

RESEARCH ARTICLE

# CDA Formulations to Make Health Profession Great Again

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## Abstract

Health profession has glorious histories and dark histories. A dark history was the inability to win the presidential assignment of War on Cancer during 1971-1976. Solution of top killing diseases is an important issue of national interest. But the solution of top killing diseases is always on the low priority of politicians, unless the killing disease is a communicable disease like COVID-19. The objective of this article is to point out that the inability to win the War on Cancer was the mishandlings of cancer establishments, not the difficult of cancer which could be easily solved if the solution was right. The right solution of cancer was advised by Virchow in 1858, who introduced the concept of cancer evolving due to wound unhealing. Cancer establishments directed cancer therapies against his advice by killing cancer cells (CCs) to create wounds to stir up cancer as a giant killer to claim 10 million mortality annually around the world. Wound healing requires the proliferation and the terminal differentiation (TD) of progenitor stem cells (PSCs). Wound if not healed will force PSCs to evolve into cancer stem cells (CSCs) and then to progress to faster growing cancer cells (CCs). Wound unhealing is the cause and proliferation of CCs is the symptom of cancer. Solution of cancer can be based on the elimination of cause or symptom. Elimination of symptom is the choice of western medicine that can produce immediate effect to achieve therapy that may not last very long. Elimination of cause can achieve therapy to last lifelong. Since cancer evolves due to wound unhealing, elimination of symptom by creation of wound is obviously incorrect. Unfortunately, that incorrect approach became the adopted policy of cancer therapy and the shrinkage of tumor became a requirement of cancer drugs. The requirement of tumor shrinkage as cancer drugs in essence blocks the solution of cancer, because the solution of cancer requires induction of TD of PSCs and CSCs to heal the unhealed wounds. Thus, inability to win the War on Cancer is the fault of cancer establishments to employ a wrong approach of creation of wounds. Health profession is an authoritarian profession. The bad policy put up by cancer establishments is not allowed to be challenged by health professionals. The bad policy carries on to damage the reputation of health profession and to hurt cancer patients. It will take government officials with authority greater than the health establishments such as President Trump or Secretary of Health Robert Kennedy Jr to correct the mistakes of health establishments. President Trump is known for unconventional handling of businesses and Secretary of Health Kennedy has demonstrated willingness to challenge vaccination policy favored by health establishments. Together they can replace health establishments to make health profession great again to save 0.61 million of cancer patients and 0.92 million of cardiovascular patients killed annually in the USA. Cardiovascular diseases (CVDs) also evolve due to wound unhealing that can be solved with CDA formulations, which are drugs to heal wounds.

**Keywords:** Cancer and Cardiovascular Therapies, CDA Formulations, War on Cancer, President Trump, Wound Healing.

## 1. Introduction

Health is a great concern of ordinary people. It is critically tied to vote. Only democratic nations pay

attention to health issue. But the priority is very low, unless the threat to health is a communicable disease like COVID-19. Cardiovascular diseases (CVDs)

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and cancer are the top killing diseases which kill patients far more than COVID-19. These top killing diseases receive very little attention from politicians of democratic nations and no attention at all from politicians of authoritarian nations. Presidents Nixon and Biden were the two exceptional presidents to pay attention to the welfare of ordinary people to declare War on Cancer by President Nixon in 1971 and Cancer Moonshot Initiative by President Biden in 2022. War on Cancer was a presidential project which had a commitment of national resources but with a time limit of 5 years. Cancer Moonshot Initiative was a quasi-presidential project without national commitment and time limitation. Nevertheless, it expressed President Biden's wish to save 50% cancer patients in 25 years, a much modest demand than the War on Cancer. The health profession was very disappointing to fail the presidential assignment of War on Cancer [1], which did not require difficult technologies. War on Cancer was the third presidential project in the history of USA. Presidential projects deal with the monumentally important issues of the nation. Nuclear physicists achieved Manhattan project under President Roosevelt to conclude World War II, and rocket engineers achieved Moonshot Project under President Kennedy to show mighty technological superiority of USA. USA was the leader of health around the world. That leadership could not stand the test of War on Cancer. The failure to win the War on Cancer was a very shameful record of health profession, which did not require difficult technologies like the previous two presidential projects. The success to win the War on Cancer did require the smart brains of Virchow and Liau et al. [2, 4], which were ignored by the cancer establishments. Cancer establishments were trapped in belief that the elimination of CCs, the most outstanding symptom of cancer, by cytotoxic agents could win the War on Cancer, which was incorrect [3]. Cancer evolving due to wound unhealing was a valid concept of cancer introduced by Virchow in 1858 [4], which might be too ancient to remain in the memory of recent cancer authorities. Virchow's valid concept on cancer was brought up again by Dvorak in 1986 in a very popular medical journal that ought to catch the attention of recent cancer authorities [5]. Obviously, Virchow's valid concept of cancer was introduced too early to influence the decision of recent cancer authorities, and too late by Dvorak to change their mind. The adoption of cytotoxic cancer therapy was a tragic byproduct of World War II. During the war, toxic sulfur mustard gas bombs were employed. Victims of toxic gas all displayed deficiency of leukocytes in their blood specimens, which inspired

