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RESEARCH ARTICLE

CDA Formulations for the Standard Care of Breast Cancer

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Abstract

Breast cancer is notoriously easy to metastasize at the early stage. Despite the fact that breast is an external organ easy to detect cancer at the early stage to achieve lifelong cure and the availability of multiple therapeutic modalities, breast cancer remains a top killer. The objective of this article is to attribute inability of cancer authorities to handle unhealed wound and cancer stem cells (CSCs) as the primary reasons for the failure of breast cancer therapy and to offer cell differentiation agent (CDA) formulations as the only option to heal the unhealed wound and to eradicate CSCs, which are critically linked to unhealed wound, to win the war on breast cancer. Cancer evolving due to wound unhealing was a valid concept of cancer introduced by R. Virchow in 1858. Western medicine is totally unprepared to handle diseases evolving due to wound unhealing. Western medicine likes to solve diseases based on the elimination of symptoms. Perpetual proliferation of cancer cells (CCs) is the most outstanding symptom of cancer. Thus, killing of CCs became the favored approach of cancer therapies, and the disappearance of tumor became a requirement of cancer drugs and a standard diagnosis on the success of cancer therapy. Both were wrong, because killing of CCs to create wound clearly violated the advice of Virchow. Since killing of CCs was incorrect for cancer therapy, disappearance of tumor was also incorrect for the evaluation of cancer therapy. We pursued cancer therapy unknowingly to follow the advice of Virchow to discover abnormal methylation enzymes (MEs), chemo-surveillance and the mechanism of wound healing. Wound healing requires the proliferation and the terminal differentiation (TD) of progenitor stem cells (PSCs). PSCs are the most primitive stem cells to initiate the development of organs and tissues during the embryonic stage of fetal development. So, wound healing is an extension of embryonic program of organ and tissue development. PSCs express telomerase, MEs of telomerase expressing cells are abnormal due to the great affinity of MEs and telomerase to form complex, which changes kinetic properties of MEs and the regulation of cell growth greatly in favor of the promotion of cell growth. Wound healing comes naturally, because the nature creates chemo-surveillance and immuno-surveillance to ensure perfection of wound healing. Human body produces cell differentiation agents (CDAs) to function as chemo-surveillance, which is selectively destroyed in cancer patients for cancer to evolve and to progress. The restoration of chemo-surveillance is very critical to the success of breast cancer therapy, which can be achieved by the administration of CDA formulations. CDA-2 was a preparation of wound healing metabolites we purified from urine for cancer therapy, which has been approved by the Chinese FDA for the therapy of breast cancer as an adjuvant agent to supplement cytotoxic cancer therapy and as a mono-therapeutic agent for the therapy of myelodysplastic syndromes, which are diseases attributable entirely to the propagation of CSCs. Since CSCs play a very prominent role on the pathology of breast cancer displaying to cause metastasis at the early stage and the emergence of triple negative breast cancer cells to resist therapies currently available, CDA formulations are naturally the standard care of breast cancer.

Keywords: Breast Cancer, CDA Formulations, CSCs, Chemo-Surveillance, MEs, PSCs, Wound Healing.

1. Introduction

Breast cancer is notoriously easy to metastasize at the early stage. Lymph node involvement is frequently detected during the surgery of early stage breast cancer. Despite the fact that breast is an external organ easy to detect cancer at the early stage and the

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availability of specific instrument mammogram to detect cancer at the early stage to achieve lifelong cure, and the availability of multiple therapeutic modalities specifically for breast cancer such as tamoxifen and HER2/neu cancer target in addition to cytotoxic cancer therapies, breast cancer remains a top killer of female cancers next only to lung cancer. Ineffectiveness of available cancer therapies on CSCs is to blame for the high mortality of breast cancer. CSCs became known in 1997 [1]. The discovery of CSCs unraveled CSCs as the cells to initiate tumor growth and the cells responsible for metastasis [2]. CSCs were also the cells to contribute to major fatal effects of cancer, fatal effects such as metastasis, drug resistance, radiation resistance, angiogenesis, unresponsiveness and recurrence were all the making of CSCs [3-9]. Thus, the solution of CSCs is very critical to the success of cancer therapy. CSCs constitute only a small subpopulation less than 2% of the primary tumor mass, which are often neglected by the cancer authorities even though their contribution of fatal effects is recognized. 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 for the solution of CSCs which were critically linked to unhealed wounds to cause the evolution of cancer. Cancer evolving due to wound unhealing was a concept introduced by the German pathologist R. Virchow in 1858 [10]. Killing cells to create wound definitely was in violation of Virchow's advice. Virchow was well respected as a pioneer of cancer. However, the concept of cancer evolving due to wound unhealing was not accepted by cancer authorities who preferred to develop cancer drugs that killed cancer cells (CCs) to eliminate the most outstanding symptom of cancer displaying as perpetual replication of CCs. 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. We pursued cancer therapy unknowingly to follow his advice to discover abnormal MEs [11-13], chemo-surveillance [14-16], and the mechanism of wound healing [17-20]. We in essence independently produced experimental data to support the validity of Virchow's concept of cancer evolving due to wound unhealing. Thus, we were also extremely talented to decode the logic of wound unhealing to the evolution of cancer. We were thus in a unique position to solve the issues of wound unhealing and CSCs which are critically linked to wound unhealing. Since CSCs contribute prominent role on the pathology of breast cancer to display metastasis at the early stage and the emergence of triple negative cancer cells unresponsive to therapies currently available, effective solution of CSCs is very important to the therapy of breast cancer. CDA formulations are the best drugs for the therapy of CSCs, therefore, CDA formulation can be the standard care of breast cancer. The progression of CSCs to faster growing CCs is also caused by wound unhealing, but the replication of CCs is not critically linked to wound unhealing as that of CSCs. Replication of CCs attracts the attention of cancer authorities to neglect the more important issue of CSCs. Breast cancer remains a top killer of female cancers.

