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RESEARCH ARTICLE

Lessons to Learn from the Failures of Cancer and Cardiovascular Disease Therapies to Give Rise to CDA Formulations for the Standard Cares of Cancer and Cardiovascular Diseases

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Abstract

There is an old saying that failure is the mother of success. Diseases that persist for a very long time are often due to incorrect therapies. Lessons to learn from the failures can give rise to successful solutions. Difficult cancer and cardiovascular diseases can be easily cured, if the solutions are right. Health profession is an authoritarian organization. Health authorities make policies for health professionals to follow. Intelligent health authorities can put up good policies to enhance the reputation of health profession and to benefit patients. But inept health authorities can put up bad policies to damage the reputation of health profession and to hurt patients. Policies in health profession, good or bad, once become established are very difficult to change. Protection of good policies is laudable, but protection of bad policies is rotten. Health profession has a rotten tradition to punish the challengers trying to correct the mistakes of bad policies. So that bad policies carry on to damage health profession as a dumb profession unable to solve an easy presidential project to win the war on cancer. Health profession is totally unprepared to handle diseases evolving due to wounds caused by toxic chemicals, which can only be cured by targeting on the causes of diseases. Western medicine tends to focus on the elimination of symptoms to search for the solution. Perpetual proliferation of cancer cells (CCs) is the most outstanding symptom of cancer. Killing of CCs becomes the top choice of cancer authorities for cancer therapy, which is clearly wrong in violation of the advice of cancer evolving due to wound unhealing introduced by Virchow in 1858. The strategy of killing CCs to cure cancer was unsuccessful to put cancer away during 1971-1976 to wage the War on Cancer declared by President Nixon, during 1996-2016 to develop anti-angiogenesis therapy, and during 2016-2036 to develop immunotherapy. Since cancer evolves due to wound unhealing, healing the unhealed wound is the right strategy for cancer therapy. Cell differentiation agent-2 (CDA-2) was a preparation of wound healing metabolites purified from urine for cancer therapy we developed, which has been approved by the Chinese FDA for the therapy of cancer and myelodysplastic syndromes (MDSs). MDSs are diseases attributable entirely to the propagation of cancer stem cells (CSCs). Solution of CSCs is essential to the success of cancer therapy. CDA-2 was the best drug for the therapy of MDSs. Therefore, CDA formulations patterned after CDA-2 can be the standard care of cancer. Antineoplastons were preparations of wound healing metabolites purified from urine by different reverse phase chromatographic system than that of CDA-2, which have been used by Burzynski to demonstrate excellent cancer therapy during 1976 to 1990, which were unfortunately blocked by the cancer authorities because of ideological difference. It is going to be a difficult battle to get CDA formulations approved for cancer therapy, since killing of CCs and induction of terminal differentiation (TD) by CDA formulations are contradictory to one another.

Cardiovascular diseases (CVDs) also evolve due to wound unhealing like cancer, which trigger the infiltration of leukocytes and the deposit of lipoprotein to build up plug in the unhealed wound to cause high blood pressure. Wound unhealing is the cause and high blood pressure is the symptom. CVDs authorities choose

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hypotensive agents to combat CVDs without good success. Perfection of wound healing is a better approach for the therapy of CVDs. The acceptance of CDA formulations for the perfection of wound healing by CVDs authorities is easier, since both CDA formulations and hypotensive agents act synergistically to reduce blood pressure.

The objective of this article is to call for the lessons to learn from the failures of cytotoxic cancer therapies and the hypotensive CVDs therapy to give rise to CDA formulations for the standard cares of cancer and CVDs. Solutions of difficult diseases are the common objective of health authorities and their challengers. Cooperation instead of hostile antagonism is the best policy to benefit patients.

Keywords: Cancer Therapy, CVDs Therapy, CDA Formulations, Wound Healing.

1. Introduction

Cancer therapy had a bad start to rely on toxic chemicals to kill CCs. 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 depletion of leukocytes in their blood specimens, which inspired oncologists to employ toxic chemicals to eliminate leukemia cells. Indeed, toxic chemicals were very effective to eliminate leukemia cells to achieve the elimination of the most outstanding symptom of cancer. Targeting on the symptoms is the most favored strategy of western medicine. Cytotoxic cancer therapy thus becomes the standard care for not only hematological cancers, but also for solid cancers and the disappearance of tumor became the standard evaluation on the success of cancer therapy of solid tumors. Both were wrong, because killing of CCs was clearly in violation of the advice of Virchow who introduced the concept of cancer evolving due to wound unhealing [1]. 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. He did not produce experimental data to advance his excellent concept. Virchow was a German pathologist, who was respected as a pioneer of cancer. On the history of cancer, Virchow was the first person mentioned as a significant pioneer of cancer. It is regrettable that current cancer authorities did not remember his important advice on cancer. His advice on cancer was brought up again by Dvorak in the recent time of 1986 in the most popular medical journal that ought to catch the attention of current cancer authorities [2]. The inept current cancer authorities ignored the good advice of Virchow and Dvorak [1, 2] to proceed with their wrong approach of cancer therapy based on the killing of CCs. The consequence was as expected that cancer mortalities kept on increasing to reach 0.61 million annually in the USA and 10 million annually around the world [3]. Cancer mortality is the top killer of Taiwanese people for the last 44 years when the Bureau of Health and Welfare of Taiwan government started to compile top 10 killers of Taiwanese people every year [4]. Cancer mortalities are still on the trend to escalate at an annual rate of 0.2% in the USA, and 5% around the world to go along with the increase of incidence. The continuous escalation of cancer mortalities is an indication that cancer therapies are ineffective based on the elimination of symptom to kill CCs.