oncologists to employ toxic chemicals to treat leukemia patients. Indeed, toxic chemicals were very effective to eliminate leukemia cells. Cytotoxic chemotherapy of cancer thus became the standard care of not only hematological cancers but also solid cancers, and the disappearance of tumor became a standard diagnosis of the success of cancer therapy. Health profession is an authoritarian profession. Once cytotoxic cancer therapy was adopted as the standard care of cancer therapy it became the guiding principle of cancer therapy that could not be challenged by health professionals. The health profession has a bad tradition like that of communist regimes that the big bosses' policies are not allowed to be challenged. So, when the big bosses make mistakes, the mistakes carry on to damage the reputation of health profession and to hurt patients. Cancer and CVDs evolve due to wound unhealing that can be easily put away by CDA formulations to heal the wounds [6, 7]. But cancer establishments put up a rule to block CDA formulations as cancer drugs and CVDs establishments did not even know CVDs were caused by wound unhealing. The health establishments were set to remove symptoms to kill CCs or to reduce hypertension, but the mortalities of cancer and CVDs keep on escalating. Health establishments do not like to be challenged, that is why simple diseases such as cancer and CVDs cannot be solved. Health establishments are very powerful that can only be removed by more powerful authorities. President Trump and Secretary of Health Robert Kennedy Jr are the only government officials with authorities above health establishments. President Trump is known for conducting businesses unconventionally. He has changed defense department into war department to initiate wars with Venezuela and Iran. Secretary of Health Robert Kennedy Jr has demonstrated willingness to challenge vaccination policy favored by health establishments. Together, they can replace health establishments to make health profession great again to save 0.61 million cancer patients and 0.92 million CVDs patients killed annually in the USA. CVDs are also caused due to wound unhealing that can be cured by CDA formulations, which are wound healing drugs to target on abnormal methylation enzymes (MEs) [6, 7].

## 2. CDA Formulations to Make Health Profession Great Again and Discussion

### 2.1 Persistent Failures of Cancer therapies

Cancer mortality is the most faithful indicator of the success of cancer therapy. Ever since cancer became

a known disease, the mortality of cancer keeps on escalating. Every year the bureau of health and welfare of Taiwan government lists 10 top killers of Taiwanese people and cancer is always on the very top of the list for the last 44 years [8]. Cancer is the second top killer of many countries including the leader of health USA. CVDs are the top killer of many countries around the world, claiming 20.5 million mortality annually and cancer is the second top killer claiming 10 million mortality annually [8]. Perpetual proliferation of CCs is the most outstanding feature of cancer. Naturally, killing of CCs to stop proliferation of CCs is a top choice of cancer therapy. Cytotoxic cancer therapy was a tragic byproduct of World War II as described in the introduction, the elimination of which became the guiding principle of cancer therapy. When President Nixon declared War on Cancer in 1971, cytotoxic cancer therapies were the choice of cancer establishments to combat cancer, which did not reduce cancer mortality [1]. The failure to achieve a presidential assignment was inexcusable because the solution of cancer did not require difficult technologies as the previous two presidential projects. The failure was obviously the mistake of cancer establishments in charge of War on Cancer. Cancer establishments are a group of leaders with different approaches on cancer therapies. At the time of War on Cancer during 1971-1976, cytotoxic cancer therapy was in charge. The failure of War on Cancer convinced cancer establishments that cancer could not be cured by cytotoxic agents and shifted the development of cancer drugs from cytotoxic agents to other approaches, but kept failed cytotoxic cancer therapy that was inappropriate, since differentiation therapy and hormone therapy were also accepted cancer therapies at that time. Therapeutic endpoints of differentiation and hormone therapies were TD of CCs unable to cause tumor shrinkage. These therapies were out of consideration to replace cytotoxic cancer therapy. Therapeutic endpoint of gene therapy was also the induction of TD of CCs not favored by cancer establishments. Studies of chromosomal abnormalities have received many Nobel prizes to win the first choice to replace cytotoxic agents. The dominance of cancer therapy shifted from cytotoxic cancer therapy to gene therapy during 1976-1996. Chromosomal abnormalities were important factors of cancer to promote cell replication. But the solutions of chromosomal abnormalities such as mutations, translocations and deletions were very difficult. Cancer establishments finally gave up on the attempt to develop gene therapy and went back to their favored choice of killing CCs. The failure