2. CDA Formulations for the Standard Care of Breast Cancer, and Discussion

2.1 Cytotoxic Drugs Aimed to Kill CCs are Incorrect for the Therapy of Breast Cancer

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 treat leukemia patients. Indeed, toxic chemicals were very effective to eliminate leukemia cells to achieve immediate therapeutic effect. Elimination of symptoms is a favored approach of western medicine to solve diseases. Elimination of symptoms can offer immediate therapeutic effects which may or may not last very long. On diseases displaying symptoms such as pain, fever or cough, elimination of symptoms is an excellent approach. Western medicine is oriented toward the elimination of symptoms. Perpetual replication of CCs is the most outstanding symptom of cancer. Toxic chemicals became the choice of cancer authorities not only for the therapy of hematological cancers, but also for solid cancers, and the disappearance of tumor became a standard evaluation on the success of cancer therapy. Both were wrong, which clearly violated the advice of Virchow [10]. Virchow's advice was given too anciently to remain in the memory of recent cancer authorities. Virchow's concept of cancer evolving due to wound unhealing was brought up again by Dvorak in 1986 in a very popular medical journal that ought to catch the attention of recent cancer authorities [21]. Recent cancer authorities were unmoved to continue their quest of cancer therapies based on the killing

of CCs. They have failed using that approach to win the War on Cancer, a presidential project declared by President Nixon during 1971-1976. Presidential projects are serious businesses, dealing with the monumentally important issues of the nation. Solution of top killing diseases is obviously an important issue of the national. Cardiovascular diseases (CVDs) are the top killer of American people, followed by cancer as the next top killer. Heart attack and stroke contributing to the fatality of CVDs are too difficult to overcome. So, President Nixon chose easier cancer as his presidential project. Health profession failed to meet the challenge, which was a very shameful record to fail a presidential assignment. A presidential project can receive unlimited support of national resources to ensure success, but with a time limit of five years. There were two precedents. Nuclear physicists achieved the Manhattan Project under President Roosevelt and racket engineers achieved the Moonshot Project under President Kennedy, both required very difficult technologies. Health professionals failed the War on Cancer Project which did not require difficult technology. Had they followed the advice of Virchow, they could also achieve the War on Cancer Project, which was the easiest of the three. Virchow's advice was the only solution to win the War on Cancer [22-24]. The failure to achieve the War on Cancer was a decisive verdict that cytotoxic cancer drugs were wrong for cancer therapy [25-29]. After the failure of War on Cancer, the cancer authorities started to search for the alternatives to replace cytotoxic agents. Meanwhile they kept using failed cytotoxic drugs for the treatment of cancer patients that was inappropriate. The consequence was as expected that cancer mortalities kept on escalating. They should suspend failed cytotoxic drugs and used whatever approved drugs available. The first choice of alternative therapy was gene therapy during 1976-1996, which was endorsed by multiple Novel prizes to award the discoveries of oncogenes and suppressor genes. The choice of developing gene therapy was justified, which played important roles on the regulation of cells growth closely related to cancer. But correction of chromosomal abnormalities such as translocations to activate oncogenes or deletions to inactivate suppressor genes was really very difficult. It was beyond their abilities to accomplish. They wasted 20 years without developing a gene therapy drug. They managed to sequence the entire human genome during this period, which was a remarkable accomplishment, although without help on cancer therapy. They also managed to develop several targeted signal transduction inhibitory (STI) agents. It was a good thing that cancer authorities failed to develop gene therapy. If it was successful, we would be trapped in a very difficult approach of cancer therapy like we are now trapped in the unattainable cytotoxic cancer therapies which are partially successful to benefit a small minority of cancer patients in the early stage. The success on early stage cancer patients was not entirely the credit of cytotoxic cancer therapies. The collapse of chemo-surveillance of the early stage cancer patients was not fatal, which could be restored to the functional state to subdue the surviving CSCs which were not responsive to cytotoxic assault [3-9]. The restoration of chemo-surveillance played a decisive role on the success of cytotoxic cancer therapy on early stage cancer patients.

Next choice of alternative therapy to replace cytotoxic cancer therapies was to develop anti-angiogenesis therapy during 1996-2016. They successfully developed Avastin for anti-angiogenesis therapy. But the success of Avastin therapy ended up causing the death of patients due to internal bleeding. That echoed the failure of cytotoxic cancer therapy. The success of cytotoxic cancer therapy often caused the death of patients due to adverse effects or recurrence,

