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RESEARCH ARTICLE

CDA Formulations to Remove Cancer and Cardiovascular Diseases as the Top Killers of Humans

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Abstract

Cardiovascular diseases (CVDs) are the top killers and cancer is the next top killer in the USA and worldwide. The fact that these diseases remain top killers for a very long time is an indication that therapies currently available are not very effective. Hypertension is the most outstanding symptom of CVDs, which is caused by the damage to the artery's inner lining triggering the buildup of plague in the arteries to result in fatal symptoms of heart attacks and strokes. Typical therapies of CVDs involve the blockers of calcium channel to reduce blood pressure and statins to cut down the production of cholesterol associated with low density lipoprotein (LDL). These therapies are helpful to alleviate the symptom of hypertension, but miss the very important issue of wound unhealing to contribute to CVDs as the top killers.

Perpetual proliferation of cancer cells (CCs) is the most outstanding symptom of cancer which is caused by abnormal methylation enzymes and chromosomal abnormalities to activate oncogenes or to inactivate suppressor genes. Cancer establishments focus on the elimination of CCs to aggravate the critical issue of cancer stem cells (CSCs) to result in cancer as the second top killer.

Wound healing requires the proliferation and the terminal differentiation of progenitor stem cells which are the most primitive stem cells to initiate the development of organ or tissue during embryonic development of the fetus. Wound unhealing can force PSCs to evolve into CSCs and then to progress to CCs. Wound unhealing in the case of CVDs produces fatal symptoms of heart attacks and strokes. Fatality is the end point. Wound unhealing must be not fatal for cancer evolution to become established. Inability to complete the terminal differentiation of PSCs and CSCs is the etiology of both cancer and CVDs. Perfection of wound healing employing CDA formulations is thus the only option and the best approach for the therapy of cancer and CVDs to remove these diseases as the top killers of humans.

Keywords: CVDs, CSCs, Hypertension, PSCs, Therapies of Cancer and CVDs, Wound Healing.

1. Introduction

CVDs are the top killers in the USA and worldwide for a very long time, contributing to 0.92 million mortality in 2023 in the USA and 20.5 million in 2021 around the world [1]. Cancer is the next top killer in the USA and worldwide also for a very long time, contributing to 0.61 million mortality in 2024 in the USA and 10 million in 2019 around the world [1]. The fact that these diseases remain top killers for a very long time is an indication that therapies currently available are not very effective. Hypertension is the most outstanding symptom of CVDs, which is caused by the damage to the artery's inner lining triggering the buildup of plague in the arteries to result in fatal symptoms of heart attacks and strokes. Typical therapies of CVDs involve the blockers of calcium channel to reduce blood pressure and statins to cut down the production of cholesterol associated with LDL, also aimed to reduce hypertension. Such therapies may be effective to alleviate the symptom of hypertension, but is not curative to eventually lead patients to fatal heart attacks or strokes. CVDs thus become the top killers

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of humans. Perpetual proliferation of CCs is the most outstanding symptom of cancer. Killing of CCs is the choice of cancer therapy by cancer establishments, which is apparently incorrect to stir up cancer as a giant killer [2, 3].

CVDs are caused by the damage to the artery's inner lining and cancer evolves due to wound unhealing [4]. Wound healing requires the proliferation and the terminal differentiation of PSCs [5]. Wound if unhealed can result in the display of clinical symptoms such as tissue fibrosis and organ failures [6-8], and CVDs and cancer brought up in this article. Wound unhealing if producing symptoms that are fatal such as the white lung of COVID-19 infection or heart attacks and strokes of CVDs, fatality is the end point. Only unhealing wound that is not fatal such as chronic viral infection or carcinogenesis can force PSCs to evolve into CSCs. Therapy of CVDs requires the completion of terminal differentiation of PSCs of the unhealed wound and therapy of cancer requires the completion of terminal differentiation of PSCs and CSCs which are critically linked to wound unhealing. If CSCs have progressed to CCs, therapy must also include CCs which are not critically linked to wound unhealing. Induction of terminal differentiation is the only option to solve PSCs and CSCs [3, 9-14]. CCs can be eliminated by the induction of terminal differentiation or cell killing. Cell killing is incorrect [2, 10]. But that is the choice of cancer establishments to result in cancer as the second top killer of humans. Apparently, perfection of wound healing by the employment of CDA formulations is the only option and the best approach for the therapy of cancer and CVDs to remove these diseases as the top killers [3, 9-14].