to develop gene therapy was a good thing. If it was even partially successful, we would be trapped in a very difficult approach of cancer therapy like we are now trapped in cytotoxic cancer therapy. Cytotoxic cancer therapy was partially successful to save cancer patients in the early stage, approximately 25% of cancer patients that included stage I & II cancer patients without evidence of metastasis, Gleason scores of prostate cancer patients below 7, CSCs count below 1% [9], and CDA levels above 2.5 [10], whereas 75% of cancer patients in the advanced stage could not be helped by cytotoxic cancer therapy [11]. After the failure to develop gene therapy, the emphasis of cancer therapy was shifted to the development of anti-angiogenesis therapy to kill cancer cells by starving during 1996-2016. The development of anti-angiogenesis therapy was successful. But the success of anti-angiogenesis therapy ended up causing the deaths of cancer patients due to internal bleeding. That echoed the failure of cytotoxic cancer therapy. The failure of cytotoxic cancer therapy is often attributable to the adverse effects or recurrence. Radiotherapy of nasopharyngeal carcinoma is excellent to result in instant complete remission. But most patients succumb to stroke within a short period. Cytotoxic cancer therapy can also achieve complete remission easily. But the patients often succumb to recurrence within a short period. The inability of cytotoxic cancer therapies to eliminate CSCs, which are not responsive to cytotoxic agents [12-18], and the contribution to damage chemo-surveillance are the reasons to cause the failure of cytotoxic cancer therapies. Now, we are in an attempt of developing immunotherapy to replace cytotoxic cancer therapy during 2016-2036. The discovery of programmed death antigen to mark pathological cells to be eliminated by immune mechanisms was a remarkable scientific accomplishment, which was awarded Nobel prize in 2025. Immunotherapy is a targeted cancer therapy to spare adverse effects on unipotent stem cells (UPSCs). Immunotherapy is definitely a better choice than cytotoxic agents to show selectivity on CCs. But immunotherapy also cannot affect CSCs like cytotoxic agents. CSCs are PSCs without ten-eleven translocator-1 (TET-!). The cell feature, antigenicity and cell mission of CSCs are exactly the same as those of PSCs. The only difference between CSCs and PSCs is the responsiveness toward contact inhibition. PSCs observe contact inhibition which has no effect to limit the growth of CSCs. Immunotherapy is like cytotoxic cancer therapy unable to affect CSCs which are the most vicious cells to cause the fatal effects of cancer. Fatal effects of cancer such as metastasis,

drug resistance, anti-apoptosis, angiogenesis, unresponsiveness and recurrence are all the making of CSCs. Immunotherapy tends to produce tumor necrosis factor (TNF) which is very damaging to chemo-surveillance [10]. Therefore, immunotherapy has the same problem of cytotoxic cancer therapy to show ineffectiveness against CSCs and to contribute to the damage of chemo-surveillance, the reasons contributing to the failure of cytotoxic cancer therapy. Immunotherapy may spare excruciating toxic side effects of cytotoxic agents, but cannot improve cancer mortality. The development of immunotherapy has lasted 10 years, but the cancer mortality is still on the way to escalate at 0.2% annually. Cancer is basically a problem of growth regulation going awry. Immunology has nothing to do with growth regulation. Cancer establishments must have run out of choices to put the hope on immunotherapy. So far, cancer establishments have not produced effective cancer drugs that can turn around cancer mortality from escalation to deceleration.

## 2.2 Intolerance of Challenges Contributes to Persistent Failure of Cancer Therapies

Health profession is an authoritarian profession very much like communist regimes to share a bad tradition of intolerance to challenges. We were the victims of the intolerance. Once upon a there was a dispute on the arrangement of 18S and 28S rRNA genes in the 45S precursor. It was not an important issue. But scientists are always very picky on scientific details. The president of American Cancer Society assigned 28S rRNA at the 5'-end based on their erratic findings. Our data showed 18S rRNA at the 5'-end [19]. We won the arguments, but lost the livelihood. We were accused of trying to create controversy and the grant from American Cancer Society to Professor Hurlbert was terminated, which was a lifetime grant to award his contribution on the establishment of pyrimidine pathway. Without grant support, Professor Hurlbert was forced to retire early, and his associate Liau was dismissed from MD Anderson Cancer Center. Health establishments do not like to be challenged even on issues not very important. They can punish the challengers mercilessly, that is why health professionals are afraid to challenge the establishments. The mistakes health establishments made could not be corrected by health professionals. Cancer evolves due to wound unhealing [4]. Thus, healing wounds is the correct strategy of cancer therapy [20-23]. Burzynski initiated the use of Antineoplastons, which were wound healing metabolites purified from urine, for cancer therapy during 1975-1990 to produce impressive therapeutic

efficacy to attract 20/20 news report [10, 24, 25], which were unfortunately blocked by cancer establishments around 1990, again due to the intolerance of challenges by cancer establishments. There are intelligent health professionals to put away cancer, but these intelligent health professionals are blocked by cancer establishments. Cancer establishments are not only unable to provide solutions but also to block solutions [26]. Since cancer establishments are responsible for the blockade of the solution of cancer, a drastic change of cancer establishments is necessary to save cancer patients [27]. Cancer establishments are the bosses to control the lifelines of health professionals. They can remove health professionals, but health professionals cannot remove them. It will take government officials with authority above them to remove them. President Trump certainly has the authority above cancer establishments, who is known to do businesses unconventionally. He has changed defense department to war department to initiate wars with Venezuela and Iran. He may be willing to declare war on cancer establishments. Secretary of Health Robert Kennedy Jr also has the authority above cancer establishments, who has challenged vaccination policy favored by health establishments. May be he will be willing to challenge cancer establishments for putting up cytotoxic agents to kill his uncle, the distinguished senator Edward Kennedy and 0.61 millions cancer patients annually in the USA. Together, both of them can make health profession great again [2, 7, 28]!