We pursued cancer therapy unknowingly to follow the advice of Virchow to discover abnormal methylation enzymes (MEs) [5-7], chemo-surveillance [8-10], and the mechanism of wound healing [11-14]. Thus, we independently produced experimental data to support the valid concept of cancer evolving due to wound unhealing introduced by Virchow [1]. We were also extremely talented to decode the logic of wound unhealing to the evolution of cancer [15-17]. Virchow and Liau et al. became the only intelligent scientists able to provide the solution to win the war on cancer, on CVDs and on a series of fatal diseases evolving due to wound unhealing [18-20]. But the cancer authorities declined to accept CDA formulations as cancer drugs, because CDA formulations could not make tumor to disappear. We have done our duty to provide the solutions of cancer and CVDs. The acceptance of these solutions is beyond our reach.

2. Lessons to Learn from the Failures of Cancer and CVDs Therapies to Give Rise to CDA Formulations for the Standard Cares of Cancer and CVDs, and Discussion

2.1 Establishing a Valid Concept on Cancer and CVDs for the Correct Solutions of These Diseases

It is essential to establish a valid concept on a disease to solve that disease correctly [21]. Western medicine is well prepared to solve wounds caused by infectious agents. Antibiotics and vaccinations are the

creation of western medicine that greatly enhance the reputation of health profession and benefit patients. But western medicine is totally unprepared to handle wounds caused by toxic chemicals and let unhealed wounds to evolve into fatal diseases such as cancer, CVDs and a series of fatal organ failures such as the white lung of COVID-19 infection, renal failure and Alzheimer's diseases [13, 18-20]. Health profession is an authoritarian organization, authorities on the very top make policies for the health professionals to follow. Intelligent authorities can put up good policies of antibiotics and vaccinations to enhance the reputation of health profession and to benefit patients. But inept authorities can put up bad policies of cytotoxic cancer therapies and ineffective hypotensive agents to damage the reputation of health profession as a dumb profession unable to achieve the easiest presidential project and to hurt patients. Inept health authorities are often arrogant and obnoxious unwilling to admit making mistakes, and abuse their authorities to punish the challengers trying to correct bad policies. So, the bad policies carry on to result in huge mortalities [22-29]. The problems of cancer and CVDs unable to solve are the fault of inept authorities who are not only unable to provide correct solutions but also to block correct solutions. In political arena, revolution is a solution. In health arena, revolution is impossible. Victims of cancer can be as great as kings such as King Charles of England, King Hussein of Jordan and Emperor Showa of Japan or presidents such as Presidents Biden and Carter of USA, but these powerful figures can only be the helpless victims of inept health authorities. It is a very discouraging impasse!

Cancer evolving due to wound unhealing was a correct concept of cancer introduced by Virchow in 1858 [1]. 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. Cancer became completely known through the discovery of cancer stem cells by Bonnet and Dick in 1997 [30] and wound healing became completely known through the discovery of the mechanism of wound healing by Liau and Craig in 2021 [12]. Cancer authorities are extremely dumb unable to understand the logic of cancer evolving due to wound unhealing at a time when both cancer and wound healing have become known completely to continue on the wrong approach of cancer therapies based on the creation of wounds to kill CCs, stirring up cancer as a giant killer of humans claiming 10 million cancer mortality annually around the world with an annual increment of 5% to go along with the increase of cancer incidence according to the experts of NCI [3, 31-33]. Inept cancer authorities are responsible for the huge cancer mortality. Making mistake to cause death is not an unforgivable crime. The creator of the nature makes mistakes too. The evolution of CSCs from PSCs and the progression of CSCs to become CCs in an attempt to heal wounds are clearly wrong, which are not helpful to heal wounds. Unwilling to admit making mistakes to cause death is an unforgivable crime, clearly in violation of malpractice laws, resulting in huge mortality. Failure can be the mother of successes. Lesson to learn from failure is essential to become the mother of successes. If inept cancer authorities are unwilling to admit making mistakes to learn the lessons from failures, the failures can never become the mothers of successes. Evidently, wound healing is a very 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 and immuno-surveillance to heal wounds created by infectious agents. On wound healing, chemo-surveillance and immuno-surveillance can act synergistically to heal wounds to avoid unhealed wounds to become clinical symptoms. Wound healing comes naturally, because the nature creates chemo-surveillance and immuno-surveillance for the perfection of wound healing. The health profession is very well aware of immuno-surveillance, but totally neglects on chemo-surveillance [29]. Chemo-surveillance was a terminology we created to describe an observation that healthy people were able to maintain a stead 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 Tabel 1, which is reproduced from the reference [8] to show chemo-surveillance selectively destroyed in cancer patients. DIs are metabolites capable pf eliminating telomerase from abnormal MEs, and DHIs are inhibitors of MEs capable of potentiating the activity of DIs [7, 34, 35]. Data presented in Table 1 are quantitative data of plasma and urinary peptides. Peptides share chemical and physical properties similar to DIs and DHIs. Thus, peptides can be used as surrogate molecules to represent DIs and DHIs in the plasma and urine.

