971-1976, have failed to develop gene therapy during 1976-1996, have failed to develop anti-angiogenesis therapy during 1996-2016, and now half way on immunotherapy during 2016-2036 still unable to turn around cancer mortality from escalation to deceleration [1,2,51]. Cancer establishments have failed miserably so far, what is the next if they fail the attempt of immunotherapy. We hope they will pick CDA therapy. Had they pick CDA therapy following the advice of Virchow, they could claim victory of war on cancer during 1971-1976 to equal the accomplishments of other professions and to avoid so many agonizing failures. We have made attempt to compare therapies in practice on important parameters of cancer such as CSCs, CCs, unipotent stem cells (USCs), chemo-surveillance, immuno-surveillance, tumor shrinkage and life-long survival, and shows the results in Table 2.

Table 2: A Comparison of Cancer Therapies on CSCs, CCs, USCs, Chemo-surveillance, Immuno-Surveillance, Tumor Shrinkage and Life-Long Survival

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

Targeted	-	A	-	+	0	-	+

Effects on CSCs: + means able to induce terminal differentiation and – means unable to induce terminal differentiation; on CCs: A means induction of terminal differentiation and B means cell killing; on unipotent stem cells (USCs): + means can damage and – means no affect; on chemo-surveillance: + means can improve and – means can damage; on immuno-surveillance: 0 means no effect, - means can damage and + means can improve; on Tumor Shrinkage: - means cannot cause tumor shrinkage and + means can cause tumor shrinkage; on Life-long Survival: + means patient can survive until natural death and – means patient' death is attributable to cancer or its treatments, + Early means life-long survival for early stage cancer patients and – Late means late stage cancer patients are most likely to die from cancer or its treatments.

Gene therapy and anti-angiogenesis therapy are not included because these therapies have been rejected by the cancer establishments as alternates of cytotoxic agents which they knew were not good for cancer therapy, but kept on using them because they could not find the alternates. The alternate is clearly CDA formulations, but they do not like CDA formulations that cannot cause tumor to disappear. CDA formulations are the clear winner of the war on cancer, but the winner's status is denied by the cancer establishments. Cancer establishments are trapped in belief that killing of CCs is the best strategy to solve cancer. That strategy is only successful on the early stage cancer patients. The early stage cancer patients may include CDA levels above 2.5, stage I and II patients without evidence of metastasis, Gleason scores below 7 and CSCs count below 1% [52]. The success of cytotoxic cancer therapy on the early stage cancer patients is actually due to the restoration of chemo-surveillance to subdue CSCs, not by cytotoxic agents. If cancer establishments insist on the commanding principle of killing CCs, immunotherapy is a better version. It is a targeted therapy on program death antigen of CCs to spare excruciating toxic agents of chemotherapy and radiotherapy. Actually, CDA therapy and immunotherapy can make a perfect combination of cancer therapy everybody can accept, CDA therapy to eradicate CSCs to achieve life-long survival and immunotherapy to cause the shrinkage of tumor cancer establishments like.

Wound healing is not a big deal. It comes naturally. Take surgical wound for example, suture and antibiotic application are subsidiary to speed up the healing and to prevent infection. Healing comes naturally because people are protected by chemo-surveillance. But if chemo-surveillance is not functioning at its proper level, healing may not come naturally. The appearance of cancer is an indication that chemo-surveillance has been badly damaged as shown in Table 1. There is a need to increase CDA levels to the healthy level of 5.0 to ensure perfection of wound healing to achieve therapy of cancer. Cancer therapy will not come naturally as the healing of wound. But if the therapy is following the course of wound healing, the therapy of cancer can be as easy as wound healing. If the therapy does not follow ithe course of wound healing, the therapy is likely to fail.

CDA Formulations to Win the War on Cancer

We have carried out extensive studies of natural and non-natural DIs and DHIs for the manufacture of CDA formulations [2,9,11,22,53-60]. Active DIs and DHIs are summarized in Table 3 and 4. ED25, 50, and 75 of DIs and reductive index0.5 (RI0.5) of DHIs are included to facilitate manufacture of CDA formulations. RI0.5 of a DHI is equivalent to ED25 of a DI, which can be determined by the procedure presented in the reference [56].

