

## CDA Formulations to Fulfill Cancer Moonshot and to Win the War on Cancer

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### ABSTRACT

*The objective of this study is to call for approval of cell differentiation agent (CDA) formulations as the right cancer drugs to save cancer patients. Moonshot was a presidential project to set a classic record of success attributable to the right approach and war on cancer was another presidential project to set a classic record of failure attributable to the wrong approach. Cancer moonshot was brought up by President Biden to urge health profession to rely on right approaches to save cancer patients. Perpetual replication of cancer cells (CCs) is the most outstanding feature of cancer. Naturally, killing of replicating CCs becomes the top choice of cancer establishments to combat cancer. Killing of CCs is actually a wrong approach of cancer therapy, because cancer is caused by wound unhealing due to the collapse of chemo-surveillance, which is a natural mechanism to ensure perfection of wound healing. Killing of CCs by cytotoxic agents promotes cancer stem cells (CSCs) to proliferate in order to repair the damages created by cytotoxic agents, eventually pushing CSCs to reach a high proportion to become unresponsive to further treatments. Killing of CCs is a wrong approach that causes the failure of cancer solution.*

*To save cancer patients, we have to drastically change past practices. Apparently, wound healing process is the right approach of cancer therapy. Induction of terminal differentiation of PSCs is the most critical mechanism of wound healing, which is achieved by differentiation inducers (DIs) and differentiation helper inducers (DHIs). CDA is a collective term of the preparations consisting of different proportions of DIs and DHIs. Therefore, CDA formulations are the best solution of cancer to fulfill cancer moonshot and to win the war on cancer. CDA formulations display the features as pro-wound healing that can eliminate both CSCs and CCs by inducing these cells to undergo terminal differentiation, and to restore the functionality of chemo-surveillance, which is the creation of the nature to prevent the buildup of cells with abnormal MEs. A perfect cancer drug must have the ability to eliminate both CSCs and CCs, and to restore the functionality of chemo-surveillance. CDA formulations fit the description as perfect cancer drugs to fulfill cancer moonshot and to win the war on cancer.*

### Keywords

Cancer moonshot, Cytotoxic agents, CDA, CSCs, PSCs, Terminal differentiation, War on cancer, Wound healing.

### Introduction

Cancer is a medical problem badly handled by the medical profession in the past to result in high mortality. Cancer deaths are only next to cardiovascular diseases worldwide [1]. Cancer is the top killer of most industrialized rich nations except USA. In 2019, there were 18.6 million new cases and 10.0 million cancer

related deaths worldwide [1]. NCI predicted that both incidence and mortality were on the way up by an increment of 0.5 million annually. Cancer establishments tend to pay attention to the more visible but not essential issues of cancer and to neglect the less visible but very critical issues of cancer [2]. Thus, they are unable to solve cancer. Perpetual proliferation of CCs is the most outstanding feature of cancer. So, they put up all efforts on the killing of CCs, which is a wrong approach of cancer therapy because cancer is caused by wound unhealing [3]. They totally neglected CSCs, which constituted less than 2% in most popular

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cancers and replicated slowly. This not so visible subpopulation, however, contributes the most fatal effects of cancer such as metastasis, recurrence, drug resistance and angiogenesis [4]. They neglected CSCs, because they could not handle CSCs, which were protected by drug resistant and anti-apoptosis mechanisms. Their negligence on CSCs was a major factor to cause the failure of war on cancer, and all failing events of cancer thereafter [5]. Cancer establishments are responsible for the failure to solve cancer, and their failure result in the deaths of cancer patients [6]. The only way to save cancer patients is to appoint cancer leaderships who are willing to correct the mistakes made by cancer establishments in the past. But there are no mechanisms within the health profession to replace inept leaderships. Only presidents of USA have the authorities to replace leaderships in charge of federal agencies. The replacement of leaderships of federal health agencies can have immense impact to correct the wrong doings of past cancer establishments to save cancer patients.

## **Commentaries and Discussions**

### **Moonshot and War on Cancer Set Classis Records of Success and Failure**

Moonshot was a presidential project initiated by President Kennedy in 1962 and war on cancer was another presidential project initiated by President Nixon in 1971. A presidential project must deal with a monumentally important issue, which carries a 5-year limit with an unlimited support of national resource. There were only three presidential projects in the history of USA. Manhattan project to develop atomic bomb of President Roosevelt was the third presidential project, which was successful. Moonshot was an immensely difficult project. USA was the only nation able to achieve this difficult challenge. The success of moonshot was attributable to the right approach, and the failure of war on cancer was attributable to the wrong approach [7]. Thus, a right approach is the determinant of success no matter how difficult is the challenge. On the other hand, a wrong approach always leads to failure even dealing with a simple matter. Cancer and wound healing are the same issue. Wound healing is a simple matter. Therefore, cancer should also be a simple matter. Cancer establishments made it impossible to solve by pursuing wrong approaches.