2. CDA Formulations to Remove Cancer and CVDs as the Top Killers of Humans and Discussion

2.1 The Logic of Wound Unhealing to the Evolution of Cancer and CVDs

Cancer and CVDs are the top killers of humans. Cancer is a fearful disease, because the treatments are excruciating and ineffective. Patients in the final moment are very painful to scream day and night. When they are no longer screaming, they are dead. Cancer should be eliminated at all cost to put away miserable suffering. Deaths from CVDs are instant without miserable suffering. Nevertheless, it is always a plus to eliminate diseases, particularly the top killing diseases. Virchow was a very respected cancer pioneer from German. He was extremely talented to comprehend the logic of wound unhealing to the evolution of cancer at a time neither cancer nor wound healing was completely known [4]. Had we followed his advice on cancer, solution of cancer was like wound healing that came naturally without having to put up any effort. Obviously, wound healing is an important health issue, so that the nature creates chemo-surveillance and immuno-surveillance to ensure perfection of wound healing to avoid disastrous consequences of wound unhealing, chemo-surveillance on take care of wounds from toxic chemicals or physical means and immuno-surveillance to take care of wounds from infectious agents. On the issue of wound healing, chemo-surveillance and immuno-surveillance can act synergistically to heal the wound. Chemo-surveillance was a terminology we created to describe an observation that healthy people could maintain a steady level of metabolites active as differentiation inducers (DIs) and differentiation helper inducers (DHIs), whereas cancer patients tended to show deficiency of such metabolites as shown in Table 1, which is reproduced from the reference [15]. DIs are metabolites capable of eliminating telomerase from abnormal methylation enzymes (MEs), and DHIs are inhibitors of MEs capable of potentiating the activity of DIs. MEs are a ternary enzyme complex consisting of methionine adenosyltransferase (MAT)-methyltransferase (MT)-S-adenosylhomocysteine hydrolase (SAHH) [16]. MEs in cells expressing telomerase are associated with telomerase [17]. The association of MEs with telomerase changes kinetic properties of MAT-SAHH isozyme pair by raising K_m values 7-fold higher and the

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

Plasma/Urine Peptide Ratios	CDA Levels	Number of Patients	% Distribution
0.83 – 0.80 (Normal)	5.0	2	1.8
0.80 – 0.60	4.3	7	6.5
0.60 – 0.4 (Responsive)	3.1	18	16.7
0.40 – 0.20	1.8	38	35.2
0.20 – 0.10	0.9	24	22.2
0.10 – 0.02 (Unresponsive)	0.37	19	17.6

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

regulation of growth greatly in favor of cell growth [18, 19]. MEs play a pivotal role on the regulation of cell growth and differentiation. Because of this important regulatory role, MEs are exceptionally subjected to double allosteric regulations [20]. On the individual enzymes, SAHH is the receptor of steroid hormone to regulate the association of active ternary enzymes and the dissociation to inactive individual enzymes. On the enzyme complex, MEs are allosterically regulated by telomerase which changes the kinetic properties of MAT-SAHH isozyme pair to increase the stability of MEs in favor of cell growth. The increased K_m values implies cells expressing telomerase have larger pool sizes of S-adenosylmethionine (AdoMet) and S-adenosylhomocysteine (AdoHcy) which are important for the promotion of the growth of cells expressing telomerase. The study of Prudova et al. indicated that AdoMet could protect the protein against protease digestion [21]. Thus, larger pool size of AdoMet can improve the stability of proteins in association with AdoMet. MEs are the likely enzymes to gain stability. The study of Chiva et al. indicated that when HL-60 cells were induced to undergo terminal differentiation the pool sizes of AdoMet and AdoHcy shrank greatly [22]. Thus, larger pool sixes of AdoMet and AdoHcy are needed to support the growth of cells expressing telomerase. CSCs are evolved from PSCs and CCs are progressed from CSCs which all express telomerase. Obviously, the advantage to promote cell growth is required for the development of fetus and wound healing as well as malignant growth. Abnormal MEs carry out normal functions for the development of fetus and wound healing, whereas the function of abnormal MEs in malignant growth results in the display of clinical symptoms. The difference is that the function of abnormal MEs in fetal development and wound healing is protected by safety mechanisms such as contact inhibition, ten-eleven translocator-1 enzyme (TET-1) and chemo-surveillance, whereas these safety mechanisms are dysfunctional to result in malignant growth becoming uncontrollable. Attempt to interrupt the normal function of abnormal MEs can be detrimental to cause malformation of body parts, noticeably the malformation of limbs induced by thalidomide. Malformation of limbs is non-lethal. Malformation of vital organs such as brain or heart can result in stillbirth. It appears that the seed of cancer and CVDs is sown at the very beginning of life, namely the fertilization of the egg with a sperm to activate the totipotent stem cell which expresses telomerase. The expression of telomerase spreads through pluripotent stem cells during the embryonic development of the fetus, but secedes when pluripotent stem cells undergoing lineage transitions to reach unipotent stem cells. DIs and DHIs are wound healing metabolites created by the nature to induce terminal differentiation of PSCs to heal the wound. If maternal DIs and DHIs get into fetal blood circulation these metabolites may produce detrimental effects like thalidomide. Placenta must have an important function to prevent the entry of hydrophobic DIs and DHIs metabolites, allowing only the entry of hydrophilic thalidomide to cause birth defects. The nature has a perfect design to avoid mishaps to take place.