Table 3: 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

DIs and DHIs can be excellent cancer drugs, which are not regarded highly by cancer establishments, because these drugs cannot make tumor to disappear. These excellent cancer drugs are primarily used in the treatment of hematological cancers. ATRA, a DI, is the standard care of acute promyelocytic leukemia [61] and gleebec, a DHI, is the standard care of chronic myeloid leukemia [62]. ATRA requires the expression of the receptor of ATRA, namely RAR, to achieve the therapy. RAR is a repressor of the gene oligoisoadenylate. The association of RAR with ATRA activates oligoisoadenylate gene transcription to produce oligoisoadenylate synthetase [63]. The product of this enzyme, oligoisoadenylate, is the DI to act on abnormal MEs. So, ATRA is actually an indirect DI. It requires the cancer cells that express RAR for ATRA to become an effective DI. The rest of DIs presented in Table 3 are direct DIs to act on abnormal MEs. Arachidonic acid (AA) and its metabolites prostaglandin (PG) derivatives are natural DIs to involve in chemo-surveillance. BIBR1532 and boldine are non-natural DIs, which have been approved for cancer therapy as telomerase inhibitor. PGJ2 and PGE2 have also been approved for delivery. Change of indication of the approved drugs does not take long clinical trials as the new drugs which usually take 10 years to complete clinical trials.

Table 4: Active DHIs

SAHH Inhibitors (μM)	$RI_{0.5}$ (uM)	STIs	$RI_{0.5}$ (uM)
Pyrvinium Pamoate	0.012	Sutent	0.28
Vitamin D3	0.61	Berberine	1.62
Dexamethasone	0.75	Vorient	10.1
Beta-Sitosterol	1.72	Gleevec	11.9
Dehydroepiandrosterone	1.79	Selenite	19.7
Prenisolone	2.22	Polyphenols	$RI_{0.5}$ (μM)
Hydrocortisone	4.59	Tannic Acid	0.37
Pregnenolone	7.16	EGCG	0.62
MT Inhibitors	$RI_{0.5}$ (μM)	Resveratrol	1.16
Uroerythrin	1.9	Curcumin	1.24
Hycanthone	2.1	Kuromanin	1.43
Riboflavin	2.9	Coumestro	1.95
MAT Inhibitors	$RI_{0.5}$ (μM)	Genisteine	2.19
Indol Acetic Acid	220	Pyrogallol	3.18
Phenylacetylvaline	500	Silibinin	3.80
Phenylacetylleucine	780	Caffeic Acid	3.87
Butyric Acid	850	Ellagic Acid	4.45
Phenyl Butyric Acid	970	Gallic Acid	5.35
		Ferrulic Acid	7.41
		Phloroglucinol	36.82

As shown in Table 4, inhibitors of SAHH and MTs are better DHIs than inhibitors of MAT. The stability of the three MEs is proportional to the mass [29]. SAHH is the smallest of the three, which requires a stabilizing factor such as a steroid hormone to assume a stable configuration to form a dimeric enzyme complex with MT. The mass of MAT equals the mass of dimeric complex of MT-SAHH. MAT is the largest and the most stable enzyme of the three MEs. The association of MAT with telomerase further increases it stability. So, it takes large amounts of inhibitors to function as DHIs. Inhibitors of SAHH and MT are much better DHIs than inhibitors of MAT. Although pregnenolone is not a very active DHI, we consider it as a very valuable DHI. It is the master substrate of all biologically active steroids. It is also a single metabolite to have profound influence on the development of cancer. According to Morley, the production of pregnenolone is bell shape in relation to ages with a peak daily production of around 50 mg at the ages of 20-25 [64]. The youngest and the oldest people produce the least amounts of pregnenolone, and these two age groups are the most vulnerable to develop cancer. It is our top choice of DHI to make CDA-CSC formulations.

DIs are more important than DHIs on the induction of terminal differentiation. But DIs alone cannot achieve differentiation to reach completion., because elimination of telomerase from abnormal MEs tends to cause the dissociation of MEs into individual enzymes. MT as a monomer has a tendency to be modified by protease to become nuclease, which can create damage to disrupt differentiation process. The damage can be repaired to cause recurrence. The therapy of acute promyelocytic leukemia with ATRA is excellent, but the majority of patients recur within a year [61]. The inclusion of SAHH or MT inhibitors can keep MT-SAHH dimer intact to prevent modification of monomeric MT to become nuclease to disrupt differentiation process. It is a good idea to have both DIs and DHIs to make CDA formulations. The findings of signal transductions inhibitors (STIs) as excellent DHIs is expected, since signal transductions (STs) always lead to the production of factors to stimulate the activity of MEs. The finding of polyphenols as excellent DHIs is a surprise. Epigallocatechin-3-gallate (EGCG) has been reported as a good STI to inhibit MT [65]. It is possible that STI is the mechanism of action of polyphenols as DHI. Polyphenols are generally considered as healthy foods. The finding of polyphenols as excellent DHIs adds the credibility of polyphenols as healthy foods.