### **Cancer Arises as a Consequence of Wound Unhealing**

The concept of cancer as wound unhealing was first introduced by the great German scientist Virchow in the 19<sup>th</sup> century [8]. It was again brought up by Dvorak in 1986 [9]. The close relationship between cancer and wound healing was noticed by MacCarthy-Morrhough and Martin [10]. We provided the most important details on this subject that included abnormal methylation enzymes (MEs) to block differentiation [11-13]; chemo-surveillance as the creation of the nature to ensure perfection of wound healing to avoid cancer [14-17]; DIs, which are chemicals capable of eliminating telomerase from abnormal MEs, and DHIs, which are inhibitors of MEs capable of potentiating the activity of DIs, as wound healing metabolites and also as active players of chemo-surveillance [14-17]; hypomethylation of nucleic acids as the most critical mechanism for the induction of terminal differentiation of cells with abnormal MEs [18]; the mechanism of wound healing

to involve the proliferation and the terminal differentiation of PSCs [19-22]; and the evolution of CSCs from PSCs due to wound unhealing [3,23,24]. These studies clearly established that cancer arose as a consequence of wound unhealing. Our carcinogenesis studies confirmed the validity of such findings [3]. Our studies revealed that the host tissue was actively engaged in the repair of damages caused by carcinogen challenge through replication of PSCs, which displayed abnormal MEs as numerous tiny hyperplastic nodules. Most of these nodules disappeared, indicating successful wound healing. Only a few nodules which did not heal the wound completely later developed to become large carcinomas [25]. If the functionality of chemo-surveillance could be sustained at the healthy level to ensure perfection of wound healing, then carcinogenesis could be prevented [26,27]. Chemo-surveillance is indeed a very beneficial creation of the nature to avoid cancer.

### **Chemo-surveillance as an Important Issue of Wound Healing**

Wound healing comes naturally. Treatments such as suture and antibiotic are basically subsidiary to speed up the healing process and to prevent infection. Wound healing is a very important health issue so that the nature creates chemo-surveillance to ensure perfection of wound healing to avoid bad consequences from wound unhealing that include tissue fibrosis, dementia, organ failure and the worst cancer [28]. Evidently abnormal MEs, chemo-surveillance, PSCs, membrane permeability and cachexia are very important issues closely related to wound healing. CSCs are evolved from PSCs by a single hit to silence TET-1 enzyme [3,23,24]. Both PSCs and CSCs display similar cell features and biological missions. Problems related to PSCs are also the problems of CSCs. Chemo-surveillance, PSCs and CSCs are the most critical issues of cancer. Likewise, they are also the most critical issues of wound healing.

Chemo-surveillance was a term we created to describe a natural defense mechanism against cancer [14]. Human body produces metabolites that can inhibit the growth of cancer cells. Such active metabolites can be purified from urine by reverse phase chromatography on C18, which Burzynski gave the names Antineoplastons [29]. Active components of Antineoplastons are DIs and DHIs. Both are inhibitors of abnormal MEs to target telomerase or MEs [30-37]. We used XAD-16 instead of C18 to purify wound healing metabolites from urine and gave the name cell differentiation agent-2 (CDA-2) [38]. Peptides are important active components of Antineoplastons, which cannot be retained by XAD-16. Common important DIs of Antineoplastons and CDA-2 include arachidonic acid in liposomal complex with pregnenolone or in association with membrane fragments. Acidic peptides present only in Antineoplastons. Common important DHIs include pregnenolone, uroerythrin, amino acid derivatives, fatty acid derivatives, pregnenolone and steroid metabolites. Active DIs of Antineoplastons and CDA-2 are remarkably similar to wound healing metabolites identified by Ho et al. [39] as arachidonic acid and its prostaglandin derivatives. It is very convincing that chemo-surveillance is the nature's creation to ensure perfection of wound healing to avoid bad consequences of wound unhealing.