## 2.3 Establishing A Valid Concept of Cancer to Confront Cancer Successfully

Wound healing comes naturally, because the nature put up chemo-surveillance and immuno-surveillance to ensure perfection of wound healing. Virchow was extremely talented to comprehend the logic of wound unhealing to the evolution of cancer at a time neither cancer nor wound healing was completely known [4]. He did not produce experimental data to advance his excellent concept of cancer evolving due to wound unhealing. Wound healing is an important health issue. It is the mistake of health profession to ignore it as an important health issue to let diseases evolving due to wound unhealing to become the top killers of humans that include cancer, cardiovascular diseases and a series of fatal diseases such as the white of COVID-19, HIV, Alzheimer's disease and kidney failure [7, 28]. It is very important to catch up on the study of wound healing to put out top killers of humans. Wound healing is actually an extension of the embryonic program of organ and tissue development. PSCs are the most primitive stem cells to initiate the

development of organ and tissue, which are pluripotent stem cells. Pluripotent stem cells express telomerase. MEs of cells expressing telomerase are abnormal due to the affinity of MEs to form complex with telomerase [29]. Telomerase is a recognized oncogenic protein. Its association with MEs to promote malignant growth is the most important factor to contribute telomerase as an oncogenic protein. MEs are a ternary enzyme complex consisting of methionine adenosyltransferase (MAT)-methyltransferase (MT)-S-adenosylhomocysteine hydrolase (SAHH) [30]. MEs play a pivotal role on the regulation of cell replication and differentiation by virtue of the fact that DNA MEs control the expression of tissue specific genes [31] and rRNA MEs control the production of ribosome [32] which in turn controls the initiation of cell replication. [33]. If the enhanced production of ribosome is locked in place, it becomes the driving force to promote carcinogenesis [34]. Because of this important regulatory role on cell replication and differentiation, MEs are subjected to exceptional double allosteric regulations [35]. Enzymes involved in important biological regulation are often subjected to delicate regulations. Allosteric regulation is the most pervasive biological regulation. Single regulation is very common. Double regulations are exceptional. On the individual enzymes, MEs are under allosteric regulation of steroid hormone or related factors. In steroid hormone target tissues, SAHH is the steroid hormone receptor to control the activity of MEs via promotion of active ternary enzyme complex or inactive dissociated state [30]. The association of MEs with telomerase changes kinetic properties of MEs and the regulatory role of MEs greatly in favor of cell growth. The  $K_m$  values of telomerase associated  $MAT^{LT}$ - $SAHH^{LT}$  isozyme pair are 7-fold higher than the  $K_m$  values of normal  $MAT^L$ - $SAHH^L$  isozyme [29, 36]. Higher  $K_m$  values indicate that abnormal MEs are much more stable, since the study of Prudova et al. showed that S-adenosylmethionine (AdoMet) could protect associated protein against protease digestion [37] and larger pool sizes of AdoMet, S-adenosylhomocysteine (AdoHcy) and homocysteine (Hcy) are required to promote cell growth of cells expressing telomerase, since the study of Chiba et al. showed that when HL-60 cancer cells were induced to undergo terminal differentiation, the pool sizes of AdoMet and AdoHcy shrank greatly [38]. Therefore, abnormal MEs play an important role to promote the growth of cells expressing telomerase that include embryonic pluripotent stem cells and cancer cells derived from pluripotent stem cells. The growth of pluripotent stem cells is exceptional growth

under strict growth control, whereas the growth of CSCs and CCs is exceptional growth deviated from growth control.

MEs of cells expressing telomerase are abnormal, which are shared by pluripotent embryonic stem cells and cancer cells. It appears that the seed of cancer is sown at the very beginning of life, namely the fertilization of the egg with a sperm that activate the totipotent stem cell which expresses telomerase. The expression of telomerase spreads through pluripotent stem cells, but secedes when pluripotent stem cells undergoing lineage transitions to reach UPSCs. Exceptional growth of cells expressing abnormal MEs is required for the development of fetus and wound healing. Interruption of the normal function of abnormal MEs is detrimental. Abnormal MEs can be interrupted by thalidomide, which is hydrophilic that can pass through placenta, whereas maternal wound healing metabolites are hydrophobic that cannot pass through placenta. By interruption of the function of abnormal MEs thalidomide can cause malformation of body parts. Malformation of limbs is frequently observed in pregnant women treated with thalidomide during pregnancy. Malformation of limbs is non-fatal. But if the malformation is the vital organs such as brain or heart that can kill the fetus to cause still birth. Interruption of normal function of abnormal MEs is bad for the development of fetus. Likewise, interruption of normal function of abnormal MEs is also bad for wound healing. Kidney failure is caused by the damage to glomerulus to stop filtration function of the kidney, resulting in the accumulation of low molecular metabolites that include wastes and wound healing metabolites. The accumulation of wound healing metabolites may cause premature TD of PSCs in the process of wound healing just like the interruption of proliferation of pluripotent stem cells in the development of the fetus. Wound unhealing in most instances is caused by the loss of wound healing metabolites due to TNF to trigger excessive excretion of low molecular weight metabolites [39, 40]. In such instances, the administration of CDA formulations is the right solution. Brain compartment is a unique body part protected by blood brain barrier in opposition to placenta to exclude hydrophilic metabolites. The brain compartment is normally enriched with hydrophobic wound healing metabolites. Wound unhealing in the brain compartment is very likely to cause by premature TD of PSCs. The treatment of Alzheimer disease is like the treatment of kidney failure to promote the proliferation of PSCs through growth factors or prostaglandins (PGs) instead of to promote the TD of