Quantitative determinations of plasma and urinary peptides presented in Table 1 were important experimental data we produced to support the validity of cancer evolving due to wound unhealing introduced by Virchow [4]. DIs and DHIs are hydrophobic wound healing metabolites produced in the body. Peptides share physical-chemical properties similar to DIs and DHIs. Therefore, peptides can be used as surrogate molecules to represent DIs and DHIs. As a matter of fact, acidic peptides were major DIs of Antineoplaston preparations, which were wound healing metabolites purified from urine by Burzynski for cancer therapy [23-26]. It appears that wound healing metabolites are constantly produced by the body as chemo-surveillance to ensure perfection of wound healing. Evidently, pathological assaults may cause the breakdown of chemo-surveillance to interfere with wound healing to result in wound unhealing that may constitute a pathological basis for the evolution of PSCs to become CSCs, and then to progress to faster growing CCs through chromosomal abnormalities. Pathological basis must be non-lethal for cancer evolution to become established. If pathological basis of wound unhealing is lethal as in the cases such as white lung of COVID-19 infection or CVDs, fatality is the end result. There will be no cancer evolution. Regardless of the consequences of wound unhealing, perfection of terminal differentiation of PSCs is the best approach to eliminate consequences of wound unhealing. During our studies of hepatocarcinogenesis, we noticed the appearance of numerous tiny hyperplastic nodules soon after the application of hepatocarcinogens to the animals, which displayed abnormal MEs [27]. These tiny hyperplastic nodules must represent proliferation of PSCs in the process of active wound healing created by hepatocarcinogens. Most of these tiny hyperplastic nodules disappeared shortly, and only a few large size hepatocarcinomas appeared later from unhealed tiny hyperplastic nodules. If Antineoplaston A10, namely phenylacetylglutamine, was given to the animals after

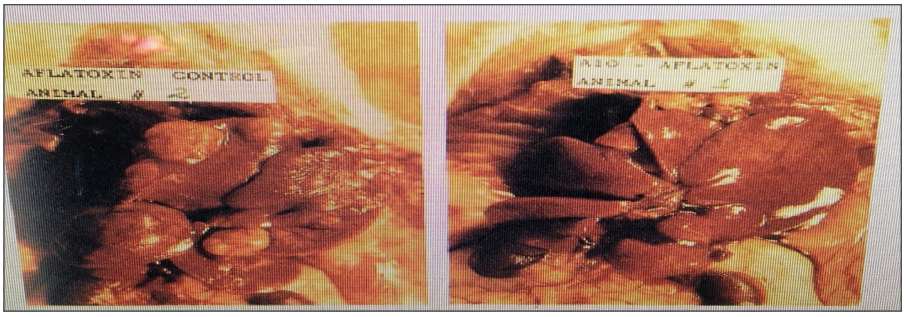


Figure 1. *Effective Prevention of Hepatocarcinogenesis by Antineoplaston A10.*
The figure on the left is the control liver receiving aflatoxin B_1 only, and the figure on the right is the liver receiving Antineoplaston A10 after the administration of aflatoxin B_1.

the application of hepatocarcinogen aflatoxin B_1, the appearance of hepatocarcinomas could be effectively prevented as shown in Fig. 1, which is reproduced from the reference [28].

Antineoplaston A10 is biologically inactive chemical. Nevertheless, it can effectively antagonize the effect of tumor necrosis factor (TNF) to prevent the loss of wound healing metabolites to keep the functioning of chemo-surveillance intact [15]. TNF is a oncogenic protein responsible for initiation of myelodysplastic syndromes (MDSs) [29-31]. TNF is also named cachectin after its notorious effect to cause cachexia symptoms. A manifestation of cachexia symptoms is the excessive urinary excretion of low molecular weight metabolites due to the blood vessel hyper-permeability induced by TNF [32, 33], wound healing metabolites are among low molecular weight metabolites excreted resulting in the collapse of chemo-surveillance. Collapse of chemo-surveillance is responsible for wound unhealing to result in the evolution of CVDs or cancer. Figure 1 is another very important experimental datum we produced to support the concept of cancer evolving due to wound unhealing introduced by Virchow [4].