We have studied peptide profiles of body organs, and only the peptide profile of spleen extract fitted the plasma peptide profile [40]. We, thus, suggested that plasma peptides were the degradative products of hemoglobins because spleen was the organ to process dead erythrocytes. Peptides can be retained by C18 like active DIs and DHIs of wound healing metabolites. Therefore, peptides can serve as the surrogate molecules of wound healing metabolites. Quantitative assays of plasma and urinary peptides revealed that healthy people could maintain a steady level of plasma/urinary ratio around 0.8 [12,40]. We assigned the ratio of 0.8 as the healthy CDA5. Cancer patients all showed CDA levels less than 5. The distribution of cancer patients in percentages among CDA levels of 5: 4: 3: 2: 1: 0.5 were 1.8: 6.5: 16.7: 35.2: 22.2: 19.6 [14]. Only the patients with CDA level above 3 can benefit from the therapy based on killing of CCs. The treatment with cytotoxic agents further causes CDA levels to go down, and the levels above 3 must be the levels that can allow patients to achieve complete remission and to restore the level of CDA back to 5 of the healthy state to subdue the surviving CSCs which cannot be eradicated by cytotoxic agents [41]. Patients with CDA levels below 3 have no chance of recovery to the healthy status. The killing of CCs triggers the proliferation of CSCs to repair the damage cytotoxic agents created, gradually the proportion of CSCs will reach the level unresponsive for further treatment. Most popular cancers have CSCs less than 2% in the primary state, which are manageable by cytotoxic therapies for a short while not allowing CSCs to reach the level unmanageable. This level is around 10%. The primary malignant brain tumors are enriched with CSCs to the level of around 10%, which are untreatable by conventional cytotoxic therapies [42]. Cancer mortalities remain at historical high, because therapies based on killing of CCs can only benefit cancer patients in early state with CDA level above 3. The majority of patients eventually will become unresponsive to further treatments as President Jimmy Carter and Jane Fonda to contribute to high cancer mortalities [2]. Advanced patients at CDA below 3 who are lucky to reach complete remission will also succumb to recurrence, because CDA levels are too low to subdue surviving CSCs.

Apparently, wound healing is a very important issue of health, so that the creator creates chemo-surveillance to ensure perfection of wound healing. The protection of the functionality of chemo-surveillance is, therefore, extremely important to dictate the success of wound healing and cancer therapy [41,43]. Cytotoxic agents contribute to the damage of chemo-surveillance, which are bad for cancer therapy. CDA formulations restore the damaged chemo-surveillance, which are good for cancer therapy.

### **CSCs at the Center of Cancer Problems**

PSCs are at the center of wound healing problems. Wound healing requires the proliferation and the terminal differentiation of PSCs [20]. Efficient terminal differentiation of PSCs dictates the success of wound healing [43]. Likewise, efficient terminal differentiation of CSCs dictates the success of cancer therapy. CSCs constitute only a small minority of cancer population, usually less than 2%. Most fatal effects of cancer such as metastasis, recurrence, drug

resistance, and angiogenesis are the making of CSCs. CSCs must be eliminated to make therapy of cancer successful. Cytotoxic agents are ineffective against CSCs, because these cells are protected by drug resistance and anti-apoptosis mechanisms. The biological missions of CSCs are like PSCs to carry out repairment. Cytotoxic agents create damages, which promote the proliferation of CSCs, eventually causing the patient to become unresponsive to further treatments and fatality [2,6]. Even the lucky patients achieving complete remission are eventually succumbed to remission, if the functionality of chemo-surveillance cannot be restored to subdue surviving CSCs. CDA formulations are the partners of CSCs on their repair missions [6]. Therefore, CDA formulations are the ideal medicines to eradicate CSCs. Myelodysplastic syndrome (MDS) is a classic disease to illustrate the evolution of cancer due to wound unhealing, and wound healing metabolites as the best solution of MDS.