Table 1. *Chemo-surveillance Selectively Destroyed in Cancer Patients*

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

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

DIs and DHIs are hydrophobic metabolites that can be purified from the plasma and urine by reverse phase chromatography employing C18-80% methanol system [8, 36, 37]. C18 is a reverse phase chromatographic system particularly good for the recovery of peptides and low molecular weight hydrophobic metabolites, but not good for high molecular weight hydrophobic metabolites such as membrane fragments containing phosphatidylinositol designated as pigment peptides-0 (PP-0), which are the major DIs of CDA-2. PP-0 are only minor DIs of Antineoplaston preparations. Acidic peptides are the major DIs of Antineoplaston preparations, which are not recovered by the reverse phase chromatographic system employing XAD16-100% ethanol system we used to prepare CDA-2 [38, 39]. Despite differences in chemical compositions, CDA-2 and Antineoplaston A5 have comparable activities to induce TD of HL-60 cancer cells. Induction of TD is a common anticancer mechanism of CDA-2 and Antineoplaston preparations. Antineoplastons may have additional anticancer activity contributed by peptides not recovered in CDA-2. Plasma peptides are apparently derived from the degradation of dead erythrocytes. Peptide profiles of organ extract from spleen resemble those of plasma peptides [40]. Spleen is an organ known to process dead erythrocytes. It is very likely that the degradation products of erythrocytes are the major sources of wound healing metabolites that include acidic peptides, pigment peptides-0 (PP-0} which are the membrane fragments containing phosphatidylinositol and organic acid-0.79 (OA-0.79) which are liposomal complexes consisting of arachidonic acid (AA) or dicyclo-prostaglandin E2 (PG-E2) with pregnenolone [39, 41-43] as DIs and uroerythrin as an important DHI [35]. Degradation of erythrocytes takes place when erythrocytes reach their life span of 110 days. Other active steroid metabolites as DHIs must come from organs involved in the metabolism of steroid metabolites. It is very likely that the production of DIs and DHIs is always operating at the maximum capacity. Healthy people are able to maintain a steady equilibrium of production and excretion of DIs and DHIs. Once that equilibrium is destroyed due to excessive excretion, there is no mechanism to replenish the lost DIs and DHIs. Excessive excretion is a major reason for the collapse of chemo-surveillance. Tumor necrosis factor (TNF) comes into play to dictate the integrity of chemo-surveillance. TNF is a cytokine produced by immune competent cells to assist immunotherapy, which is a toxic protein to kill target cells. 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 due to membrane hyperpermeability created by TNF [44, 45]. Wound healing metabolites are among low molecular metabolites excreted, resulting in the collapse of chemo-surveillance unable to heal wound. TNF was the molecule identified to cause the incidence of myelodysplastic syndromes (MDSs) [46], which was strongly supported by the finding of antibody of TNF to prevent the progression of MDSs [47]. Therefore, the production of TNF is to blame for the collapse of chemo-surveillance to result in wound unable to heal, and wound unhealing is the reason to trigger the evolution of cancer [1, 2]. It must be the immunological disorder to cause the production of TNF to result in the collapse of chemo-surveillance to initiate the evolution of CSCs from PSCs, and the progression of CCs which express programmed death antigen to invite immunological response, and the immunological response produce more TNF to aggravate the damage of chemo-surveillance [12]. Eventually, cancer patients become totally defenseless to succumb to cancer. Phenylacetylglutamine is a major metabolite present in the plasma and urine, which is also a major chemical component of Antineoplastons and CDA-2. Phenylacetylglutamine, which was code named Antineoplaston A10 by Burzynski, was found very effective to antagonize TNF to

prevent the loss of wound healing metabolites [8]. By keeping the functionality of chemo-surveillance intact, Antineoplaston A10 could effectively prevent hepatocarcinogenesis challenged with a potent hepatocarcinogen aflatoxin B_1 as shown in Figure 1, which is reproduced from the reference [48].

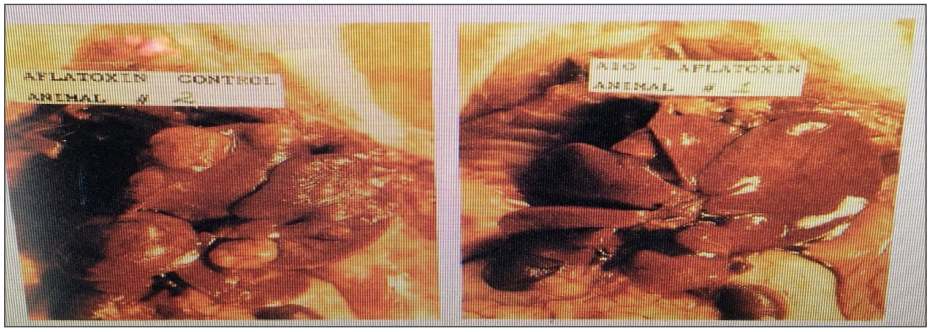


Figure 1. *Effective Prevention of Hepatocarcinogenesis by Antineoplaston A10*

Antineoplaston A10 is biologically inactive. It is remarkable that such an inactive chemical by keeping the operation of chemo-surveillance intact could effectively prevent hepatocarcinogenesis induced by potent hepatocarcinogen aflatoxin B_1. Antineoplaston A10 is a harmless chemical to produce a great benefit to prevent cancer from taking place, which should be welcome by both western and oriental medicines. It is a major chemical component of Antineoplastons and CDA-2, which should be a component of all cancer drugs to restore chemo-surveillance badly destroyed in cancer patients as shown in Table 1. CDA level of 2.5 is very likely a threshold level to dictate the responsiveness to cytotoxic cancer therapy. Above 2.5, there is a possibility of restoration to the functional state to subdue surviving CSCs which are not responsive to cytotoxic cancer therapies, neither to immunotherapy [50-58]. Below 2.5, the damage is too far gone to restore to the functional state. The study of Thon et al. was very alarming on the success of cytotoxic cancer therapy, who showed that astrocytomas with CSCs counts less than 1% were responsive to cytotoxic cancer therapies, whereas gliomas with CSCs counts above 3% were unresponsive to cytotoxic cancer therapies [59]. The responsiveness margin to successful cytotoxic cancer therapies is so narrow for cytotoxic cancer therapies to achieve cancer therapy. No wonder that cytotoxic cancer therapies dominate cancer therapies in the past for a very long time, but cannot put away cancer. Brain compartment is very unique, protected by blood brain barrier to exclude hydrophilic metabolites. Hydrophobic wound healing metabolites tend to accumulate in the brain compartment. Malignant brain tumors must have very high CSCs to prevail in this compartment [59-61], which are not responsive to cytotoxic cancer therapy. Growth hormone is produced in the pituitary gland located in the brain compartment, thus, brain compartment is also enriched with growth hormone to support the growth of benign brain tumors and malignant astrocytomas with very low CSCs counts. Cytotoxic cancer drugs create wounds to promote the proliferation of CSCs to heal the wounds, eventually increasing CSCs to reach a level above 3% to become unresponsive to cytotoxic cancer therapy [62]. There are so many factors to prevent the success of cytotoxic cancer therapies. Suspension of cytotoxic cancer therapies is a good policy to benefit cancer patients. Cytotoxic cancer therapies are so excruciating and contraindication to contribute to huge casualty, which were the major drugs employed in the War on Cancer declared by President Nixon during 1971 to 1976, but failed to achieve the goal to put out cancer [63]. Unable to achieve a presidential assignment is a very shameful record of health profession. Incidentally, war on cancer was the only presidential project failed to achieve its goal. Presidential projects deal with the most important issues of the nation. There were two precedents: the Manhattan Project under President Roosevelt and the Moonshot Project under President Kennedy. Presidential projects have the benefit of unlimited support from the national resources, but have a time limit of 5 years. Nuclear physicists accomplished the Manhattan Project and rocket engineers accomplished the Moonshot Project, both of which require extremely difficult technologies. War on Cancer did not require difficult technology, but the health profession failed to accomplish the presidential assignment. Virchow could put cancer away [1], but he was long gone before cancer became a giant killer. Liau et al. could also put cancer away [5-29], but the career of Liau was destroyed by the American Cancer Society because he used the grant awarded to Professor Robert B. Hurlbert from American Cancer Society to discredit the President of American Cancer Society, who erroneously assigned 28S rRNA at the 5'-end of