The third choice was to develop immunotherapy during 2016-2036, which was endorsed by Novel prize in 2025. The discovery of programmed death antigen on pathological cancer cells to be eliminated by immunological means was a remarkable accomplishment deserved Novel prize. It is a targeted killing of CCs, and the target is a membrane glycoprotein which is much better than non-specific cellular DNA. Besides, changing genetic structure is a very dangerous attempt. It may produce monstrous cells nobody can handle. Immunotherapy definitely is a better choice than cytotoxic cancer therapies. Immunotherapy, however, has the same problem of cytotoxic cancer therapies to show ineffectiveness against CSCs, and to contribute to the damage of chemo-surveillance which are the reasons to cause the failure of cytotoxic cancer therapies. CSCs are PSCs without ten-eleven translocator-1 (TET-1) enzyme. The cell feature, antigenicity and cell mission of CSCs are exactly the same as those of PSCs. PSCs are tolerable to the natural immune mechanisms. So, CSCs are also tolerable to the natural immune mechanisms. There are several immunotherapeutic drugs approved. But the cancer mortalities during the past 10 years are still on the trend to escalate at 0.2% annually [30]. It does not look promising that immunotherapy can win the war on cancer. Cancer is basically a problem of growth regulation going

awry. Immunology has nothing to do with growth regulation. Cancer authorities must have run out of choices to put the hope on immunotherapy. It definitely is an improvement over cytotoxic cancer therapies which should be suspended in 1976 after the failure to achieve the War on Cancer. So far, the cancer authorities do not have a successful record to develop cancer drugs based on the elimination of symptom to kill CCs. Targeting on the cause through CDA formulations for the perfection of wound healing and the elimination of CSCs is the only option to win the war on breast cancer [24, 31-34].

2.2 CDA Formulations as the Standard Care of Breast Cancer

Wound healing comes naturally, because the nature creates immuno-surveillance and chemo-surveillance to ensure perfection of wound healing, immuno-surveillance to heal wounds created by infectious agents and chemo-surveillance to heal wounds created by toxic chemicals or physical means. On wound healing, immuno-surveillance and chemo-surveillance act synergistically to heal wounds to prevent disastrous consequences of wound unhealing. The health profession is well prepared to handle wounds created by infectious agents. Antibiotics and vaccinations are good policies put up by the health profession to handle the issue of wounds created by infectious agents. Still some infectious agents remain a serious concern of human cancers such as papilloma virus, hepatitis virus, HIV virus and Helicobacter pylori bacteria. The health profession is poorly prepared to handle the issue of wounds created by toxic chemicals and let the unhealed wounds to evolve into giant killers such as cancer, CVDs and organ failures [10, 18-24, 29, 31-34].

Wound healing requires the proliferation and the TD of PSCs. PSCs are the most primitive stem cells to initiate the development of organs or tissues during the embryonic stage of fetal development. Small number of PSCs, usually less than 2% of the organ or tissue mass, are preserved in the organ or tissue for future expansion or repair. Wound healing is actually an extension of the embryonic program of organ or tissue development. Primitive embryonic stem cells express telomerase which has a great affinity with MEs to form complex to turn MEs into abnormal MEs to promote the growth of cells expressing telomerase needed for the development of fetus or healing of wound. The association of telomerase with MEs changes the kinetic properties of MEs and the regulation of MEs greatly in favor of promoting cell growth. MEs are a ternary enzyme complex consisting of methionine adenosyltransferase (MAT)-methyltransferase (MT)-S-adenosylhomocysteine hydrolase (SAHH) which plays a pivotal role on the regulation of cell replication and differentiation [35]. K_m values of telomerase associated isozyme pair MAT^{LT}-$SAHH^{LT}$ are 7-fold higher than the normal isozyme pair MAT^{L}-$SAHH^{L}$ [11-13]. The higher K_m values are an indication that abnormal MEs have higher bound S-adenosylomethionine (AdoMet) to become more stable and active since the study of Prudova et al. indicated that AdoMet could protect protein against protease digestion [36]. The higher K_m values are also an indication that larger pool sizes of AdoMet and S-adenosylhomocysteine (AdoHcy) are needed to promote the exceptional growth of cells expressing abnormal MEs since the study of Chiva et al. indicated that when cancer cell HL-60 were induced to undergo TD, the pool sizes of AdoMet and AdoHcy shrank greatly [37]. MEs becoming abnormal are actually the most important issue of cancer by virtue of the fact that DNA MEs control the expression of tissue specific genes [38] and rRNA MEs control the production of ribosome [39], which in turn dictate the cell to enter cell cycle to replicate [40]. If enhance production of ribosome is locked in place, it becomes a factor to drive carcinogenesis [41]. Both abnormal MEs and chromosomal abnormalities to activate oncogenes or to inactivate suppressor genes are closely related to the evolution of cancer, abnormal MEs to block differentiation to keep cell in cell cycle replicating and chromosomal abnormalities to drive cell replication. Chromosomal abnormalities received most attention including many Novel prizes and the designation on the development of gene therapy during 1976-1996 without success. 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 exit cell cycle to undergo TD, these genes have no roles to play. Therefore, destabilization of abnormal MEs to achieve TD is an easier solution of chromosomal abnormalities. Actually, it is not feasible to develop gene therapy. If a difficult gene therapy is achieved, there may soon pop up another chromosomal abnormality to negate the previous effort. We will be trapped in endless struggles of developing gene therapies. One stroke to destabilize abnormal MEs to achieve TD can also put to rest chromosomal abnormalities. That was the reason we considered abnormal MEs as the bullseye of cancer target [23, 24, 32, 42-47]. MEs becoming abnormal are the most critical issue of cancer. It appears that the seed of cancer is sown at the very

beginning of life, namely the fertilization of the egg with a sperm to activate 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 unipotent stem cell (UPSC). The growth of UPSC is under the regulation of steroid hormone or related factors [35].