The manufacture of CDA formulations can be the following formula to reach plasma concentrations as ED25 of a DI + 3xRI0.5 of a DHI, or a ED50 of a DI + 2xRI0.5 of a DHI, or ED75 of a DI + 3xRI0.5 of a DHI [9]. We recommend to make two sets of CDA formulations: one set CDA-CSC consisting of AA + pregnenolone to get access to CSCs, and another set CDA-CC consisting of BIBR1532 + pyrvinium pamoate to resist enzymatic degradation of active components to target CCs. The application of phenylacetylglutamine is also recommended to antagonize the effect of TNF, which can be administered independently from CDA formulations as capsule preparation and monitored independently on the CDA levels. The therapeutic endpoint can be a steady recovery of CDA to the healthy level of 5.0 of the Table 1. That is not sufficient. We have to establish more convincing endpoint such as the drop of carcinoembryonic antigens to the level of healthy people. In consideration on the selection of DIs and DHIs to make CDA formulations, we must also take into considerations non-cancer issues such as blood brain barrier of brain tumors, hypoxia factors of melanomas, and collagen envelop of pancreatic cancers. Those non-cancer issues are also very important to dictate the effectiveness of cancer therapy. These are all new endeavors. A lot of work remains to be done to overcome the difficult hurdles.

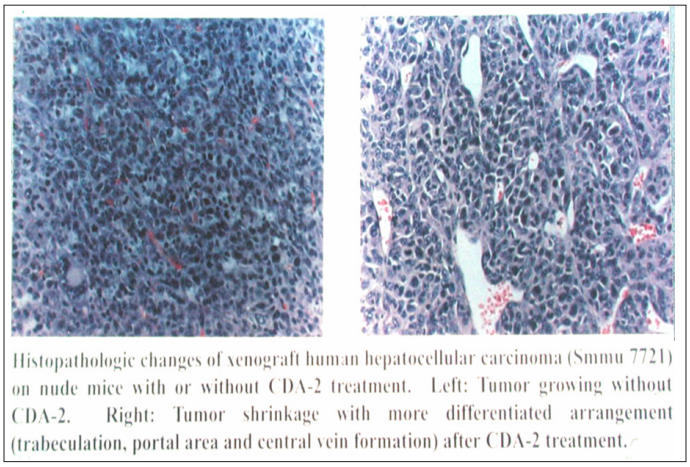
Promotion of CDA Formulations to Win the War on Cancer

Whatever happens naturally is the creation of the nature to benefit humans. Photosynthesis is a prime example. Photosynthesis

converts carbon dioxide into oxygen and to generate glucose as the source of energy to sustain the living of all organisms. Immuno-surveillance and chemo-surveillance are also the creation of the nature to benefit humans. Chemo-surveillance in particular is the design of the nature for the perfection of wound healing to avoid cancer. Virchow was exceptionally talented to comprehend the nature's creation to introduce the concept of cancer evolving due to wound unhealing, which was not accepted by the cancer establishments. The cancer establishments preferred to see the disappearance of tumor to combat cancer. It failed to win the war on cancer during 1971-1976; failed to develop anti-angiogenesis therapy during 1996-2016; and is still failing to develop immunotherapy during 2016-2036. The development of gene therapy during 1976-1996 was the only period cancer establishments were pursuing a valid approach on cancer therapy, because 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 events critically related to mess up growth regulations. Chromosomal abnormalities attracted most attention. The cancer establishments picked gene therapy as the first choice to replace cytotoxic chemotherapy, which they knew was unable to solve cancer. Gene therapy and CDA therapy are competing therapies on growth regulation, CDA to block differentiation to keep cells in cell cycle, and chromosomal abnormalities to accelerate cell cycle to promote perpetual cell growth. We were convinced that abnormal MEs were more important than chromosomal abnormalities, because abnormal MEs took place at the beginning of the life and shared by all cancers as described in the section of 2.1, whereas chromosomal abnormalities took place on CSCs, a late event, and varied among different cancers. The primary causes of chromosomal abnormalities are translocations to activate oncogenes and deletions or silencing by DNA methylation to inactivate suppressor genes. Silencing by DNA methylation is easier to fix, but chromosomal translocations and deletions are very difficult to fix. Actually, gene therapy is not a good choice. These genes are cell cycle regulatory genes which have important roles to play when cells are in cell cycle replicating. But if cells exit cell cycle to undergo terminal differentiation, they have no roles to play. So, induction of terminal differentiation is a smarter way to solve the issue of chromosomal abnormalities. The cancer establishments wasted 20 years to learn the difficult of gene therapy. Had they succeeded in developing a gene therapy, it was not going to last very long, as there were multiple ways to cause gene abnormalities.