MDS often starts with a display of an immunological disorder [44], which prompts the local production of inflammatory cytokines, tumor necrosis factor (TNF) is the critical factor related to the development of MDS [45]. It causes excessive 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 symptoms. A manifestation of cachexia symptoms is the excessive excretion of low molecular weight metabolites. Wound healing metabolites are among such low molecular weight metabolites excreted, resulting in the decrease of CDA from the healthy level 5 downward as found in cancer patients above described. The proliferation of PSCs to repair wound is limited by the space of wound through contact inhibition. If wound is not healed properly to eliminate the symptoms created by the wound, pressure will build up to force the evolution of PSCs to become CSCs in order to escape contact inhibition. MDS is at the stage of PSCs evolving into CSCs. The propagating pathological cells of MDS have been identified as CSCs [46]. Since MDS is attributable entirely to CSCs. This is the disease to evaluate the effectiveness of cancer drugs against CSCs, which are the most important issue of cancer. Cancer establishments ignore CSCs as an important issue of cancer. They are more concerned with more visible issues of CCs, but the solution of CCs alone cannot solve cancer. MDS is a disease to serve as a good model for the Litmus test of right cancer drugs. A right cancer drug must be able to induce pathological cells of MDS to differentiate into functional cells to eliminate anemia. We have brought up the argument that the winner of the contest to eradicate CSCs win the contest of cancer therapies, and apparently, CDA formulations are the winner [47].

CDA-2, vidaza and decitabine are the three drugs approved by the health authorities for the therapy of MDS, CDA-2 by the Chinese FDA in 2017 [48]. Vidaza and decitabine were approved by the Chinese and US FDA much earlier. We have carried clinical trial of CDA-2 on MDS during 2004 and 2007 in collaboration with Professor Jun Ma, the Director of the Institute of Hematology and Oncology of Harbin, China, who was instrumental on the clinical trials of vidaza and decitabine in China. We have collaborated

on the clinical trial of 117 MDS patients. Based on two cycles of treatment protocol, each 14 days, CDA 2 had slightly better therapeutic efficacy based on cytological evaluation, and markedly better therapeutic efficacy based on hematological improvement evaluation, meaning patients were no longer dependent on blood transfusion. The elimination of symptoms created by wound is a very important issue of cancer therapy. Induction of terminal differentiation of pathological cells is the only way to eliminate the symptom created by the wound. Cytotoxic agents are ineffective on MDS. They cannot solve the symptoms caused by deficiency of erythrocytes, platelets and neutrophils, which require the terminal differentiation of pathological cells. Only drugs effective to affect abnormal MEs can accomplish this goal. CDA-2 naturally is the drug of choice for the therapy of MDS, which has demonstrated better therapeutic efficacies and devoid of adverse effects, whereas vidaza and decitabine are proven carcinogens [49,50], and quite toxic to DNA [51-53]. Obviously, induction of terminal differentiation of CSCs is a critical mechanism to achieve therapeutic effect on MDS, CDA-2 by the destabilization of abnormal MEs through DIs and DHIs, and vidaza and decitabine by titrating out DNA methyltransferase by covalent bond formation between 5-azacytidine incorporated into DNA and methyltransferase. So, destabilization of MEs is a critical mechanism to achieve wound healing and elimination of CSCs. Apparently, destabilization of abnormal MEs is a better choice than nucleoside analogs [54,55]. MDS is a good model for the test of right cancer drugs. Apparently, CDA-2, vidaza and decitabine can pass the test as the right cancer drugs. All other cancer drugs approved by cancer establishments cannot pass this test. Consequently, they are all wrong cancer drugs. That is why cancer mortalities remain at historical high. NCI experts predicted in 2019 that cancer mortalities worldwide would have an annual increment of 0.5 million to keep in pace with increased incidence [1].

### **Abnormal MEs as the Bullseye of Cancer Target**

Induction of terminal differentiation through destabilization of abnormal MEs is the critical mechanism of wound healing and the eradication of CSCs. MEs are made up by ternary enzyme complex consisting of methionine S-adenosyltransferase (MAT)-methyltransferase-S-adenosylhomocysteine hydrolase (SAHH) [56]. The association of MEs with telomerase turns MEs abnormal to display  $K_m$  values of abnormal MAT-SAHH isozyme pair 7-fold higher than the normal isozyme pair [11-13]. Evidently, the increased  $K_m$  values are important for the maintenance of malignant growth, since Prudova et al. [57] demonstrated that association with S-adenosylmethionine (AdoMet) could protect protein from protease digestion, and Chiba et al. [58] showed that when HL-60 cells were induced to undergo terminal differentiation, their AdoMet and S-adenosylhomocysteine (AdoHcy) pool sizes shrank greatly. The association of telomerase with MEs plays an important role on the stability and activity of MEs to regulate cell growth and differentiation. Cell mass is very important for the development of fetus and wound healing. TET-1 enzyme is functional in normal primitive cells, which can carry out lineage transitions. The expression of TET-1 enzyme marks the difference between normal primitive stem cells and CSCs. The differentiation capability of