Evidently, CVDs are also caused due to wound unhealing. Damage to the artery's inner lining is the initial event to trigger the buildup of PSCs in an attempt to heal the damage. Aberrant DNA methylation displaying as global hypomethylation and regional hypermethylation is a hallmark of cancer, namely cells with abnormal MEs [34-36]. Aberrant DNA methylation is implicated in the onset and progression of atherosclerosis, heart failure and cardiac arrythmia [37-39]. High level of homocysteine and aberrant hypermethylation of critical genes are identified as the risk factors of CVDs. These risk factors are clearly related to the metabolical activities of cells with abnormal MEs. Cells with abnormal MEs have larger pool sizes of AdoMet and AdoHcy [22], consequently higher level of homocysteine to contribute to a risk factor of CVDs [39]. CpG of human atherosclerotic aortic samples were hypermethylated in many genomic loci versus non-atherosclerotic controls [37, 38]. These are clear indication that metabolical activities of PSCs during the process of wound healing play important roles to the pathological process of CVDs. Perfection of wound healing is a therapy based on the elimination of cause of the diseases. Therapy based on the elimination of the cause is always superior than the therapy based on the elimination of symptom [40]. Cytotoxic cancer therapies and therapies of CVDs are aimed to eliminate symptoms, which are not as effective as CDA formulations to eliminate causes of the diseases. Cytotoxic cancer therapies and CDA therapy are conflicting rivalries [2, 3, 10-14]. Only one is the right solution. The acceptance of CDA therapy requires a revolution to beat cancer establishments that is not easy [41]. CDA therapy aimed at the elimination of the cause of CVDs and anti-hypertension therapies aimed at the elimination of symptom can be synergistic to benefit CVDs patients. The acceptance of CDA formulations for the therapy of CVDs is much easier.

2.2 On the Mechanism of Wound Healing

Wound healing requires the proliferation and the terminal differentiation (TD) of PSCs [5]. Wound usually triggers biological and immunological responses. The biological response involves the release of arachidonic acid (AA) from membrane bound phosphatidylinositol through phospholipase A2 for the synthesis of prostaglandins (PGs) by cyclooxygenases and PG synthases [42, 43]. Although AA and PGs are active DIs [44, 45], the induction of TD of PSCs at the initial stage of wound is not the primary objective of PDs. Rather, the localized inflammation caused by PGs [42] 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 cells with abnormal MEs such as PSCs. The brake provided by DIs and DHIs must be released for PSCs to proliferate to produce enough cells to heal the wound. PGs are metabolically unstable [42]. 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 chemo-surveillance. The stable end products of PGs may participate in the final stage of wound healing, which are also active as DIs although not as active as PGs [44].

The immunological response triggered by wound is not good for wound healing. Immunological response tends to trigger the production of cytokines, which are toxic proteins to assist immunotherapy. These toxic proteins create wounds to aggravate the already bad situation of wound unhealing. TNF among cytokines is particularly bad for wound healing as above described. It appears that immunological response can also act antagonistically to chemo-surveillance. It is the balance of biological response and immunological response to dictate the consequence of wound healing. If biological response prevails, wound is healed. If immunological response prevails, wound cannot be healed to display clinical symptoms. The clinical symptoms can be wide varieties, not just limited to CVDs and cancer brought in this article. CDA formulations can put away two top killers of humans and many more other diseases from organ failures. Acute wounds in general favor wound healing, whereas chronic wounds are most likely to result in wound unhealing.