Wound can trigger biological and immunological responses [48]. The biological response involves the release of arachidonic acid (AA) from membrane bound phosphatidylinositol by phospholipase A2 for the synthesis of prostaglandins (PGs) by cyclooxygenases and PG synthases [48, 49]. Although AA and PGs are active DIs [50, 51], the induction of TD of PSCs at the initial stage of the wound is not the primary objective of AA and PGs. Rather, the localized inflammation caused by PGs [52] 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 which is the primary objective of PGs to orchestrate the healing process. Chemo-surveillance mediated through differentiation inducers (DIs) and differentiation helper inducers (DHIs) normally function as a brake to prevent the buildup of PSCs. This brake must be released in order for PSCs to produce enough cells for the repair of the wound. PGs are metabolically unstable [49]. 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, which is selectively destroyed in cancer patients. Chemo-surveillance was a terminology we created to describe an observation that healthy people were able to maintain a steady level of metabolites active as DIs and DHIs, whereas cancer patients tended to show deficiency of such metabolites as shown in Table 1, which is reproduced from the reference [14].

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

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

Plasma Peptides: *nmoles/ml; Urine 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. Data presented in the Table 1 are quantitative data of plasma and urinary peptides. Peptides share physical and chemical properties similar to DIs and DHIs. Thus, peptides can be used as surrogate molecules to represent DIs and DHIs in the plasma and urine. As a matter of fact, acidic peptides are the major DIs of Antineooplaston preparations Burzynski purified from urine for cancer therapy [53-55]. Obviously, pathological conditions created by wounds are responsible for the collapse of chemo-surveillance. Wounds also trigger immunological response to induce infiltration of leukocytes in the wound area that produce cytokines to initiate the incidence of myelodysplastic syndromes (MDSs) [56]. Among cytokines produced, tumor necrosis factor (TNF) is most closely related to the development of MDSs, since antibody of TNF was found effective to prevent the progression of MDSs [57]. TNF is a well known oncoprotein to induce cancer. It is also named cachectin after its effect to induce cachexia symptoms. A manifestation of cachexia symptoms is the excessive excretion of low molecular weight metabolites because of the membrane hyperpermeability caused by TNF [58, 59]. Wound healing metabolites DIs and DHIs are among low molecular weight metabolites excreted resulting in the collapse of chemo-surveillance unable to heal wounds. Chemo-surveillance is always operating at the maximum capacity. There is no mechanism to increase the supply of DIs and DHIs when these metabolites are lost due to excessive excretion. The pressure will build up to force the proliferation of PSCs. But the proliferation of PSCs is limited by contact inhibition. PSCs are then forced to evolve into CSCs to escape the limitation of contact inhibition. It takes a single hit to silence TET-1 to convert PSCs to become CSCs, which is an easy task for PSCs to accomplish, since these cells are equipped with exceptionally active MEs. Therefore, the functionality of chemo-surveillance is extremely

important for the perfection of wound healing to avoid cancer evolution [15]. Antineoplaston A10, which was a code name of phenylacetylglutamine by Burzynski, was very effective to antagonize TNF to protect the functionality of chemo-surveillance [14]. By protecting the functionality of chemo-surveillance, Antineoplaston A10 was found very effective to prevent hepatocarcinogenesis induced by potent hepatocarcinogen aflatoxin B_1 as shown in Figure 1, which is reproduced from the reference [60].

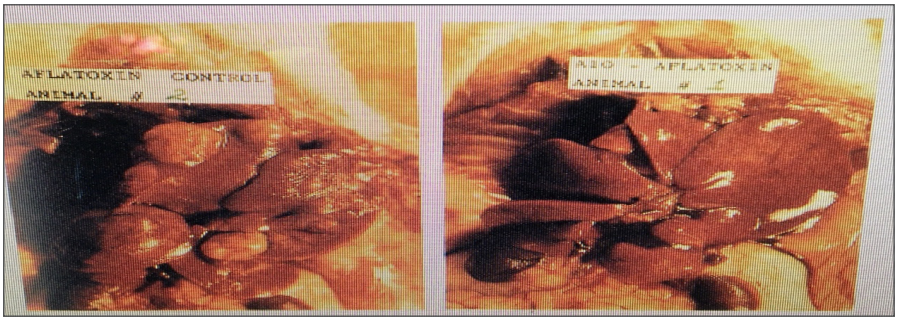


Figure 1. *Effective Prevention of Hepatocarcinogenesis by Antineoplaston A10*

Antineoplaston A10 is biologically inactive chemical. It is remarkable that by antagonizing the biological effect of TNF it can effectively prevent hepatocarcinogenesis challenged with a potent hepatocarcinogen aflatoxin B_1. Drugs that can prevent diseases from taking place are considered the best drugs by oriental medicine [61]. Western medicine also considers preventive drugs very valuable. Antibiotics and vaccination are the creation of western medicine. Western medicine actually has the edge on preventive medicine. Antineoplaston A10 showing excellent cancer prevention activity should be acceptable as a cancer prevention drug by both oriental and western medicine. Antineoplaston A10 is a major chemical component of Antineoplastons purified from urine for cancer therapy by Burzynski [53-55] and CDA-2 purified from urine for cancer therapy by Liau [62]. Antineoplastons employed reverse phase chromatographic system of C18-80% methanol, whereas CDA-2 employed that of XAD16-100% ethanol. Chemical compositions of Antineoplastons and CDA-2 are not exactly the same. Peptides are the major chemical compositions of Antineoplastons, which are not recovered by XAD16. Active DIs designated as pigment peptides-0 (PP-0) are membrane fragments containing phosphadidylinositol are the major active DIs of CDA-2, which are only minor active DIs of Antineoplastons. Active DIs designated as organic acids-0.79 (OA-0.79) are present in both preparations. OA-0.79 are AA or dicycloPGs, the end products of PGs, in liposomal complex with pregnenolone. Despite differences in chemical compositions, both Antineoplastons and CDA-2 showed excellent activities in the induction of TD of HL-60 cells. Destabilization of abnormal MEs to induce TD of PSCs, CSCs and CCs is the critical mechanism of anticancer effects of wound healing metabolites purified from urine.

