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RESEARCH ARTICLE

Negligence on Unhealed Wounds is a Grave Mistake of Health Profession

Ming C. Liau , Christine L. Craig , Linda L. Baker

CDA Therapeutics, Inc., 3308 Sky Run Court, Missouri City, TX 77459, USA.

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Corresponding Author: Ming C. Liau, CDA Therapeutics, Inc., 3308 Sky Run Court, Missouri City, TX 77459, USA.

Abstract

Wound healing comes naturally. The issue of wound unhealing is often neglected. Health profession is unable to handle diseases evolving due to wound unhealing. Western medicine tends to develop drugs to target on the symptoms of diseases to achieve faster therapeutic effects. But diseases evolving due to wound unhealing can only be cured by targeting on unhealed wounds. Targeting on the elimination of symptoms is incorrect or ineffective for the therapy of diseases evolving due to wound unhealing. Diseases evolving due to wound unhealing become the persisting killers of humans that include cancer, cardiovascular diseases (CVDs) and organ failures to contribute to major mortalities. The objective of this article is to urge health profession to pay attention to unhealed wounds in the handling of diseases evolving due to wound unhealing.

Cancer evolving due to wound unhealing was a valid concept introduced by Virchow in 1858. We pursued cancer therapy unknowingly to follow his guidance to discover abnormal methylation enzymes (MEs), chemo-surveillance and the mechanism of wound healing. Thus, we in essence independently produced experimental data to support the validity of his concept. The nature creates chemo-surveillance, which is a mechanism of wound healing mediated through wound healing metabolites produced by the body, to ensure perfection of wound healing. Wound healing requires the proliferation and the terminal differentiation (TD) of progenitor stem cells (PSCs). Chemo-surveillance is selectively destroyed in cancer patients. Evidently, the destruction of chemo-surveillance is the reason to result in PSCs unable to undergo TD to heal the wound. Wound unhealing can produce fatal symptoms to end in fatality or non-fatal symptoms to end in the evolution of PSCs to become cancer stem cells (CSCs), and then the progression of CSCs through chromosomal abnormalities to become faster growing cancer cells (CCs). Diseases evolving due to wound unhealing can only be cured by the perfection of unhealed wounds. The solution of cancer requires the induction of TD of PSCs, CSCs and CCs and the solution of CVDs requires the induction of TD of PSCs. Elimination of CCs alone can only cure cancer in the early stage, relying on the restoration of chemo-surveillance to subdue surviving CSCs and PSCs. Chemo-surveillance is too far damaged in advanced cancer patients to restore to the functional state to benefit from cytotoxic chemotherapy or immunotherapy. Hypotensive drugs are ineffective to prevent the rupture of hardened blood vessels due to wound unhealing. Therefore, the ultimate solution of diseases evolving due to wound unhealing is the perfection of wound healing by the employment of CDA formulations. Residual tumor mass is harmless terminally differentiated cancer cells, which can be safely removed by surgery if it becomes a concern.

Keywords: Cancer, Cardiovascular Diseases, Chemo-Surveillance, Wound Healing.

1. Introduction

Cancer and CVDs are top killing diseases in most countries. Solution of top killing diseases is a national priority to most countries, particularly cancer which is a feared disease because cytotoxic cancer therapy is so excruciating and the death from cancer is very

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painful. Cancer is a disease that must be eradicated at all cost. President Nixon was an exceptional president to display passionate concern of the welfare of ordinary people to declare War on Cancer in 1971. War on Cancer was a presidential project. A presidential project is to deal on a monumentally important national issue which can receive unlimited support from national resources to ensure success, but has a time limit of 5 years. There were two precedents, the Manhattan Project under President Roosevelt and the Moonshot Project under President Kennedy. Both projects required very difficult technologies. Nuclear physicists successfully achieved the Manhattan Project and rocket engineers successfully achieved the Moonshot Project. Health profession failed to win the War on Cancer using up half a century which did not required difficult technologies [1]. The failure to achieve the presidential project is a very shameful record of health profession. Cancer is actually a disease not difficult to cure if the solution is right. The health profession had a very talented fellow, the German pathologist R. Virchow, who has advised a right solution of cancer in 1858 [2]. Virchow introduced an excellent concept of cancer evolving due to wound unhealing. Therefore, the right solution of cancer is to pursue perfection of wound healing [3-9]. Virchow's advice was too ancient to remain in the memory of recent authorities. His excellent concept was brought up again by Dvorak in 1986 in a very popular medical journal that ought to catch the attention of recent authorities [10]. Recent cancer authorities were unswayed to stay on their failed approach of cancer therapies to focus on the creation of wounds to eliminate CCs. Thus, cancer mortality stays on the trend to escalate [11]. So far, cancer establishments have failed to win the war on cancer during 1971-1976, failed to develop gene therapy during 1976-1996, failed to develop anti-angiogenesis therapy during 1996-2016, and also is not successful to develop immunotherapy during 2016-2036, because the cancer mortality keeps on escalating during the past 10 years [12].