CDA formulations and cytotoxic agents are also competing on the solution of perpetual proliferation. CDA formulations to put out CSCs and CCs by the induction of terminal differentiation, whereas cytotoxic agents by killing of CCs. CDA formulations have the advantage to eradicate CSCs to achieve life-long survival, but have a disadvantage not able to remove residual tumor. Cytotoxic agents have the blessing of the cancer establishments to achieve reduction of tumor mass, but are unable to eradicate CSCs to save advanced cancer patients. Obviously, CDA formulations are the nature's creation to win the war on cancer, but the commanding principle of killing CCs is favored by cancer establishments. To win the approval of cancer establishments becomes the most difficult issue of cancer. We have to develop a strategy to overcome the blockade of cancer establishments.

Strategies to develop CDA formulations are to win the approval of hematological oncologists, surgical oncologists and oncologists in attendance of metastatic, unresponsive and recurrent cancer patients. Tumor shrinkage is not an issue in hematological cancer. The endpoint of hematological cancers is the disappearance of cancer cells, which have morphology distinctly different from terminally differentiated cells. There are no arguments on the endpoint either using CDA to induce terminal differentiation or using cytotoxic agents to kill CCs. Hematological oncologists accept differentiation therapy as well as cytotoxic therapy. They may like differentiation therapy better, because differentiation therapy is not as excruciating and fatal as cytotoxic therapy. If the evaluation of the therapeutic efficacy of solid tumor is also based on the examination of the morphology like hematological cancers, differentiation therapy can produce distinctly different morphological feature vastly different from the morphology of undifferentiated tumor as shown in Figure 3, which is reproduced from the reference [66].



Histopathologic changes of xenograft human hepatocellular carcinoma (Smmu 7721) on nude mice with or without CDA-2 treatment. Left: Tumor growing without CDA-2. Right: Tumor shrinkage with more differentiated arrangement (trabeculation, portal area and central vein formation) after CDA-2 treatment.

Figure 3: Induction of Histological Modification of Hepatoma by CDA-2

Unfortunately, radiological image can only detect size difference, but cannot reveal morphological details.

Tumor shrinkage is also not a concern of surgical oncologists. The most important concern of surgeons is the dissemination of metastasis. Metastasis is the making of CSCs [5], and CDA formulations are the best drugs to handle CSCs as described in the section 2.2. We have published an article to call for the collaboration of surgeons and cancer patients to push for the approval of CDA formulations to make surgery a top choice of cancer therapy [67].

CSCs are a dominant issue of metastatic, unresponsive and recurrent cancer patients. There are no drugs available for the treatment of CSCs. These patients are often advised to undergo hospice care. Metastasis is caused by severe damage to chemo-surveillance. Unresponsiveness is due to the build-up of CSCs above 3% of the tumor mass [68]. Recurrence is due to the build-up of CSCs. Metastasis, unresponsiveness and recurrence are all attributable to CSCs, which can only be rescued by CDA formulations, the only drugs effective to eradicate CSCs [69]. CDA formulations are indeed persuasive good cancer drugs with excellent therapeutic efficacy without adverse effects [70-75] to help oncologists to take care of desperate cancer patients unresponsive to cytotoxic therapies. So, CDA formulations can save approximately 75% of cancer patients in the desperate state, and cytotoxic cancer therapies can only save 25% of cancer patients in the early state.

Conclusion

Cancer evolves due to wound unhealing because of the collapse of chemo-surveillance, which is a safety mechanism created by the nature for the perfection of wound healing to avoid cancer. Restoration of chemo-surveillance with CDA formulations is the nature's choice to win the war on cancer. Cancer establishments prefer killing CCs exactly the opposite to the advice of Virchow to result in ever-escalation of cancer mortality to reach 10 million annually worldwide. Cancer establishments are unable to win the war on cancer. But they are very powerful to block CDA formulations to deny the success to win the war on cancer. We have to seek the collaboration of hematological oncologist, surgical oncologists, and oncologists in attendance of metastatic, unresponsive and recurrent cancer patients to overcome the blockade of cancer establishments.

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Conflicts of Interest

The authors declare no conflicts of interest.

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