Immunological response triggered by wound is bad for wound healing. Immunological response tends to produce cytokines which are toxic proteins to assist immunotherapy. TNF is particularly bad to contribute to the collapse of chemo-surveillance. It is the balance of biological and immunological effects to dictate the outcome of wound healing. If biological response prevails, wound is healed. But if immunological response prevails, wound cannot be healed to produce clinical symptoms. If the symptoms are fatal such as the white lung of COVID-19 infection, or heart attack and stroke of CVDs, fatality is the end point. If the symptoms are not fatal such as those of carcinogens, there is a good possibility that PSCs will be forced to evolve into CSCs as above described. Thus, cancer evolving due to wound unhealing was a valid concept introduced by Virchow [10]. MDSs are classical diseases to prove the validity of Virchow' concept. MDSs are at the stage of PSCs evolving to become CSCs. The propagating pathological cells have been identified as CSCs [63]. MDSs represent the classical cases of cancer development, which start with a display of immunological disorder prompting the production of inflammatory cytokines [56], TNF being the critical factor related to the development of MDSs [57]. It causes excessive apoptosis of bone marrow stem cells, thus severely affecting the ability of the patient to produce hematopoietic cells such as erythrocytes, platelets, or neutrophils. TNF is also responsible for the collapse of chemo-surveillance to result in the evolution of PSCs to become propagating CSCs of MDSs. Further progression can take place to force the activation of oncogenes or inactivation of suppressor genes to become full blown acute myeloid leukemia.

Therapy of MDSs require the drugs that can antagonize TNF and induce TD of CSCs to produce depleted

erythrocytes, platelets, or neutrophils. CDA-2 is ideal for the treatment of MDSs, which contains phenylacetylglutamine to antagonize TNF, and DIs and DHIs to induce TD of CSCs as above described [14, 32, 44-47, 62]. Vidaza and Decitabine also can inactivate MT by covalent bond formation between MT and 5-azacytosine incorporated into cellular DNA [64]. The action of CDA-2 is selective to target on the cells with abnormal MEs, whereas the action of Vidaza and Decitabine is non-selective that can also affect normal UPSCs. Professor J. Ma was instrumental in conducting clinical trials of these three drugs for the approval 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 noticeable better therapeutic efficacy by cytological evaluation, although slower to reach complete remission, and a markedly better therapeutic efficacy by hematological improvement evaluation, meaning becoming independent on blood transfusion to stay healthy as shown in Fig. 2, which is reproduced from the reference [65].

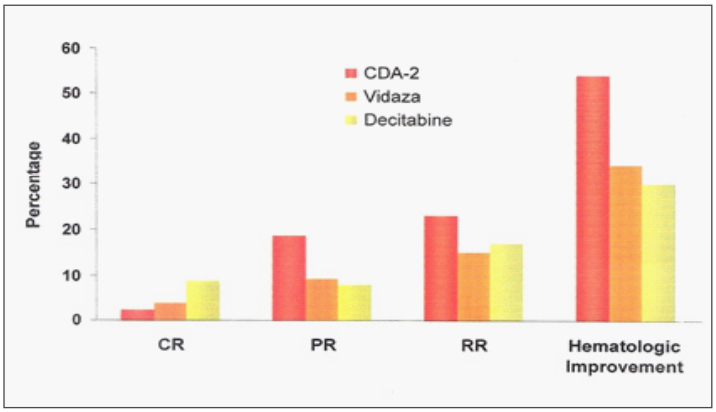


Figure 2. *CDA-2 as the Best Drug for the Therapy of MDSs*

CDA-2 was definitely the best drug for the therapy of MDSs displaying better therapeutic efficacies and devoid of adverse effects, whereas Vidaza and Decitabine were demonstrably worse on therapeutic efficacies, and also unacceptable as proven carcinogens [66, 67] and very toxic to DNA, particularly toward cardiac cell DNA [68-70]. Obviously, CDA-2 is the drug of choice for the therapy of MDSs and the only drug effective against CSCs. We have predicted that the winner of the contest to eradicate CSCs won the contest of cancer therapies [71]. We were the clear winner, but our winner's status was denied by the cancer authorities who put up tumor shrinkage as a condition to qualify as a cancer drug. The therapeutic endpoint of CDA-2 is the TD of CSCs and CCs that cannot make tumor to shrink. Evidently induction of TD of CSCs is the only option to solve the issue of CSCs which are critically linked to wound unhealing [32, 46]. Induction of the TD of PSCs is the critical mechanism of wound healing. CCs are not critically linked to wound unhealing, which can be eliminated by killing or induction of TD to become cells unable to proliferate. Killing is incorrect which creates wound against the advice of Virchow [25]. Induction of TD of CCs is also a better choice of cancer therapy [72-74]. Cancer cells undergoing TD become cells with specific function and no longer capable of proliferation. Terminally differentiated cancer cells display histology distinctly different from histology of CCs as shown in Figure 3, which is reproduced from the reference [42].