Antineoplastons were preparations of wound healing metabolites Burzynski purified from urine by means of reverse phase chromatography employing a system of C18 and 80% methanol [13, 14]. Antineoplastons were used by Burzynski to treat cancer patients during 1976-1990 to produce impressive therapeutic effects that attracted 20/20 national broadcasting coverage. The success alerted cancer establishments to block the use of Antineoplastons purified from urine for cancer therapy. Cancer establishments were not only unable to provide effective solutions, but also to block effective cancer drugs which they did not like. They only liked cancer drugs that could kill CCs to cause the tumor to disappear which were incorrect cancer drugs [16]. Liau was convinced that Antineoplastons were excellent cancer drugs. He went to China in 1993 to develop cell differentiation agent-2 (CDA-2) which was also a preparation of wound healing metabolites purified from urine by means of reverse phase chromatography employing a system of XAD-16 and ethanol [16]. Chemical compositions of Antineoplaston A5 and CDA-2 are not exactly the same, but both preparations have comparable activities to induce TD of HL-60 cancer cells. CDA-2 was approved by the Chinese FDA for cancer therapy as an adjuvant drug to improve cytotoxic chemotherapy and as a mono-therapeutic drug for the therapy of myelodysplastic syndromes (MDSs). MDSs are diseases attributable entirely to the propagation of CSCs [17]. So, wound healing metabolites are excellent cancer drugs effective against CSCs and CCs. Unfortunately, these excellent cancer drugs were blocked by cancer establishments. A drastic change of cancer leaderships is necessary to save cancer patients [18, 19]. The blockade of excellent cancer drugs such as Antineoplastons and CDA-2 is a political issue that can only be resolved by government officials with authorities above health establishments.

2.Negligence on Unhealed Wounds is a Grave Mistake of Health Profession and Discussion

2.1 Negligence on Unhealed Wound is a Grave Mistake of Health Profession

Wound healing comes naturally. It is a very simple matter unable to attract attention. Thus, wound unhealing is often neglected. That is a grave mistake, because if wound is not healed, it can lead to disastrous consequences. Wound healing is actually a very important medical 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. Therefore, chemo-surveillance and immuno-surveillance can act synergistically to prevent diseases to evolve due to wound unhealing. Wound healing requires the proliferation and the TD of PSCs which are the most primitive stem cells to initiate the development of organs or tissues during embryonic stage of fetal

development [20]. Wound healing is actually an extension of the embryonic program of organ or tissue development. Wound can trigger biological and immunological responses [20, 21]. The biological response involves the release of arachidonic acid (AA) from membrane bound phosphatidylinositol through phospholipase A2 for the synthesis of prostaglandins (PGs) by cyclooxygenase and PG synthase [21, 22]. Although AA and PGs are active differentiation inducers (DIs) [23], 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 [24] is responsible for the increase of membrane permeability to facilitate the extravasation of plasma proteins and regulatory factors in the wound area to result in edema response to orchestrate the wound healing process. Chemo-surveillance mediated through DIs and differentiation helper inducers (DHIs) normally functions as a brake to prevent the buildup of PSCs [25]. This brake must be released for the proliferation of PSCs to produce enough PSCs to heal the wound. PGs are metabolically unstable [22]. 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 PDs, whereas the induction of TD of PSCs at the final stage of wound healing is accomplished by DIs and DHIs of chemo-surveillance. The stable end products of PGs are also active as DIs, although not as active as PGs [23]. DHIs can boost the relative inactive end products of PGs. The immunological response of wound involves infiltrations of leukocytes that tend to pile up in the wound area to create plugs to increase blood pressure if the wound in taking place in the blood vessels. The immunological response also triggers production of cytokines which are bad for wound healing. TNF among cytokines produced is particularly damaging to chemo-surveillance. 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 caused by TNF [26, 27]. Wound healing metabolites are among low molecular weight metabolites excreted resulting in the collapse of chemo-surveillance to affect wound healing. TNF is a known oncoprotein. The contribution of TNF to the collapse of chemo-surveillance is the reason to account for TNF as an oncoprotein. Therefore, immunological response of wound is antagonistic to biological response. It is the balance of biological response and immunological response to dictate the outcome of wound healing. If biological response prevails, the wound is healed. But if immunological response prevails, the wound cannot be healed to produce clinical symptoms of wound unhealing. If clinical symptoms of wound unhealing are fatal like the white lung of COVID-19 infection, heart attack or stroke of CVDs, the fatality is the end point. But if clinical symptoms of wound unhealing are not fatal like the symptoms created by carcinogens, there is a good possibility that PSCs will be forced to evolve to become CSCs. Wound unhealing in most instances is caused by the destruction of chemo-surveillance. Chemo-surveillance is executed by metabolites active as DIs and DHIs. DIs are metabolites capable of eliminating telomerase from abnormal MEs [28-30] and DHIs are inhibitors of MEs capable of potentiating the activity of DIs [31-33]. DIs and DHIs are always produced at the maximum capacity. The production of TNF contributes to the destruction of chemo-surveillance as above described. Antineoplaston A10, namely phenylacetylglutamine, can effectively antagonize the effect of TNF to cause the damage to chemo-surveillance [25]. By the protection of the function of chemo-surveillance, Antineoplaston A10 was shown effective to prevent hepatocarcinogenesis induced by potent hepatocarcinogen aflatoxin B_1 as shown in Fig. 1, which is reproduced from the reference [34].