the 45S precursor molecule w [64]. The arrangement of two rRNA in the 45S precursor molecule is not an important issue. Even on such an unimportant issue, health authorities abused their authorities to punish Liau and Hurlbert by cutting off the lifetime grant to Professor Hulbert, which was to award his contribution on the establishment of pyrimidine pathway, resulting in the early retirement of Professor Hurlbert and the dismissal of Liau from MD Anderson Cancer Center. It is a very bad tradition of health profession to punish challengers trying to correct the mistakes made by cancer authorities. The health profession used to have a collection of very bright young students. The inept authorities managed to train these very bright young students to become dumb followers of bad policies unable to learn the lessons of failures to correct bad policies put up by inept authorities.

2.2 Lessons to Learn from the Failures of Cancer and CVDs Therapies

Health profession must learn the lessons of failures to give rise to successes. Creation of wounds is incorrect for cancer therapy [32]. Cytotoxic cancer therapy and radiotherapy were the major molarities employed by the cancer authorities to wage the War on Cancer during 1971 to 1976 as a presidential project, but failed to achieve its goal, which was a decisive verdict on cytotoxic cancer therapy and radiotherapy as incorrect therapies for cancer. Ineffectiveness of cytotoxic agents and radiation against CSCs and the contribution to damage chemo-surveillance are the reasons for cytotoxic cancer therapy and radiotherapy to fail to win the War on Cancer. CSCs express ABCG2 gene to resist cytotoxic agents, genes of anti-apoptosis and DNA repair to resist radiotherapy, and aldehyde dehydrogenase for detoxification [50-58]. Creation of wounds triggers immunological response to produce TNF to result in the collapse of chemo-surveillance to initiate cancer evolution and progression as above described. Obviously, wound unhealing is the reason for cancer to evolve as suggested by Virchow and his follower Dvorak [1, 2]. Wound healing requires the proliferation and the TD of progenitor stem cells (PSCs). PSCs are the most primitive stem cells to initiate the development of organs and tissues during embryonic stage of fetal development. Thus, wound healing is actually an extension of embryonic program of organ and tissue development. Wound usually triggers biological and immunological responses. The biological response involves the release of arachidonic acid (AA) from membrane bound phosphatidylinositol by phospholipase A2 for the syntheses of prostaglandins (PGs) through cyclooxygenases and PG synthases [65, 66]. Although AA and PGs are active DIs [43], the induction of TD of PSCs at the initial stage of wound is not the primary objective of PGs. Rather, the localized inflammation caused by PGs [67] is responsible for the increase of membrane permeability to facilitate the extravasation of plasma proteins and regulatory factors into the wound resulting in edema response that is the primary objective of PGs to orchestrate the healing process. Chemo-surveillance mediated through DIs and DHIs normally functions as a brake to prevent the buildup of PSCs. This brake must be released in order for PSCs to proliferate to produce enough cells to heal the wound. PGs are metabolically unstable [65]. Their biological effects are most likely brief and confined to the wound area. Thus, the promotion of the proliferation of PSCs is the primary objective of PGs on wound healing, whereas the induction of TD of PSCs at the final stage of wound healing is accomplished by wound healing metabolites involved in chemo-surveillance. The stable end products of PGs may participate in the final stage of wound healing. The stable end products of PGs are also active as DIs, although not as active as PGs [43]. The immunological response triggered by wound is not good for wound healing, which prompts the production of TNF to create damage to chemo-surveillance. It is the balance of biological and immunological responses to dictate the outcome. If biological response prevails, wound is healed. If immunological response prevails, wound cannot be healed to produce clinical symptoms. Clinical symptoms can be very severe such as the white lung of COVID-19 infection, or heart attack and stroke of CVDs. In such cases, fatality is the end point. If clinical symptoms are not fatal such as those caused by carcinogens, there is a good possibility that unhealed wounds will force PSCs to evolve to become CSCs in an attempt to heal the unhealed wound. Chemo-surveillance is always operating at the maximum capacity. When it is damaged by TNF to cause excessive excretion. There is no mechanism to increase the production of DIs and DHIs. Instead, the pressure is building up to force the proliferation of PSCs. But the extent PSCs can proliferate is limited by contact inhibition. PSCs are then forced to evolve into CSCs to escape contact inhibition. It takes a single hit to silence ten eleven translocator-1 (TET-1) enzyme to convert PSCs to become CSCs [68, 69], that is an easy task for PSCs to accomplish since these cells are equipped with exceptionally

active MEs. The evolution of CSCs is still unable to heal the wound, because the reason to cause wound unhealing is the collapse of chemo-surveillance. CSCs are then forced to progress to faster growing CCs through chromosomal abnormalities such as translocations to activate oncogenes or deletions to inactivate suppressor genes to become full blown cancer. The evolution of PSCs to become CSCs and the progression of CSCs to become CCs are body's responses to wound unhealing. Perfection of wound healing is, therefore, the right and the only option for the solution of CSCs which are critically linked to unhealed wound in the primary tumor [12, 15-20]. CCs are not critically linked to unhealed wound, which can be eliminated by induction of TD or killing. Killing is the choice of cancer authorities that can only benefit patients in the early stage, approximately a quarter of cancer patients. Early stage cancer patients responsive to cytotoxic cancer therapies include stage I and II patients without metastasis, Gleason score below 7 of prostate cancer patients, CDA levels above 2.5 of Table 1, and CSCs counts below 1% [59]. Induction of TD is a better choice, which can benefit cancer patients of all stages [18-29, 31-33, 38, 42, 49, 62].