PSCs by CDA formulations. CDA formulations are the nature's design to keep cells with abnormal MEs in check. The growth of cells with abnormal MEs is necessary for the normal development of the fetus and wound healing, which are strictly under the regulation of contact inhibition and chemo-surveillance. If such regulatory mechanisms become dysfunctional, the clinical symptoms will show up. It appears that abnormal MEs are the most critical issue of cancer [41, 42]. Cancer is basically a problem of growth regulation going awry. Abnormal MEs and chromosomal abnormalities are the important factors to account for the mess up of growth regulation. Chromosomal abnormalities attracted the most attentions, including many Nobel prizes and the commitment of Cancer establishments to develop gene therapy during 1976-1996. But did not produce drugs to benefit cancer patients. Actually, it is not feasible to develop gene therapy. One gene therapy is developed, there may soon pop up another chromosomal abnormality to negate the previous effort. It is going to be an endless struggle of developing one gene therapy after another

gene therapy. Solution of abnormal MEs is a better choice to solve chromosomal abnormalities. After all, oncogenes and suppressor genes are cell regulatory genes, which have important roles to play when cells are in cell cycle replicating. But if replicating cells are induced to undergo TD to exit cell cycle. These genes have no roles to play. Therefore, the solution of abnormal MEs can also put to rest the issues of chromosomal abnormalities, which are very difficult to achieve. The alliance of Virchow and Liau et al. offers the only intelligent solution to win the war on cancer, on CVDs and on a series of fatal diseases evolving due to wound unhealing [2].

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 DIs and DHIs, whereas cancer patients tended to show deficiency of such metabolites as shown in Table 1, which is reproduced from the reference [10].

**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

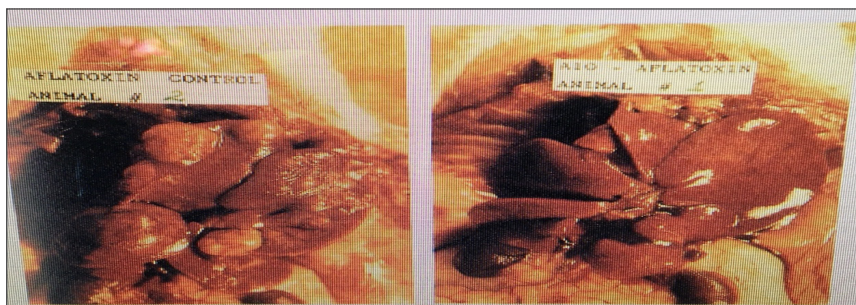
**Plasma Peptides :** nmoles/ml ; **Urinary Peptides :** nmoles/mg creatinine

DIs are metabolites capable of eliminating telomerase from abnormal MEs and DHIs are inhibitors of MEs capable of potentiating the activity of DIs. DIs are acidic peptides, membrane fragments containing phosphatidylinositol designated as PP-0, and arachidonic acid or dicycloPGs designated OA-0.79, which are most likely derived from the degradation of dead erythrocytes [10, 25, 43], whereas DHIs are produced from degradation of dead erythrocytes and organs involved in the metabolism of steroid hormones. Data presented in Table 1 are quantitative analyses of plasma and urinary peptides, which share physical-chemical properties similar to DIs and DHIs. Thus, peptides can serve as surrogate molecules to represent DIs and DHIs. Actually, acidic peptides are major DIs of Antineoplaston preparations purified from urine used by Burzynski to treat cancer patients [10, 24, 25]. DIs and DHIs are wound healing metabolites to target on cells expressing telomerase to induce TD. It is very likely that pathological conditions

inducing the production of TNF cause CDA levels to decline to result in wound unhealing that forces PSCs to evolve into CSCs, and then to progress to faster growing CCs as above described. The progression of CCs invites immunological response to produce more TNF to aggravate destruction of chemo-surveillance. Cytotoxic agents by creating wounds also invite immunological response to contribute to the decline of CDA levels. CDA level of 2.5 is very likely the threshold level to dictate the responsiveness of patients to cytotoxic cancer therapy. Above the level of 2.5, patients are able to restore CDA levels to functional levels to subdue surviving CSCs which are not responding to cytotoxic therapies [12-18]. Below the level of 2.5, cancer patients are unable to restore CDA levels to the functional state and succumb to the replication of CSCs. Data presented in Table 1 are our clinical data to strongly support the validity of Virchow's concept of cancer evolving due to wound unhealing. We have produced other

experimental data to support the validity of Virchow's concept. Antineoplaston A10, which is the code name of phenylacetyl-glutamine by Burzynski was a major chemical component of Antineoplastons and

CDA-2 purified from urine, which could effectively prevent hepatocarcinogenesis induced by potent hepatocarcinogen aflatoxin B<sub>1</sub> as shown in Fig. 1, which is reproduced from the reference [44].