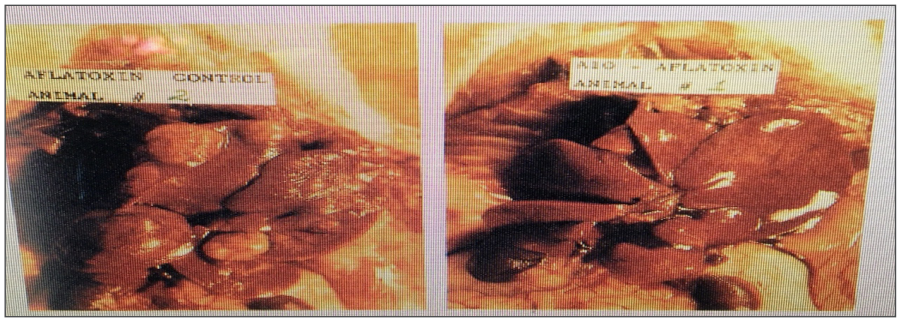

Figure 1. *Effective Prevention of Hepatocarcinogenesis by Antineoplaston A10*

Figure on the left is the control liver treated with aflatoxin B1 alone and figure on the right is the liver treated with aflatoxin B1 followed by Antineoplaston A10

Phenylacetylglutamine is a major metabolite in the plasma and urine. It is a major chemical component of Antineoplastons and CDA-2 purified from urine. Phenylacetylglutamine is biologically inactive chemical. It is remarkable that by antagonizing TNF to protect chemo-surveillance, this inactive chemical could prevent cancer induced by a potent carcinogen aflatoxin B_1. Drugs that can prevent cancer from taking place are considered the best cancer drugs by oriental and western medicines [35, 36]. Drugs effective against oncoprotein TNF are particularly relevant to the therapies based on the perfection of wound healing. Since DIs and DHIs are always produced at the maximum capacity, there is no mechanism to replenish the lost DIs and DHIs due to excessive excretion caused by TNF. The pressure is building up to force the proliferation of PSCs. The extent of 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 ten-eleven translocator-1 (TET-1) to convert PSCs to become CSCs [37, 38], that is an easy task for PSCs to accomplish since these cells are equipped with abnormally active MEs. So, CSCs are PSCs without TET-1 enzyme. The cell feature, antigenicity and cell mission of CSCs are the same as those of PSCs. The only difference between CSCs and PSCs are the growth of PSCs is limited by contact inhibition which does not affect the growth of CSCs. The escape of contact inhibition to proliferate by CSCs still cannot heal the wound, because the problem is the collapse of chemo-surveillance. Then the pressure is building up to force the progression of CSCs through chromosomal translocations to activate oncogenes or deletions to inactivate suppressor genes to become full blown CCs with much faster capability to proliferate. So, wound unhealing is the cause and the proliferation of CCs is the symptom of cancer and wound unhealing is the cause and the buildup of the plug due to leukocyte infiltration to increase blood pressure is the symptom of CVDs. Virchow was extreme 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 establishments were extremely dumb unable to understand the logic of wound unhealing to the evolution of cancer at a time both cancer and wound healing became known completely to continue on the failed approach of cancer therapy. Perfection of wound healing is the key to the solution of diseases evolving due to wound unhealing [4-9]. Negligence on unhealed wounds is really a grave mistake of health profession.