2.3 CDA Formulations as the Only Option for the Therapy of Diseases Evolving due to Wound Unhealing

MDSs are a classic model to elucidate the evolution of cancer due to wound unhealing. MDSs often start with a display of immunological disorder to prompt the production of inflammatory cytokines [46]. TNF among cytokines produced is the critical factor related to the development of MDSs [29-31]. It causes excessive apoptosis of bone marrow stem cells, thus severely affecting the production of hematopoietic cells such as erythrocytes, platelets or neutrophils. TNF is also responsible for the collapse of chemo-surveillance as above described to allow the evolution of CSCs from PSCs to escape contact inhibition which is a safety mechanism to limit the extent of proliferation of PSCs. It takes a single hit to silence TET-1 enzyme to convert PSCs to become CSCs to escape the restriction of contact inhibition. CSCs can propagate beyond the space allowed. The propagating pathological cells of MDSs patients have been identified as human CSCs [47]. So, MDSs are diseases attributable entirely to CSCs. CSCs are PSCs minus TET-1. The cell feature, antigenicity and cell mission of CSCs are exactly the same as those of PSCs. PSCs are rare and precious cells. These cells are well protected by drug resistant and anti-apoptosis mechanisms that include expression of aldehyde dehydrogenase to detoxify harmful chemicals and expression of methylguanine methyltransferase (MGMT) to repair DNA [48-54]. These cells express chemokine receptor to display a great ability to promote metastasis [55, 56]. Obviously, CSCs are most vicious pathological cells to contribute fatal effects of cancer. Fatal effects of cancer such as metastasis, drug resistance, anti-apoptosis, angiogenesis, unresponsiveness and recurrence are the makings of CSCs. Yet, these cells are not recognized by natural immune mechanisms as pathological cells marked with programmed death antigen to be eliminated. Antigenicity of CSCs is exactly the same as PSCs which are tolerable to natural immune mechanisms. CSCs can be eliminated by monoclonal antibodies, which the cancer establishments tried to develop to put CSCs away, but failed because killing was not an option to solve the issue of CSCs which were critically linked to wound unhealing. Induction of TD of PSCs and CSCs is the only option to close the issue of wound unhealing. Cytotoxic cancer therapies can only benefit a quarter of cancer patients with CDA levels above 2.5 as shown in Table 1, whose chemo-surveillance have not yet fatally damaged, relying on the recovery of chemo-surveillance to subdue surviving CSCs which are not responsive to cytotoxic therapies. The success of cytotoxic therapies is actually contributed by the perfection of wound healing [11-14]. The success of cancer therapy of early stage cancer patients is not entirely the effort of the elimination of CCs. The creation of chemo-surveillance by the creator of the nature also plays a decisive role. Actually, cancer establishments are doing more damage than benefit to cancer patients. They put up toxic agents to contribute to the fatality of the majority of cancer patients in advanced state [2, 3]. Accoring to Thon et al., astrocytomas with CSCs counts less than 1% are responsive to cytotoxic cancer therapies, whereas glioblastomas with CSCs counts more than 3% are unresponsive to cytotoxic cancer therapies [57]. Thus, ineffectiveness against CSCs and the contribution to damage chemo-surveillance

are the reasons to cause the failure of cytotoxic cancer therapies. Cancer establishments are supposed to save all cancer patients. They can only save a quarter of cancer patients in the early stage, but contribute to the fatality of three quarters of cancer patients in the advanced stage. Establishments of CVDs are not doing great either, contributing to more deaths than cancer establishments. They all should change the strategy to focus on the solution to eliminate causes of diseases instead of on the solution to eliminate symptoms to save patients.

Induction of TD of PSCs and CSCs is the critical mechanism of wound healing [19, 58, 59]. CDA-2, which was a preparation of wound healing metabolites purified from urine we developed [59], achieves destabilization of abnormal MEs by targeting on the tumor factor telomerase of abnormal MEs, whereas Vidaza and Decitabine inactivate MEs by covalent bond formation between MT and 5-aza-cytosine incorporated into DNA [60]. Vidaza, Decitabine and CDA-2 were the three drugs approved by the Chinese FDA for the therapy of MDSs in China. Vidaza and Decitabine were also approved by the US FDA for the therapy of MDSs in the USA. Professor J Ma, the Director of Harbin Institute of Hematology and Oncology, was instrumental in carrying out clinical trials of all three MDSs drugs. According to his assessments based on two cycles of treatment protocols, each 14 days, CDA-2 had a noticeable better therapeutic efficacy based on cytological evaluation, although slower to reach complete remission and a marked better therapeutical efficacy based on hematological improvement evaluation, namely becoming independent of blood transfusion to stay healthy as shown in Fig. 2, which is reproduced from the reference [61]. Fig. 2 is a very valuable datum produced by Professor