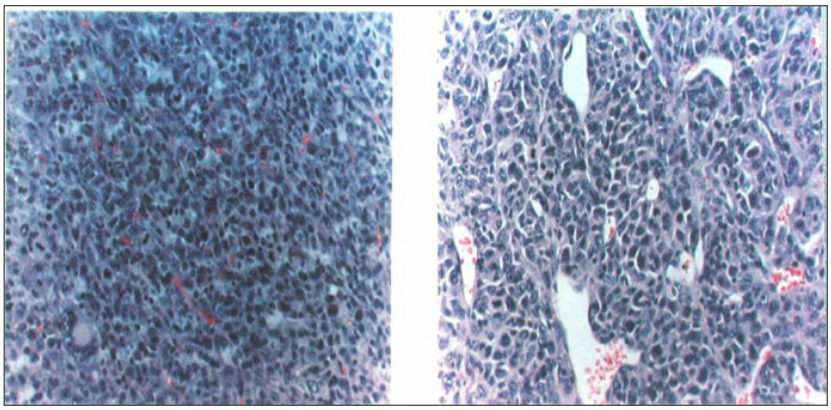


Figure 3. *Histological Change of Hepatocellular Carcinoma Smmnu 7721 Induced to Undergo TD by CDA-2*

Histologies of malignant tumor and terminally differentiated tumor residue are clearly different. Oncologists of solid tumor should be trained to distinguish the difference of malignant tissue and terminally differentiated tumor residue to make a more precise judgement on the success of cancer therapy. Hematological oncologists are able to distinguish cancer cell and terminally differentiated cell. Radiological image is too crude that can only tell tumor size that is not a correct evaluation of cancer therapy [25, 26, 76]. Oncologists of solid tumor are obviously not well trained to make a correct evaluation of cancer therapy. Tumor shrinkage based on the radiological image is the most damaging mistake of cancer authorities to block Antineoplastons and CDA-2 as legitimate cancer drugs. Antineoplastons and CDA-2 are the invention of the creator of the nature to handle the issue of wound unhealing and to solve cancer and the diseases evolving due to wound unhealing. Virchow and Liau et al. were the only rare scientists exceptionally talented to comprehend the logic of wound unhealing to the evolution of cancer at a time neither wound healing nor cancer was complete known. Cancer became completely known in 1997 through the discovery of CSCs by Bonnet and Dick [1] and wound healing became completely known in 2021 through the discovery of wound healing mechanism by Liau and Craig [18]. Cancer authorities were extremely dumb not able to understand the logic of wound unhealing to the evolution of cancer at a time when both cancer and wound healing were completely known. They are arrogant to admit the mistakes they made in the past to make cancer unable to solve. They made mistake to focus on the killing of CCs in violation of the correct advice of Virchow [10]. The American Cancer Society made a serious mistake in 1976 to terminate the lifetime grant support to Professor Robert B. Hurlbert for his contribution on the establishment of pyrimidine pathway, because he used that grant support to challenge the assignment of 28S rRNA at the 5'-end of 45S precursor molecule by the President of American Cancer Society [76]. At that time we were using the grant support from American Cancer Society to study abnormal RNA MEs that became involved in the dispute on the assignment of topographical order of 18S and 28S rRNA in the 45S precursor molecule. There were reports assigning 18S rRNA at the 5'-end of the 45S precursor molecule. Professor Harris Busch, who was the classmate of Professor Robert Hurbert studying for Ph. D. under Professor van Portor of the University of Wisconsin, was the President of American Cancer Society at that time, who erroneously assigned 28S rRNA at the 5'-end of the 45S precursor molecule. Methylated dinucleotide profiles of 18S rRNA and 28S rRNA are distinctly different, so we figured the analysis of methylated dinucleotide profiles of shorter and longer nascent rRNA chains in isolated nucleoli could resolve the controversy. Our analysis of shorter and longer nascent rRNA chains in isolated nucleoli labeled with H^3-methy-AdoMet in RNA synthesizing medium produced data clearly showed 18S rRNA at the 5'-end in opposition to the assignment of 28S rRNA by the President of American Cancer Society. The American Cancer Society was very unhappy for the use of fund from American Cancer Society to discredit the President of American Cancer Society. The lifetime grant to Professor Hurlbert was terminated to result in the termination of his research career and his associate Ming C. Liau. It happened that these two scientists were the rare breeds extremely talented to discover abnormal MEs which were the most important issue of cancer critically related to wound unhealing and CSCs. These two scientist were the only cancer scientists able to solve the issue of wound unhealing and CSCs which were not known at that time. Without grant support, Professor Hurlbert was forced to retire early and his associate Liau was dismissed from MD Anderson Cancer Center. American Cancer Society destroyed the careers of Hurlbert and Liau. It also destroyed its mission to win the war on cancer. Cancer can never be solved by the inept cancer authorities now in power [77]. The inept cancer authorities not only cannot provide the solution of cancer but also to block the solution of cancer. On the failure to provide cancer solution, the study of Thon et al. was very alarming to explain the failure of cancer therapies based on the killing of CCs, who showed malignant astrocytomas with CSCs counts leas than 1% were responsive to cytotoxic cancer therapies, whereas malignant gliomas with CSCs counts greater than 3% were unresponsive to cytotoxic cancer therapies [78]. The responsive margin to cytotoxic cancer therapies is so narrow to offer effective therapies by killing of CCs. Brain compartment is a unique compartment to have enrichment of wound healing metabolites which are hydrophobic metabolites tended to accumulate in the brain compartment. Thus, only malignant tumors with very high CSCs counts can prevail in the brain compartment. Malignant gliomas, glioblastomas and neuroblastomas all show very high CSCs counts [78-80]. Brain compartment is also enriched with growth hormone which is produced in the pituitary gland located in the brain compartment to promote