CSCs and their derivatives CCs is totally blocked without sufficient DIs and DHIs. The loss of DIs and DHIs is the primarily cause of cancer. Therefore, supplement with CDA formulations is an easy and effective solution of cancer. Therapy with CDA formulations can take care of most problems associated with cancer. Cancer is caused due to the collapse of chemo-surveillance. The administration of CDA formulations restore the functionality of chemo-surveillance to eradicate cells with abnormal MEs through induction of terminal differentiation, which is a normal process to achieve wound healing. The induction of terminal differentiation can also put to rest problems caused by chromosomal abnormalities, which are responsible for the activation of oncogenes and the inactivation of suppressor genes. Chromosomal abnormalities are an extremely important area of cancer. But the solution of these problems is very difficult. Induction of terminal differentiation is perhaps an easy way to solve the enormous difficulty problems of chromosomal abnormalities. Oncogenes and suppressor genes are cell cycle regulatory genes, which play important roles when cells are in cell cycle replicating. But if replicating cells exit cell cycle to undergo terminal differentiation, they have no roles to play. Induction of terminal differentiation is an easy approach to solve enormously difficult problems of chromosomal abnormalities. Killing of CCs can also accomplish the same mission, which has been tested and failed the mission to solve cancer.

### **Phenylacetylglutamine as an Effective Anti-cachexia Chemical to Protect Chemo-Surveillance**

Cancer arises due to the collapse of chemo-surveillance, and the collapse of chemo-surveillance is caused by pathological conditions producing elevated level of TNF. TNF is a major factor to contribute to cachexia symptoms and the collapse of chemo-surveillance. Phenylacetylglutamine is an inconspicuous chemical that can effectively counteract TNF to protect the functionality of chemo-surveillance [14,26,27]. The inclusion of phenylacetylglutamine is beneficial for the therapy of cancer. Its therapeutic target is TNF, which is quite different from abnormal MEs as the target of CDA formulations. The inclusion of phenylacetylglutamine as a supplement definitely is beneficial to the therapy of CDA formulations. We recommend to administer phenylacetylglutamine as a capsule preparation. The dosage and schedule of administration depend on the monitor of CDA levels of the patients.

### **CDA Formulations to Fulfill Cancer Moonshot and to Win the War on Cancer**

Apparently, cancer is caused due to wound unhealing as above described. Then, wound healing process should be the most appropriate modality of cancer therapy [22]. CDA formulation are therefore the best drugs to fulfill cancer moonshot and to win the war on cancer [4,7,36-38,48,54,55]. CDA formulations are the cancer drugs able to eradicate CSCs and CCs by inducing these cells to undergo terminal differentiation, which is the critical mechanism to achieve wound heading. Induction of terminal differentiation is actually an excellent approach of cancer therapy. Retinoic acid, a very good DI, is the standard care of acute promyelocytic leukemia. Imatinib mesylate, a very good DHI, is



longer treatment to boost the level back to the healthy level of 5. Killing of CCs by cytotoxic agents is clearly wrong, which causes CDA levels to drop further downward to the point of no return, probably at the level of CDA3. When patients have reached that critical low level, they have no chance of survival, either succumb to unresponsiveness or recurrence, because the treatment always cause CDA levels to go downward. Only the early stage cancer patients at CDA above 3 can allow CDA levels to recover to the healthy level of 5 to subdue surviving CSCs. CDA formulations can save most cancer patients, whereas cytotoxic agents can save only a small minority of early stage cancer patients.

## Conclusion

The progress of cancer therapy is very slow despite a major thrust was applied to declare war on cancer during 1971 to 1976. Cancer mortalities stay at historical high. In 2019, there were 10 million cancer deaths worldwide, and NCI predicted an annual increment of 0.5 million.

The high mortality is attributable to the pursuance of cytotoxic agents for cancer therapy, a wrong approach of cancer therapy displaying the feature as anti-wound healing and contra-indication of cancer therapy. Only early stage cancer patients whose CDA level is not fatally damaged can benefit from therapies based on killing of CCs. These therapies contribute to the damage of chemo-surveillance, eventually causing patients to succumb to unresponsiveness or recurrence. Cancer arises due to the collapse of chemo-surveillance, which is a natural mechanism to ensure perfection of wound healing. Wound healing process is the right approach of cancer therapy, which display the feature as pro-wound healing and the right indication of cancer therapy. CDA formulations are made up by DIs and DHIs, the active ingredients of wound healing. CDA formulations are, therefore, the right medicines to fulfil cancer moonshot and to win the war on cancer.

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