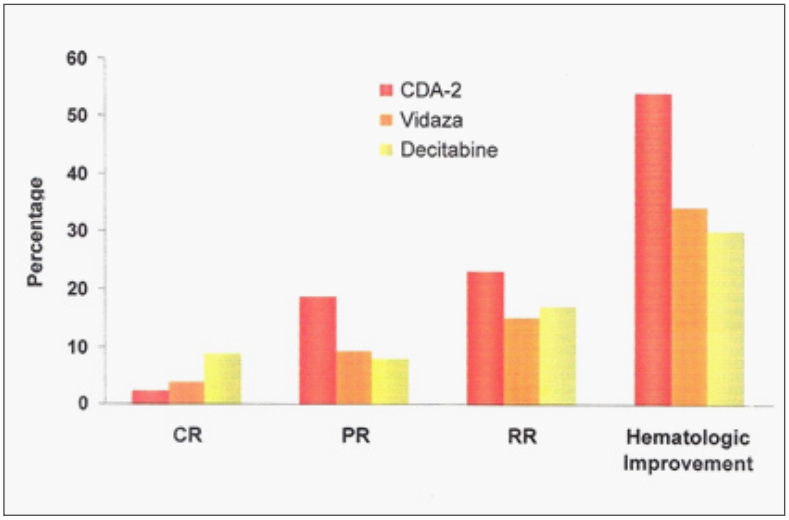


Figure 2. *CDA-2 as the Best Drug for the Therapy of MDSs*

Ma to support the validity of concept of cancer evolved due to wound unhealing. CDA-2 is clearly the drug of choice for the therapy of MDSs with superior therapeutic efficacy and without adverse effects, whereas Vidaza and Decitabine are known carcinogen [62, 63], and very toxic to DNA [64-66]. We have predicted that the winner of the contest to eradicate CSCs won the therapy of cancer therapy [67]. We are the clear winner of the therapy of cancer. Our winner's status was denied by the cancer establishments who put up a rule of tumor shrinkage as a condition of cancer drugs [68]. The same rule they put up to deny CDA formulations as cancer drugs also block their mission to win the war on cancer [69], since CDA formulations are the only option to solve the issue of CSCs [14]. The solution of CSCs is essential for the success of cancer therapy [3, 13]. CDA formulations are the effective drugs that can help patients arising due to wound unhealing that include cancer, CVDs and many more.

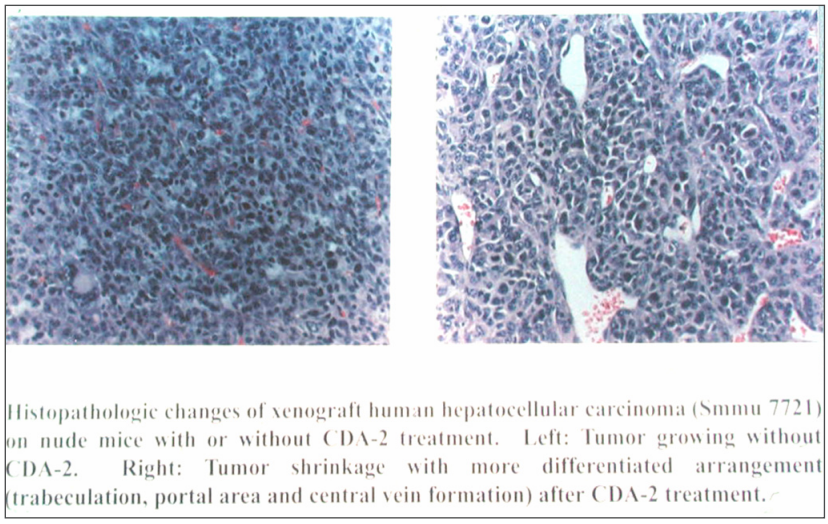
2.4 Development of CDA Formulations to Remove CVDs and Cancer as the Top Killers of Humans

Virchow [4] and Liau et al. [18] were the advocates of cancer evolving due to wound unhealing. Dvorak joined the alliance [70]. This is a very lonely alliance to stand against the whole army of health profession. We have the blessing of the creator of the nature who creates chemo-surveillance and immuno-surveillance to support the validity of our very lonely alliance.

Cancer establishments are proven failure. They failed to win the war on cancer during 1971-1976; failed to develop gene therapy during 1976-1996, which was not their favored project; failed to develop anti-angiogenesis therapy during 1996-2016; and the development of immunotherapy during 2016-2036 is

not promising, since the cancer mortality is still on the way to escalate [11, 71, 72]. Cancer is basically a problem of cell growth regulation going awry. Immunology has nothing to do with the regulation of cell growth. Cancer establishments must have run out of choices to put the hope on immuno-therapy. They still have 10 years to prove that they are right. But that is very unlikely. Three scientists discovering immunotherapy were awarded Nobel prize this year. Scientists discovering oncogenes and suppressor genes were awarded Nobel prizes which did not result in the development of cancer drugs to benefit cancer patients despite the 20 years of efforts, 1976-1996, the cancer establishments devoted to develop gene therapies. The discovery of immunotherapy was a remarkable scientific achievement to be awarded Novel prize as the discovery of oncogenes and suppressor genes. Scientific achievements and benefits to humans are two different matters.