2.3 CDA-2 as the Best Drug for the Solution of CSCs

Table 1 is a clear indication that cancer evolves due to the collapse of chemo-surveillance caused by TNF produced under immunological disorders to result in wound unhealing that force the evolution of CSCs from PSCs and then the progression of CCs from CSCs as above described. The drug that can antagonize TNF and eliminate CSCs and CCs is the best for the solution of cancer. CDA-2 is an ideal drug that is a preparation of hydrophobic metabolites to include phenylacetylglutamine that can effectively antagonized TNF as shown in Fig. 1, and restore CDA level to induce TD of CSCs and CCs [70, 71]. Incidentally, induction of TD is the only option for the solution of CSCs [17, 39]. Cancer establishments are aware of the importance of the elimination of CSCs on the success of cancer therapy. Approximately 19 years ago, the pharmaceutical giant GSK put up 1.4 billion, the most expensive investment on a cancer drug, to develop monoclonal antibodies against CSCs invented by the scientists of Stanford University, which was not successful because killing of CSCs was not an option. Induction of TD of CSCs is the only option, since CSCs are critically linked to wound unhealing. Induction of TD is the mechanism of wound healing [11, 15-20]. CDA-2 was very effective for the therapy of breast cancer [70]. Since the therapeutic end point of CDA-2 is TD, it could not cause the shrinkage of tumor to qualify as a mono-therapeutic drug. Tumor shrinkage is not a valid requirement of cancer drug [31]. CDA-2 definitely can also induce CCs to undergo TD as shown in Figure 2 to induce induction of TD of hepatoma 7721 to become histology very similar to liver, which is distinctly different from the disorganized histology of control hepatoma 7721, which is reproduced from the reference [42]. Hematological oncologists are trained to recognize the difference of cancer cell and terminally differentiated cancer cell. Solid tumor oncologists should also be trained to recognize the difference of tumor histology and terminally differentiated histology of tumor residue which are distinctly different as shown in Figure 2. Radiological image is too crude that only can reveal tumor size, but cannot reveal histological detail. Radiological image is too crude to make a precision diagnosis. If tumor shrinkage is not a requirement of cancer drug, CDA-2 could be approved as a mono-therapeutic drug instead of as an adjuvant drug to supplement cytotoxic drugs [72, 73]. As a mono-therapeutic drug, CDA-2 can get the credit of the whole therapeutic effect.

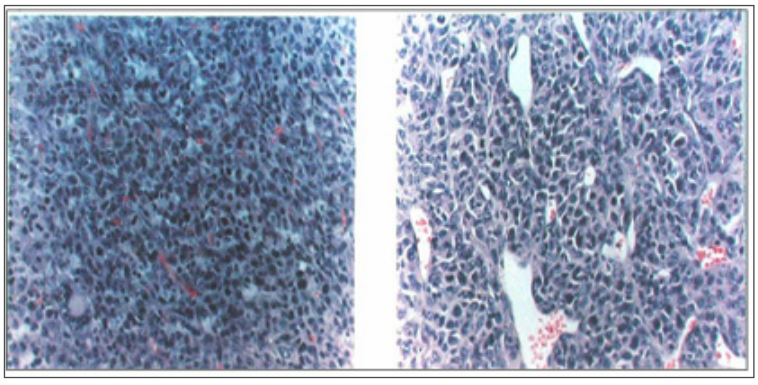


Figure 2. *Histological Change of Hepatocellular Carcinoma Smmnu 7721 Induced to Undergo TD by CDA-2*
Figure on the left is the control Smmnu 7721 tumor showing totally disorganized histology and figure on the right is CDA-2 treated tumor showing organized histology similar to that of liver.

As an adjuvant drug, cytotoxic drugs claim the major therapeutic effect. Actually, CDA-2 is producing the major therapeutic effects since CSCs play a dominant role on the pathology of breast cancer displaying metastasis at very early stage and the emergence of triple negative CSCs unresponsive to therapies currently available. Cytotoxic cancer drugs are unable to eliminate CSCs.

MDSs are diseases attributable entirely to the propagation of CSCs [74]. MDSs are typical cases of cancer evolution due to wound unhealing caused by immunological disorder to produce TNF which is responsible for the excessive apoptosis of bone marrow stem cells, thus severely affecting the ability of the patient to produce hematopoietic cells such as erythrocytes, platelets or neutrophils. TNF is also responsible for the collapse of chemo-surveillance as above described, forcing the evolution of PSCs to become CSCs. MDSs are at the stage of CSCs before progression to become acute myeloid leukemia. Therapy of MDSs requires TD of CSCs to become erythrocytes, platelets or neutrophils. Inactivation of methyltransferase (MT) or destabilization of abnormal MEs is the only options for the therapy of MDSs, which can be accomplished by Vidaza and Decitabine through covalent bond formation between MT and 5-azacytosine incorporated into cellular DNA [75] or CDA-2 through destabilization of abnormal MEs [15-20, 38, 42]. Professor J. Ma, the Director of Harbin Institute of Hematology and Oncology, was instrumental to carry out clinical trials of these three drugs for the approval of MDSs therapy by the Chinese FDA. Vidaza and Decitabine were also approved by the US FDA for the therapy of MDSs. According to the assessments of Professor Ma based on two cycles of treatment protocols, each 14 days, CDA-2 had a noticeably better therapeutic efficacy based on cytological evaluation, although slower to reach complete remission, and a markedly better therapeutic efficacy based on hematological improvement evaluation, meaning becoming independent on blood transfusion to stay health as shown in Figure 3, which is reproduced from the reference [71].