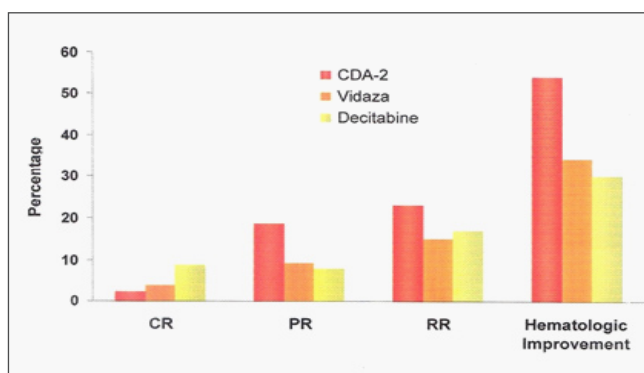
**Figure 1.** Effective Prevention of Hepatocarcinogenesis by Antineoplaston A10

The figure on the left is the control liver receiving aflatoxin B1 only, and the figure on the right is the liver receiving Antineoplaston A10 after the administration of aflatoxin B1.

Antineoplaston A10 is biologically inactive chemical. Nevertheless, it can effectively antagonize the effect of TNF to prevent carcinogenesis as shown in Fig. 1 and to cure early stage cancer patients [10]. According to oriental medicine, Antineoplaston A10 is considered the best cancer drug capable of preventing cancer from taking place [45]. Antineoplastons and CDA-2 are considered next to the best cancer drugs to target on the cause of cancer [45]. Cytotoxic agents and immunotherapeutic drugs belong to the worst category of cancer drugs [45], which are the most favored cancer drugs of western medicine. Oriental medicine appears to have a better judgement on cancer drugs.

Clinical data are more persuasive on the validity of medical hypothesis. Data presented in Table 1 are clinical data. We have produced another clinical datum to support the validity of Virchow's concept of cancer evolving due to wound unhealing. Myelodysplastic syndromes are diseases caused by immunological disorders triggering the production of TNF to induce apoptosis of bone marrow stem cells to severely affecting the patient to produce erythrocytes, platelets or neutrophils, and to cause the collapse of chemosurveillance to force the evolution of PSCs to become CSCs [46, 47]. The propagating pathological cells have been identified as human CSCs [48]. So, MDSs

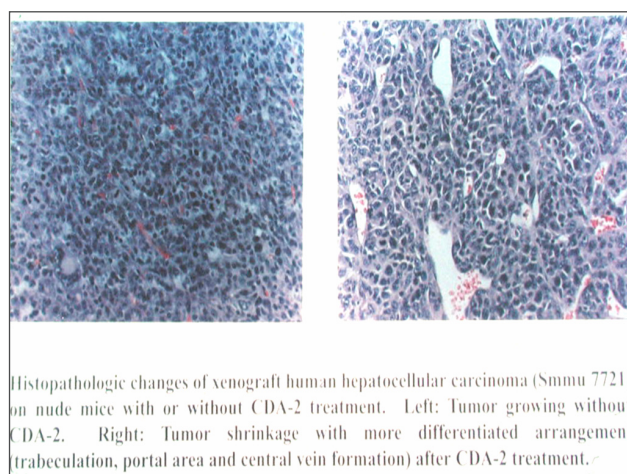
are diseases attributable entirely to the propagation of CSCs. The solution of MDSs require induction of TD of CSCs to replenish erythrocytes, platelets or neutrophils wiped out by TNF. Inactivation of MEs of CSCs is the only option for the therapy of MDSs. CDA-2 can inactivate abnormal MEs of CSCs by targeting telomerase which is a selective tumor factor [29, 36, 41, 42]. Vidaza and Decitabine can inactivate MEs by covalent bond formation of MT with 5-azacytosine incorporated into DNA which is not a selective inactivation of cancer MEs [49]. Professor Ma, the Director of Harbin Institute of Hematology and Oncology, was instrumental in conducting clinical trials of all three MDSs drugs for the approval of three MDSs drugs by the Chinese FDA. Vidaza and Decitabine were also approved by the FDA of USA. According to Professor Ma's assessments based on two cycles of treatment protocols, each 14 days, CDA-2 had a noticeable better therapeutic efficacy based on cytological evaluation, although slower to reach complete remission, and a markedly better therapeutic efficacy based on hematological improvement evaluation, namely becoming independent on blood transfusion to stay healthy as shown in Fig. 2, which is reproduced from the reference [50].