Cytotoxic cancer therapies are proven failure. CDA therapy is an unproven attempt. It has winning records. All trans-retinoid acid (ATRA), an excellent DI, is the standard care of acute promyelocytic leukemia [73], and gleebec, a good DHI, is the standard care of chronic myeloid leukemia [74]. It has to demonstrate excellent therapeutic efficacy to be designated as standard care of a particular cancer. Antineoplastons were preparations of wound healing metabolites purified from urine by Burzynski to demonstrate excellent therapy of cancer during 1976-1990 [15, 23, 24], which were unfortunately blocked by the cancer establishments because these drugs did not behave like cytotoxic agents they preferred. We were convinced that Antineoplastons were good cancer drugs to target on abnormal MEs we discovered before joining Burzynski's research Institute in 1980. We were confident that preparations like Antineoplastons could by accepted in China because they were used to Chinese herbal medicine which is a therapeutic efficacy oriented medicine, while chemical compositions can be largely unknown. We had to develop our own method of purification of urinary wound healing metabolites by reverse phase chromatography employing XAD-16-ethanol system instead of C18-80% methanol system established by Buzynski for the preparation of Antineoplastons. CDA-2, our brand of urinary preparation of wound healing metabolites was approved for the therapy of breast, lung and primary hepatomas as an adjuvant to supplement cytotoxic cancer therapy by the Chinese FDA in 2004 [75] and as a mono-therapeutic drug for the therapy of MDSs in 2018 [61]. Therapy of CDA-2 on solid tumors was excellent to eliminate both CSCs and CCs. The therapeutic endpoint of CDA-2 is the terminal differentiation displaying very different histological morphology as shown in the Fig. 3, which is reproduced from the reference [79].



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

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

If the therapeutic efficacy of solid tumors were based on the morphological changes of hemotological cancers, CDA-2 could be the standard care of solid tumors instead of as an adjuvant agent [80]. Preparations like CDA-2 and Antineoplastons are acceptable in China, but are not acceptable to the western medicine. We have carried out extensive studies on the active components of CDA-2 and Antineoplastons to produce CDA formulations with defined compositions [9, 25, 26, 44, 45, 59.76-79]. Active DIs and DHIs are listed in table 2 and 3.

ED_{25}, ED_{50} and ED_{75} of DIs and reductive index 0.5 ($RI_{0.5}$) of DHIs are included to facilitate manufacturing of CDA formulations. $RI_{0.5}$ of DHI is equivalent to ED_{25} of DI, which can be determined through procedure previously reported [76]. ATRA requires

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	40.5
DicycloPGE2	21.0	43.5	-
AA	21.0	42.0	-
BIBR1532	32.3	43.7	55.1
Boldine	60.1	78.8	94.2

the expression of the receptor of ATRA, namely RAR, to achieve the therapeutic efficacy. RAR is a repressor of the gene coding for oligoisoadenylate synthetase. The association of RAR with ATRA activates oligoisoadenylate synthetase gene transcription to produce oligoisoadenylate synthetase. The product of this enzyme oligoisoadenylate is the excellent DI to act on abnormal MEs [81]. ATRA is actually an indirect DI. The rest of DIs listed in Table 2 are direct DIs to act on abnormal MEs. AA and its metabolites PG derivatives are natural DIs to involve in the function of chemo-surveillance. BIBR1532 and boldine are non-natural DIs, which were approved cancer drugs as telomerase inhibitors. Telomerase is a recognized oncogenic protein. The association with MEs to promote malignant growth is the reason for it being recognized as an oncogenic protein. CDA formulations achieve cancer therapy by antagonizing two important oncogenic proteins, TNF and telomerase. PGs were also approved for the delivery. Changes of indication of the approved drugs does not take long clinical trial as the new drugs which usually require 10 years to complete clinical trials.

As listed in Table 3, inhibitors of SAHH and MTs are better DHIs than inhibitors of MAT. The stability of three MEs is proportional to the mass [16]. SAHH is the smallest of the three, and is the most unstable enzyme that requires steroid hormone to assume a stable configuration for the formation MT-SAHH dimer to become stable. MAT has a mass similar to the MT-SAHH dimer, which is the most stable enzyme of the three. The association with telomerase in abnormal MEs further increases its stability. Therefore, it requires very large amounts of inhibitors to function as DHIs. Inhibitors of SAHH and MTs are better DHIs.