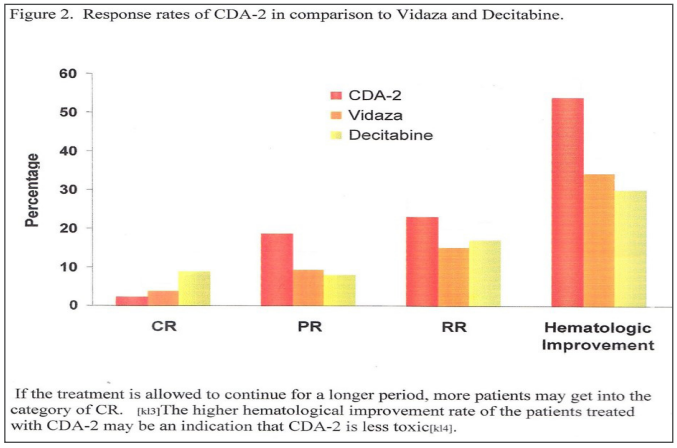


Figure 3. *CDA-2 as the Best Drug for the Therapy of MDSs*

CDA-2 is apparently the best drug for the therapy of CSCs, displaying better therapeutic efficacies and without adverse effects, whereas Vidaza and Decitabine are not as good as CDA-2 displaying worse therapeutic efficacies and unacceptable adverse effects as proven carcinogens [76, 77] and very toxic to DNA [78, 79], particularly toward cardiac cell DNA [80]. It is obvious that CDA-2 was the best drug for the therapy of CSCs with superior therapeutic efficacies and without adverse effects. We have predicted that the winner of the contest to eradicate CSCs won the contest of cancer therapies [81]. CDA-2 was the clear winner. But the winner's status of CDA-2 was denied by cancer authorities who put up tumor shrinkage as a condition to qualify for cancer drugs which was clearly incorrect [31]. Elimination of CSCs is essential for the success of cancer therapy [17, 39, 73]. We are best qualified to solve the issue of CSCs.

2.4 Abnormal MEs as the Most Critical Issue of Wound Unhealing, Cancer and CVDs

Completion of wound healing requires the TD of PSCs. Destabilization of abnormal MEs is the only option to achieve TD of PSCs as demonstrated in the therapy of MDSs shown in Figure 3. Thus, abnormal MEs are the most critical issue of wound unhealing, and wound unhealing is the cause of cancer and CVDs. Therefore, solution of abnormal MEs become the central issue of wound unhealing, cancer and CVDs.

MEs of cells expressing telomerase become abnormal due to a great affinity between telomerase and MEs to form complex [7]. The association of telomerase

with MEs changes kinetic properties of MEs and the regulation of MEs greatly in favor of promotion of cell growth. K_m values of telomerase associated MAT^{LT}-$SAHH^{LT}$ isozyme pair are 7-fold higher than those of normal MAT^{L}-$SAHH^{L}$ isozyme pair [5-7]. The high K_m values are an indication that MEs of cells expressing telomerase are much more stable and active since the study of Prudova et al. indicated that the association of S-adenosylmethionine (AdoMet) greatly stabilize protein against protease digestion [82]. The higher K_m values are also an indication that cells expressing telomerase have larger pool sizes of AdoMet and S-adenosyl-homocysteine (AdoHcy) needed to promote the growth of cells expressing telomerase, since the study of Chiva et al. indicated that when HL-60 cancer cells were induced to undergo TD, the pool sizes of AdoMet and AdoHcy shrank greatly [83]. Thus, abnormal MEs become the central issue of wound healing, and wound unhealing is the cause of many fatal diseases that include cancer, CVDs and organ failures such as the white lung of COVID-19 infection, chronic fibrosis, cancer, CVDs, Arzheimer's diseases and renal failure [1, 19, 84, 85]. Healing the unhealed wounds is the correct solution of diseases evolving due to wound unhealing [15-20, 29], which is the choice of the creator of the nature [42]. The inept cancer authorities elected to challenge the wisdom of the creator of the nature to put up cytotoxic cancer therapies in opposition to the advice of the creator of the nature, which was comprehend by Virchow and Liau et al. [1, 19]. The creator of the nature makes mistakes too. The evolution of CSCs due to wound unhealing and the progression of CSCs to faster growing CCs are clearly the mistakes of the creator of the nature. The production of wound healing metabolites is the right answer instead of evolution of PSCs to become CSCs and the progression of CSCs to become faster growing CCs. Learning the lessons of mistakes is very important to the correction of mistakes.