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

CDA-2 is clearly the drug of choice for the therapy of MDSs with superior therapeutic efficacy and without adverse effects, whereas Vidaza and Decitabine are proven carcinogens [51, 52] and very toxic to DNA [53-55]. Drugs effective against CSCs are very precious. Approximately 19 years ago, the pharmaceutical giant GSK put up 1.4 billion 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 to solve CSCs. Induction of TD is the only option to take care of the problem of CSCs which are critically linked to wound unhealing [56]. Cancer establishments spent 1.4 billion on CSCs drugs that were not working. CDA-2 that showed superior therapeutic efficacy on CSCs should worth

more than 1.4 billion. This very valuable cancer drug was denied by cancer establishments, because it could not make tumor to disappear. Disappearance of tumor was a stupid criterion of cancer diagnosis. It is incredible that cancer establishments set up a rule to defeat their mission to win the War on Cancer, because solution of CSCs is essential for the success of cancer therapy and induction of TD that cannot make tumor to disappear is the only option to solve CSCs. No wonder cancer cannot be solved. Induction of TD can also solve the issue of CCs. CCs once terminally differentiated can no longer resume proliferation. Radiological image can only reveal tumor size, but cannot reveal histological details. Induction of TD changes histological details as shown in Fig. 3, which is reproduced from the reference [41].



**Figure 3.** Histological Changes of Solid Hepatoma Smmu 7721 Induced by CDA-2

CDA-2 cannot make tumor to disappear, but can make CCs to become functional cells that is the principle of organ development and wound healing. Radiologic image is a convenient diagnostic tool, non-invasion and fast. But it is too crude to be relied to make important judgement of cancer therapy. Morphological evidence provides more precise judgement on the therapy of hematological cancers. A more precise diagnosis other than radiologic image is needed to assist diagnosis of solid tumors.

In final analysis, we have produced experimental and clinical data to strongly support the validity of Virchow's concept of cancer evolving due to wound unhealing. Establishing a valid concept of cancer is important to provide the right solution of cancer [57]. Cancer therapies based on the creation of wounds to kill CCs are obviously incorrect [3] to result in persistent failures to develop effective cancer drugs that can turn around cancer mortality from escalation to deceleration. Cancer therapies based on the promotion of wound healing are the correct cancer drugs [20-23]. The correct cancer drugs must

be able to solve CSCs. CDA-2 is convincingly the best drug to solve CSCs. We have predicted that the winner of the contest to eradicate CSCs won the contest of cancer therapies [58]. We were the clear winner, but our winner's status was stripped by the cancer establishments. The inability to win the War on Cancer is the fault of cancer establishments. They are not only unable to provide solutions of cancer, but also to block the solutions of cancer. The inability to solve cancer damages the reputation of health profession as a dumb profession unable to achieve presidential assignments in 50 years which did not require difficult technologies, whereas other smart professions could achieve presidential assignments in 5 years which required very difficult technologies. There is no mechanisms in the health profession to remove inept health establishments. President Trump and Secretary of Health must step in to remove inept health establishments to make health profession great again.

**2.4 Development of CDA Formulations to Make Health Profession Great Again**  
Perfection of wound healing is the only intelligent

solution to win the War on Cancer [2, 6, 20-23, 28]. CDA formulations are the drugs for the perfection of wound healing, which are made up by DIs and DHIs. We have carried out extensive studies of natural and unnatural DIs and DHIs for the manufacture of CDA

**Table 2.** Active DIs

DIs	ED25 ( $\mu\text{M}$ )	ED50 ( $\mu\text{M}$ )	ED75 ( $\mu\text{M}$ )
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

$\text{RI}_{0.5}$  of DHI is equivalent to  $\text{ED}_{25}$  of DI, which can be determined through procedure previously reported [61]. ATRA requires the expression of the receptor of ATRA, namely RAR, to achieve the therapeutic efficacy. RAR is a repressor of the gene coding for oligoisoadenylate synthetase. The association of RAR with ATRA activates oligoisoadenylate synthetase gene transcription to produce oligoisoadenylate synthetase. The product of this enzyme oligoisoadenylate is the excellent DI to act on abnormal MEs [67]. ATRA is actually an indirect DI. The rest of DIs listed in Table 2 are direct DIs to act on abnormal MEs. AA and its metabolites PG derivatives are natural DIs

**Table 3.** Active DHIs

SAHH Inhibitors	$\text{RI}_{0.5}$ ( $\mu\text{M}$ )	Signal Transduction Inhibitors (STIs)	$\text{RI}_{0.5}$ ( $\mu\text{M}$ )
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
Dihydroepiandrosterone	1.79	Selenite	19.7
Prenisolone	2.22		
Hydrocortisone	4.59		
Pregnenolone	7.16	Polyphenols	$\text{RI}_{0.5}$ ( $\mu\text{M}$ )
		Tannic Acid	0.37
		EGCG	0.62
MT Inhibitors	$\text{RI}_{0.5}$ ( $\mu\text{M}$ )	Resveratrol	1.16
Uroerythrin	1.9	Curcumin	1.24
Hycanthone	2.1	Kuromanin	1.43
Riboflavin	2.9	Coumestrol	1.95
		Genisteine	2.19
		Pyrogallol	3.18
MAT Inhibitors	$\text{RI}_{0.5}$ ( $\mu\text{M}$ )	Silibinine	3.80
Indol Acetic Acid	220	Caffeic Acid	3.87
Phenylacetylvaline	500	Ellagoc Acid	4.45
Phenylacetylleucine	780	Gallic Acid	5.35
Butyric Acid	850	Ferulic Acid	7.41
Phenylbutyric Acid	970	Phloroglucinol	38.82

formulations [6, 23, 28, 41, 43, 45, 59-66]. Active DIs and DHIs are presented in Table 2 and 3.  $\text{ED}_{25, 50}$  and 75 of DIs and reductive index 0.5 ( $\text{RI}_{0.5}$ ) are included to facilitate manufacturing of CDA formulations.