the growth of benign tumors and astrocytomas with very low counts of CSCs. Malignant tumors with CSCs counts above 3% are unresponsive to cytotoxic cancer therapies. Cytotoxic cancer therapies and immunotherapy kill CCs to promote the replication of CSCs to increase CSCs counts. When CSCs counts reach above 3%, the further therapies can only result in fatality [26, 72]. Therefore, cancer therapies promoted by cancer authorities are unable to put cancer away. Cancer authorities become the killers of advanced cancer patients constituting the majority of cancer population.

Antineoplastons were wound healing metabolites purified from urine used by Burzynski for cancer therapy to show excellent cancer therapy during 1976-1990 [53-55]. Wound healing metabolites are the prescription of the creator of the nature for cancer therapy. Excellent therapeutic results came naturally. Antineoplastons were not approved by FDA. Cancer authorities asked Texas government legislators to enact legislations to limit oncologists to use only FDA approved drugs to treat cancer patients. The therapeutic endpoint of Antineoplastons is the TD of CSCs and CCs that can not cause tumor to disappear. FDA put up a rule of tumor shrinkage as a condition as acceptable cancer drugs which was wrong [75]. But cancer authorities used this wrong rule to block Antineopolatons as acceptable cancer drugs around 1990. Cancer authorities successfully blocked Antinoeoplatons as acceptable cancer drugs. By blocking Antineoplastons as acceptable cancer drugs, cancer authorities also blocked their mission to solve cancer, because the solution of cancer requires the elimination of CSCs that could only be achieve by Antineoplastons. So, cancer authorities were responsible for the blockade of cancer therapy, once by terminating the grant support to Professor Robert B. Hurbert and second time by blocking Antineoplastons as legitimate cancer drugs.

CDA-2 was wound healing metabolites purified from urine by Liau to show excellent cancer therapy on breast cancer and MDSs to be approved by the Chinese FDA [62, 65, 81]. The excellent therapy on breast cancer and MDSs is because CSCs play a dominant role on the pathology of breast cancer and MDSs. As shown in Figure 2, CDA-2 was apparently the best drug for the therapy of CSCs which were the propagating pathological cells of MDSs [63]. CSCs may also play a dominant pathological role on breast to cause early metastasis and the emergence of triple negative cancer cells unresponsive to available therapies, which are very likely CSCs. MDSs did not have tumor shrinkage issue. CDA-2 was approved as a mono-therapeutic drug. On breast cancer, CDA-2 could not cause the tumor to shrink. It was approved as an adjuvant drug to supplement cytotoxic drugs to achieve the requirement on tumor shrinkage. Actually, requirement of tumor shrinkage was a bad policy put up by the cancer authorities to focus on the development of cytotoxic drugs to kill CCs which were incorrect for cancer therapy [25, 75]. The requirement of tumor shrinkage should be abandoned. CDA-2 could be the standard care of breast cancer as a mono-therapeutic agent if shrinkage of tumor was not a considering factor. If the differentiated tumor residue shown in Figure 3 is a concern, it can be safely removed by surgery without having to worry about the dissemination of metastasis. CDA formulations patterned after CDA-2 are the only drugs capable of handling CSCs [32, 42-47, 65]. Therefore, CDA formulations can be the standard care of breast cancer.

2.3 Development of CDA Formulations as the Standard Care of Breast Cancer

We have carried out extensive studies of natural and non-natural DIs and DHIs for the manufacture of CDA formulations [31-34, 42, 50, 51, 54, 55, 62, 82-85]. Active DIs and DHIs are presented in Table 2 and 3. Effective dosage$_{25,\ 50\ and\ 75}$ ($ED_{25,\ 50\ and\ 75}$) of DIs and reductive index$_{0.5}$ ($RI_{0.5}$) are included to facilitate manufacturing of CDA formulations. $RI_{0.5}$ of a DHI is equivalent to ED_{25} of a DI, which can be determined by the procedure presented in the reference [82]. DIs and DHIs can be excellent cancer drugs which are not regarded highly by the cancer authorities, because these drugs cannot make tumor to disappear. All trans-retinoic acid (ATRA), a DI, is the standard care of acute promyelocytic leukemia [86] and Gleebec, a DHI, is the standard care of chronic myeloid leukemia [87]. ATRA requires the expression of the receptor of ATRA, namely RAR, to function.

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

RAR is the repressor of the gene of oligoisoadenylate synthetase. The association of RAR with ATRA activate the expression of oligoisoadenylate synthetase. The produce of this enzyme, oligoisoadenylate, is the active DI to act on abnormal MEs. Oligoisoadenylate has to be synthesized inside the cell to function. The triphosphate structure prevents its entry into the cell from outside of the cell. ATRA is an indirect DI. The rest of active DIs presented in Table 2 are direct DIs to act on abnormal MEs. AA and PG derivatives are natural DIs to participate in chemo-surveillance. BIBR1532 and boldine are non-natural DIs, which have been approved for cancer therapy as telomerase inhibitors. PGs have also been approved for delivery. Change of indication of the approved drugs does not need long clinical trials as the new drugs which usually take 10 years to complete clinical trials for the approval.