Table 3. *Active DHIs*

SAHH Inhibitors	RI0.5 (μM)	Signal Transduction Inhibitors (STIs)	RI0.5 (μM)
Pyrivinium Pamoate	0.012	Sutent	0.28
Vitamin D3	0.61	Berberine	1.62
Dexamethasone	0.75	Vorient	10.1
Beta-Sitosterol	1.72	Gleevec	11.9
Dihydroepiandrosterone	1.79	Selenite	19.7
Prenisolone	2.22		
Hydrocortisone	4.59	Polyphenols	RI0.5 (μM)
Pregnenolone	7.16		
		Tannic Acid	0.37
MT Inhibitors	RI0.5 (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
MAT Inhibitors	RI0.5 (μM)	Genisteine	2.19
		Pyrogallol	3.18
		Silibinine	3.80
Indol Acetic Acid	220	Caffeic Acid	3.87
Phenylacetylvaline	500	Ellagoc Acid	4.45
Phenylacetylleucine	780	Gallic Acid	5.35
Butyric Acid	850	Ferulic Acid	7.41
Phenylbutyric Acid	970	phloroglucinol	38.82

Although pregnenolone is not the most effective DHI, we consider it as a very valuable DHI. It is the master substrate for all biologically active steroids. It is also a single steroid to have profound influence on the development of cancer. According to Morley, the production of pregnenolone is bell shape in relations to ages with a peak daily production of around 50 mg at the ages of 20-25 [82]. The youngest and the oldest people produce the lease amounts of pregnenolone, and these are the two age groups most vulnerable to develop cancer. It is our top choice to Make CDA-CSC.

DIs are more important than DHIs for the induction of TD. But DIs alone cannot achieve differentiation to reach completion, because elimination of telomerase from abnormal MEs tends to cause the dissociation of MEs into individual enzymes. MT as a monomer has a tendency to be modified by protease to become nuclease, which can create damage to disrupt differentiation process. The damage can be repaired to cause recurrence. The therapy of acute promyelocytic leukemia with ATRA was excellent, reaching above 90% complete remission, but most patients recurred within one year [73]. The inclusion of SAHH or MT inhibitors can keep MT-SAHH dimer intact to prevent modification of MT to become nuclease to disrupt differentiation process. It is a good idea to include both DI and DHI to make CDA formulations.

The finding of STIs as excellent DHIs is expected, since STIs always lead to the production of factors to inhibit the activity of MEs. STIs are tyrosine kinase inhibitors, but the inhibition of the activity of MEs is the consequence. STIs and inhibitors of MT become synonyms. The finding of polyphenols as excellent DHIs is a surprise. Epigallocatechin-3-fallate (EGCG) has been found as a good STI to inhibit MT [83, 84]. It is possible that all polyphenols act via inhibition of tyrosine kinases to result in the inhibition of MEs like EGCG. Vital reds is a food supplement produced by the famed cardiologist Steven Gundry, which contain polyphenols as the major active ingredients. It is effective to clear the blocked blood vessel [85]. Gundry found the solution of CVDs through perfection of wound healing, but he did not provide the correct interpretation. The correct interpretation of the therapy of CVDs by vital reds is mediated through destabilization of abnormal MEs for the perfection of wound healing just like the therapy of MDS by CDA-2 of Fig.2. Polyphenols are generally considered as healthy foods. The finding of polyphenols as excellent DHIs adds the credibility of polyphenols as healthy foods.

The manufacture of CDA formulation can be the following formula to reach plasma concentrations as ED_{25} of a DI + $3xRI_{0.5}$ of a DHI, or ED_{50} of a DI + $2xRI_{0.5}$ of a DHI, or ED_{75} of a DI + $RI_{0.5}$ of a DHI [9]. We recommend to make two sets of CDA formulations: one set CDA-CSC consisting of AA + pregnenolone to get access to PSCs and CSCs, and another set CDA-CC consisting of BIBR1532 + pyriminium pamoate to resist enzymatic degradation of natural active ingredients by faster growing cancer cells. The application of pheylacetylglutamine is also recommended to antagonize TNF, which can be administrated independently as a capsule preparation and monitored independently through quantitative assay of plasma and urinary peptides [15]. The therapeutic endpoint of phenylacetylglutamine can be the recovery of CDA to reach the healthy level of 5.0 of the Table 1. The therapeutic endpoint of CVDs can be set at blood pressure of normal value. The therapeutic endpoint of cancer can be the drop of carcino-embryonic antigens to reach the normal levels.

3. Conclusion

CVDs are the top killers and cancer is the next top killer of humans in the USA and around the world. These diseases become top killers are an indication that therapies currently available based on the elimination of symptoms are ineffective. These diseases obviously evolve due to wound unhealing. Perfection of wound healing is a therapy based on the elimination of the cause of diseases, which is a better approach for the therapy of CVDs and cancer. CDA formulations are preparations aimed to eliminate the cause of CVDs and cancer to remove these diseases as the top killers of humans.

Consent and Ethical Approval

It is not applicable.

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Competing Interests

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