to involve in the function of chemo-surveillance. BIBR1532 and boldine are non-natural DIs, which were approved cancer drugs as telomerase inhibitors. Telomerase is a recognized oncogenic protein. The association with MEs to promote malignant growth is the reason for it being recognized as an oncogenic protein. CDA formulations achieve cancer therapy by antagonizing two important oncogenic proteins, TNF and telomerase. PGs were also approved for the delivery. Changes of indication of the approved drugs does not take long clinical trial as the new drugs which usually require 10 years to complete clinical trials.

As listed in Table 3, inhibitors of SAHH and MTs are better DHIs than inhibitors of MAT. The stability of three MEs is proportional to the mass [30]. SAHH is the smallest of the three, and is the most unstable enzyme that requires steroid hormone to assume a stable configuration for the formation MT-SAHH dimer to become stable. MAT has a mass similar to the MT-SAHH dimer, which is the most stable enzyme of the three. The association with telomerase in abnormal MEs further increases its stability. Therefore, it requires very large amounts of inhibitors to function as DHIs. Inhibitors of SAHH and MTs are better DHIs.

Although pregnenolone is not the most effective DHI, we consider it as a very valuable DHI. It is the master substrate for all biologically active steroids. It is also a single steroid to have profound influence on the development of cancer. According to Morley, the production of pregnenolone is bell shape in relations to ages with a peak daily production of around 50 mg at the ages of 20-25 [68]. The youngest and the oldest people produce the least amounts of pregnenolone, and these are the two age groups most vulnerable to develop cancer. It is our top choice to make CDA-CSC.

DIs are more important than DHIs for the induction of TD. 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 was excellent, reaching above 90% complete remission, but most patients recurred within one year [69]. The inclusion of SAHH or MT inhibitors can keep MT-SAHH dimer intact to prevent modification of MT to become nuclease to disrupt differentiation process. It is a good idea to include both DI and DHI to make CDA formulations.

The finding of STIs as excellent DHIs is expected, since signal transductions always lead to the production of factors to enhance the activity of MEs. STIs are tyrosine kinase inhibitors, but the inhibition of the activity of MEs is the consequence. STIs and inhibitors of MT become synonyms. The finding of polyphenols as excellent DHIs is a surprise. Epigallocatechin-3-gallate (EGCG) has been found as a good STI to inhibit MT [70, 71]. It is possible that all polyphenols act via

inhibition of tyrosine kinases to result in the inhibition of MEs like EGCG. Vital reds is a food supplement produced by the famed cardiologist Steven Gundry, which contain polyphenols as the major active ingredients. It is effective to clear the blocked blood vessel [72]. Gundry found the intelligent solution of CVDs through perfection of wound healing, but he did not provide the correct interpretation. The correct interpretation of the therapy of CVDs by vital reds is mediated through destabilization of abnormal MEs for the perfection of wound healing just like the therapy of MDSs by CDA-2 of Fig. 2. 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 formulation can be the following formula to reach plasma concentrations as  $ED_{25}$  of a  $DI + 3xRI_{0.5}$  of a DHI, or a  $ED_{50}$  of a  $DI + 2xRI_{0.5}$  of a DHI, or  $ED_{75}$  of a  $DI + RI_{0.5}$  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 PSCs and CSCs, and another set CDA-CC consisting of BIBR1532 + pyruvium pamoate to resist enzymatic degradation of natural active ingredients by faster growing CCs. The application of phenylacetylglutamine is also recommended to antagonize TNF which can be administered independently as a capsule preparation and monitored independently through quantitative assay of plasma and urinary peptides [25]. The therapeutic endpoint of phenylacetylglutamine can be the recovery of CDA to reach the healthy level of 5.0 of the Table 1. The therapeutic endpoint of CVDs can be set at blood pressure of normal value. The therapeutic endpoint of cancer can be the drop of carcino-embryonic antigens to reach the normal levels.

### 3. Conclusion

Cancer evolves due to wound unhealing. Killing CCs to create wounds is incorrect for cancer therapy, which is insisted by the cancer establishments. Healing wounds with CDA formulations are the correct solution of cancer, which are blocked by cancer establishments. Cancer establishments are not only unable to solve cancer but also to block the solution. President Trump and Secretary of Health Kennedy must step in to remove cancer establishments to save 0.61 million cancer patients killed annually in the USA. CDA formulations can make health profession great again.

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It is not applicable.

## Competing Interests

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