Because of the important role of MEs in the regulation of cell growth and differentiation, MEs are exceptionally subjected to double allosteric regulations: one on the individual enzymes and the other on the enzyme complex [86]. Allosteric regulation is a pervasive regulation in biological field. Single regulation is very common, but double regulations on MEs is an exception, that stresses the importance of MEs. On individual enzymes, MEs are allosterically regulated by steroid hormone [87]. SAHH is the steroid hormone receptor. On enzyme complex, MEs are allosterically regulated by telomerase and chemo-surveillance. MEs play a pivotal role on the regulation of cell growth and differentiation by virtue of the fact that DNA MEs control the expression of tissue specific genes [88] and rRNA MEs control the production of ribosome [89], which in turn plays an essential role to initiate cell replication [90]. If the enhancement of ribosome production is locked in place, it becomes a factor to drive carcinogenesis [91]. Therefore, abnormal MEs are really a critical issue of cancer [92-96]. Actually, we consider abnormal methylation enzymes as the bullseye of cancer targets [97]. Unfortunately, nobody pays attention on abnormal methylation enzymes. On the causes of cancer, the activation of oncogenes and the inactivation of suppressor genes attract most attentions, including multiple Novel prizes and the designation by cancer authorities to develop gene therapy during 1976-1996. Oncogenes and suppressor genes are cell cycle regulatory genes, which have important roles to play when cell is in cell cycle replicating. But if cell exist cell cycle to undergo TD these genes have no roles to play. Abnormal MEs also have important roles to play on the regulation cell replication to keep cell in the cell cycle replicating. Destabilization of abnormal MEs to force cell to exit cell cycle to undergo TD can also put to rest abnormal oncogenes and suppressor genes. A stroke to destabilize abnormal MEs can also solve the issue of chromosomal abnormalities which are very difficult to solve. Cancer authorities wasted 20 years without developing a gene therapy drug. Actually, it is not feasible to develop gene therapy. One difficult gene therapy if successful developed, there may pop up another chromosomal abnormalities to negate the previous effort. We will be trapped in developing difficult gene therapies like we are now trapped in unattainable cytotoxic cancer therapies which have partial success on the early stage cancer patients. Destabilization of abnormal MEs is the best and the only option to achieve cancer and CVDs therapies.

2.5 Perfection of Wound Healing as the Standard Cares of Diseases Evolving due to Wound Unhealing

The white lung of COVID-19 infection is a classical case of disease evolving due to wound unhealing, which is caused by the buildup of PSCs unable to undergo TD because of the collapse of chemo-surveillance during the early phase of COVID-19 infection [84]. The unhealed wound is the cause and the white lung is the symptom both are caused by the proliferation of PSCs. Induction of TD of PSCs through CDA formulations is the correct solution to eliminate the

cause and symptom of white lung. Oriental medicine likes to develop drugs to target on the cause to achieve lifelong therapeutic effect, whereas western medicine likes to develop drugs to target on the symptom to achieve immediate therapeutic effect [98, 99]. Since the white lung of COVID-19 is caused by the proliferation of PSCs, and CDA formulations are the best solution of the proliferation of PSCs, it appears that both oriental medicine and western medicine agree on CDA formulations as the best solution of the white lung of COVID-19 infection. Vaccination against COVID-19 virus can prevent the white lung from taking place, but it is not a solution for the white lung.

CVDs are caused by the injury to the inner lining of artery and the buildup of PSCs unable to undergo TD because of the collapse of chemo-surveillance during the early phase of pathological conditions producing TNF to cause the collapse of chemo-surveillance, exactly the same situation to cause cancer [8, 9, 19, 25, 28. 29]. Large pool sizes of AdoMet and AdoHcy are a risk factor of cancer [83]. SAHH is the enzyme to carry out reversible reactions. A large pool size of AdoHcy is also a large pool size Hcy which has been identified as a risk factor of CVDs [98]. Therefore, the cause of CVDs is exactly the same as the cause of cancer due to wound unhealing. The symptoms of wound unhealing in the case of CVDs are heart attack and stroke which are fatal, but the symptoms of wound unhealing in the case of cancer are not fatal to cause the evolution of PSCs to become CSCs as above described. The correct solution of CVDs is the same as the correct solution of cancer to heal the unhealed wound [15-20]. Wound unhealing is the cause of CVDs, which triggers the infiltration of leucocytes and the deposit of low density lipoproteins to build up the plug around the unhealed wound to cause the blood pressure to increase. The unhealed wound of artery causes blood vessel to become hardened to lose elasticity to become easy to burst to result in fatality. The correct solution of CVDs is to heal the unhealed wound to remove the risk of blood vessel to break. Hypotensive agents can prevent the blood pressure to increase to the level to cause the hardened blood vessel to burst, but cannot solve the cause of hardened blood vessel. That is why hypotensive drugs are not very effective to reduce the mortality of CVDs, stirring up CVDs as the top killer in the USA and around the world, claiming 0.92 million in the USA and 20.5 million around the world annually. Inept health authorities are responsible for such huge mortalities.

Wound unhealing in most instances is caused by the collapse of chemo-surveillance to result in the loss of wound healing metabolites. But wound unhealing can also be caused by too much wound healing metabolites to induce premature induction of TD of PSCs analogous to the malformation of body parts by thalidomide. Wound healing metabolites are hydrophobic metabolites that are prevented by placenta to enter fetal blood circulation. Thalidomide is a hydrophilic wound healing chemical, very likely a DI, that can pass through placenta to interfere MEs to cause premature TD of stem cells. Malformation of limbs is non-lethal that frequently shows up in the affected babies. Malformations of vital organs such as brain and heart can also take place to result in stillbirth. Therefore, premature induction of TD of PSCs is also not good for wound healing. Renal failure is caused by the damage to glomerulus to lose the filtration function to result in the accumulation of low molecular weight metabolites that include wastes, nutrients and wound healing metabolites. The accumulation of wound healing metabolites in renal failure patients is going to interfere the healing of glomerulus to restore kidney function. The problem of kidney failure is the shortage of PSCs to heal the wound, not the shortage of wound healing metabolites. Therefore, the treatment of wound unhealing on kidney failure must be handled differently from wound unhealing caused by the collapse of chemo-surveillance. Likewise, wounds happen in the brain compartment must be handled differently from those happen in other body compartments. Brain compartment is protected by blood brain barrier which functions just opposite to placenta to restrict the entry of hydrophilic metabolites into the brain compartment. Hydrophobic wound healing metabolites tend to accumulate in the brain compartment to interfere wound healing. Alzheimer's diseases are caused by the damage of neurological cells by pathological production of β-amyloid and tau proteins and the repair of the damaged neurological cells is interfered by premature TD of PSCs like the renal failure. So, the handling of Alzheimer's diseases must focus on the shortage of PSCs.