DHIs listed in Table 3 show inhibitors of SAHH and MT are better DHIs than inhibitors of MAT. The stability of three MEs is proportional to the mass [35]. SAHH is the smallest enzyme and is the most unstable enzyme, which requires a stabilizing factor such as steroid hormone to assume a stable configuration to form dimeric complex with MT to become stable. MT-SAHH dimer has a mass similar to MAT. MT-SAHH dimer has the affinity with MAT to form a ternary enzyme complex as the stable and function unit. MAT is the largest and the most stable enzyme of the three MEs. The association with telomerase further increases its stability. It takes a large quantity of inhibitors to function as DHIs. Inhibitors of SAHH and MT are better DHIs than inhibitors of MAT. Pregnenolone is not the most active SAHH inhibitor. We consider it as the most important DHI, because it is the master substrate of all biologically active steroids. According to Morley, the production of pregnenolone is bell shape in relation to ages with a peak production of around 50 mg daily at the ages of 20-25 [88]. The youngest and the oldest people produce the least amounts of pregnenolone, and these are the two age groups most vulnerable to develop cancer.

Table 3. *Active DHIs*

SAHH Inhibitors RI0.5 ((μM))	**RI0.5 (μM)**	**STI**
Pyrvinium Pamoate 0.28	0.012	Sutent
Vitamin D3 1.62	0.61	Berberine
Dexamethasone 10.1	0.75	Vorient
β-Sitosterol 11.9	1.72	Gleevec
Dihydroepiandrosterone 19.7	1.79	Selenite
Prenisolone	2.22	
Hydrocortisone	4.59	Polyphenols
RI0.5 (μM)		
Pregnenolone	7.16	
		Tannic Acid
0.37		
MT Inhibitors	RI0.5 ((μM))	EGCG
0.62		
		Resveratrol
1.16		
Uroerythrin 1.24	1.9	Curcumin
Hycanthone 1.43	2.1	Kuromanin
Riboflavin 1.95	2.9	Coumestrol
		Genisteine
2.19		

MAT Inhibitors 3.18	RI0.5 ((μM))	Pyrogallol
		Silibinine
3.80		
Indol Acetic Acid 3.87	220	Caffeic acid
Phenylacetylvaline 4.45	500	Ellagic Acid
Phenylacetylleucine 5.35	780	Gallic Acid
Butyric Acid 7.41	850	Ferulic Acid
Phenylbutyric Acid 38.82	970	Phloroglucinol

Pregnenolone is our choice of DHI to make CDA-CSC formulation. The finding of signal transduction inhibitors (STIs) as excellent DHIs was expected, since activation of tyrosine kinase by growth factors always results in the promotion of activity of MT. STIs and MT inhibitors are synonyms. The finding of polyphenols as excellent DHIs was unexpected. But the discovery of EGCG as a good STI to inhibit MEs explains polyphenols as effective DHIs [89, 90]. So, polyphenols are MT inhibitors as excellent DHIs. Vital reds is a good product for vascular patients produced by the famed cardiologist Steven Gundry [91]. The effectiveness of vital reds to clear blocked blood vessel is attributable to the perfection of wound healing to remove the cause of the diseases of CVDs [23, 27-29, 33].

The manufacture of CDA formulation can be the following formula to provide plasma concentations of ED_{25} of a DI + 3x$RI_{0.5}$ of a DHI, or ED_{50} of a DI + 2x $RI_{0.5}$ of a DHI, or ED_{75} of a DI + $RI_{0.5}$ of a DHI [84]. DIs are more important than DHIs to promote TD. But DIs alone cannot achieve TD to reach completion, because elimination of telomerase from abnormal MEs tends to cause the dissociation of ternary MEs to become individual enzymes. MTs as monomer have a tendency to be modified by proteases to become nucleases that can create damages to disrupt differentiation process. The therapy of acute promyelocytic leukemia by ATRA was excellent reaching over 90% complete remission. But most cured patients recurred within one year [86]. Therefore, the inclusion of DHIs is essential to prevent modification of MTs to become nucleases to cause recurrence. We recommend to make two sets of CDA formulations: one set CDA-CSC consisting of AA as the DI + prgnenolone as the DHI to access CSCs and PSCs, and another set CDA-CC consisting of BIBR1532 as the DI + pyrvinium pamoate as the DHI to resist enzymatic degradation of natural DIs and DHIs by fast growing CCs which express a high level of degradative enzymes to salvage substrates for macromolecular syntheses to support fast growth. The application of phenylacetylglutamine to antagonize TNF is also recommended to remove the incidence of cancer, which can be administered as capsule preparation, and monitored independently through quantitative peptide analysis of the plasma and urine as described in Table 1. Radiation image is not a valid evaluation method of cancer therapy. The drop of carcino-embryonic antigens to the normal values is a more accurate evaluation.

3. Conclusion

CSCs play a dominant role on the pathology of breast cancer to display the metastasis at early stage and the emergence of triple negative cancer cells to resist cancer therapies currently available. Thus, breast remains a top killer of female cancers. CDA formulations are the best and the only drugs to handle CSCs, which should be developed as the standard care of breast. Inability to make tumor to disappear is the disadvantage of CDA formulations, which is not related to the effectiveness of breast cancer therapy. If residual tumor becomes a concern, it can be safely removed by surgery without having to worry about dissemination of metastasis.

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It is not applicable

Competing Interest

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