2.6 Development of CDA Formulations for the Standard Cares of Cancer and CVDs

We have carried out extensive studies of natural and non-natural DIs and DHIs to make CDA formulations for the standard cares of cancer and CVDs [34-43, 72, 92-97, 101, 102], which are summarized in Table 2 and 3.

Table 2. *Active DIs*

DIs	ED_{25} (μM)	ED_{50} (μM)	ED_{75} (μM)
ATRA	0.18	0.36	0.75
PGJ2	7.9	13.8	20.5
PGE2	20.6	32.0	46.5
DicycloPGE2	21.0	43.5	-
AA	21.0	42.0	-
BIBR1532	32.3	43.7	55.1
Boldine	60.1	78.8	94.2

Effective dosages ($ED_{25, 50 \text{ and } 75}$) of DIs and Reductive Index$_{0.5}$ ($RI_{0.5}$) of DHIs are included to facilitate the manufacturing of CDA formulations. $RI_{0.5}$ can be determined by the procedure presented in the reference [101].

DIs and DHIs can be excellent cancer drugs. ATRA, a DI, is the standard care of acute promyelocytic leukemia [103] and gleebec, a DHI, is the standard care of chronic myeloid leukemia. ATRA is an indirect DI, requiring the expression of receptor of retinoic acid to activate the expression of oligoisoadenylate to function as DI. Other DIs listed in Table 2 are direct DIs to act on abnormal MEs. PG derivatives are approved drugs for the delivery and BIBR 1532 and boldine are approved cancer drugs as telomerase inhibitors. Change of indications does not require clinical trials as long as the drugs for new indication.

Table 3. *Active DHIs*

SAHH Inhibitors	$RI_{0.5}$ (μM)	STI	$RI_{0.5}$ (μM)
Pyrvinium Pamoate	0.012	Sutent	0.28
Vitamin D_3	0.61	Berberine	1.62
Dexamethasone	0.75	Vorient	10.1
β-Sitosterol	1.72	Gleevec	11.9
Dihydroepiandrosterone	1.79	Selenite	19.7
Prenisolone	2.22		
Hydrocortisone	4.59	Polyphenols	$RI_{0.5}$ (μM)
Pregnenolone	7.16		
		Tannic Acid	0.37
MT Inhibitors	$RI_{0.5}$ (μM)	EGCG	0.62
		Resveratrol	1.16
Uroerythrin	1.9	Curcumin	1.24
Hycanthone	2.1	Kuromanin	1.43
Riboflavin	2.9	Coumestrol	1.95
		Genisteine	2.19
MAT Inhibitors	$RI_{0.5}$ (μM)	Pyrogallol	3.18
		Silibinine	3.80
Indol Acetic Acid	220	Caffeic acid	3.87
Phenylacetylvaline	500	Ellagic Acid	4.45
Phenylacetylleucine	780	Gallic Acid	5.35
Butyric Acid	850	Ferulic Acid	7.41
Phenylbutyric Acid	970	Phloroglucinol	38.82

As shown in Table 3, inhibitors of SAHH and MT are better DHIs than inhibitors of MAT. Stability of three MEs is proportional to the mass. SAHH is the smallest and the most unstable enzyme of the three. The mass of MAT is equivalent to SAHH + MT [87]. The association with telomerase further increases its stability. It takes a lot of inhibitors to function as DHIs. Inhibitors of SAHH and MT are better DHIs.

Although pregnenolone is not the best DHI, we consider it a very valuable DHI, since it is the master substrate for all functional steroids. It is also a metabolite to have profound influence on the development of cancer. According to Morley, the production of pregnenolone is bell shape in relation to ages [105], the youngest and the oldest people produce the least amounts and these two age groups are most

vulnerable to develop cancer. Thus, pregnenolone is a metabolite to exercise profound influence on the development of cancer. It is our choice of DHI for the CDA formulation of CDA-CSC.

The finding of signal transduction inhibitors (STIs) as excellent DHIs is expected, since ST is always resulted in the enhancement of MT to promote cell replication. STIs are synonyms to MTI. The finding of polyphenols as excellent DHIs is not expected. The discovery of epigallocatechin-3-gallet as an inhibitor of DNA MEs is a perfect explanation of polyphenols as excellent DHIs [106]. Vital Reds is a food supplement produced by famed cardiologist Steven Gundry to help clearing blocked blood vessels. Polyphenols are the major ingredients of Vital Reds. The clearing of blocked blood vessel by Vital Reds is very likely the perfection of wound healing as DHIs.

The manufacture of CDA formulations can be the following formula to reach plasma concentrations as ED_{25} of a DI + 3 x $RI_{0.5}$ of a DHI, or ED_{50} of a DI + 2 x $RI_{0.5}$ of a DHI, or ED_{75} of a DI + $RI_{0.5}$ of a DHI [39]. We recommend to manufacture two sets: one set as CDA-CSC consisting of AA + pregnenolone to access CSC and another set as CDA-CC consisting of BIBR1532 + pyrvinium pamoate to resist degradation of natural wound healing metabolites in faster growing CCs. We also recommend the application of phenylacetylglutamine to antagonize TNF, which can be administered as a capsule, and monitored independently through peptide assay as described in Table l. Therapeutic efficacy of CDA formulations cannot be based on the shrinkage of tumor through radiological image. Stabilization of tumor size can be an encouraging diagnosis. Other evaluation methods must be developed to provide precise evaluation of therapeutic efficacy such as the drop of carcinoembryonic antigens to the normal values, or the restoration of CDA levels to the normal values.

3. Conclusion

Lessons to learn from the failures can give rise to successful solutions. Cancer therapies based on the killing of CCs are incorrect, stirring up cancer as a giant killer. Ineffectiveness against CSCs and the contribution to destroy chemo-surveillance are the reasons to cause the failure of cancer therapies based on the killing of CCs, which can be remedied by CDA formulations. CDA formulations are the drugs best to handle CSCs and to restore chemo-surveillance. Wound unhealing is the cause of CVDs like cancer. Perfection of wound healing through CDA formulations is the best solution of CVDs.

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