2.2 Perfection of Wound Healing as the Only Option to Cure Diseases Evolving due to Wound Unhealing

On the solution of cancer, there are three different approaches: a preventive approach to develop drugs to prevent cancer from taking place, which both oriental medicine and western medicine agree; a cause oriented approach to develop drugs to target on the cause which is favored by the oriental medicine; and a symptom oriented approach to develop drugs to target on the symptom which is favored by the western medicine [36]. There are no disputes on the preventive approach such as the use of phenylacetylglutamine to antagonize oncoprotein TNF or the use of vaccination against infectious agents that cause cancer. There are disputes whether to target on the cause or symptom to solve diseases. Proliferation of CCs is the most outstanding symptom of cancer. Cancer therapies developed by western medicine are mostly based on the elimination of CCs that include cytotoxic chemotherapy that has been in practice since cancer became known up to now which can only benefit roughly 25% of cancer patients in the early stage that include stage I and II patients without metastasis, CDA levels from 2.5 to 5.0 [25], Gleason scores of prostate cancer below 7, and CSCs count below 1% [39]. The success of cancer therapy on early stage cancer patients is not entirely the credit of cytotoxic agents. The restoration of the function of chemo-surveillance plays a decisive role to subdue surviving CSCs which are not responding to cytotoxic therapy [40-46]. Cytotoxic cancer therapies and immunotherapy kill 75% of advanced cancer patients with CDA levels below 2.5 [19]. CDA level of 2.5 is very likely the threshold level, above this level chemo-surveillance has a chance to restore to the functional state [47]. Below 2.5, chemo-surveillance is too far damaged to restore to the functional state. Cytotoxic cancer therapy tends to damage chemo-surveillance, which is a contributing factor to cause the failure of cytotoxic cancer therapy. Chemo-surveillance is a terminology we created to describe an observation that health people were able to maintain a steady level of metabolites active as DIs and DHIs, whereas cancer patients tended to show deficiency of DIs and DHIs as shown in Table 1, which is reproduced from the reference [25]. Table 1 is the quantitative data of plasma and urine peptides. Peptides are hydrophobic metabolites to share physical chemical properties similar to DIs and DHIs.

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

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

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

Thus, peptides can be used as surrogate molecules to represent DIs and DHIs. As a matter of fact, acidic peptides are major DIs of Antineoplaston preparations used by Burzynski to treat cancer patients. If patients responded well to Antineoplaston therapy, CDA levels would increase to approach the normal level of 5.0 [48]. If not, CDA levels would continue to decline. It is a reliable diagnosis on the evaluation of patients responding to Antineoplaston therapy.

Another important factor to cause the failure of cytotoxic cancer therapy is the ineffectiveness of cytotoxic agents against CSCs [40-46]. The responding margin of cytotoxic agents is very narrow. According to Thon et al. [39], CSCs counts of malignant astrocytoma are all below 1% which are responding well to cytotoxic cancer therapy. CSCs counts of malignant glioma are all above 3% which are not responding to cytotoxic cancer therapy. This is why cytotoxic cancer therapy kills so many cancer patients. It kills CCs to promote the proliferation of CSCs to repair the wound it created. Pretty soon, the CSCs counts will increase to the level above 3% to become unresponsive to cytotoxic cancer therapy [3]. The killing of CCs is a bad choice, particularly the use of drugs that modify the structure of DNA, which should be suspended when the war on cancer failed to achieve its goal in 1976. Cancer establishments kept using failed cytotoxic drugs to kill cancer patients that was very inappropriate. Cytotoxic cancer therapy was a bad choice, resulting in the creation of huge mortality, 0.61 million annually in the USA and 10 million annually around the world [11].

The emergence of CSCs is critically linked to wound unhealing. Induction of TD is the only option for the solution of CSCs [49-52]. Of course, cancer establishments knew solution of CSCs was very important to the success of cancer therapy. Approximately 19 years ago, the pharmaceutical giant GSK put up 1.4 billion to develop monoclonal antibodies against CSCs invented by the scientists of Stanford University, which was unsuccessful, because the killing of CSCs was not an option. The cancer establishments kept doing the wrong approaches to solve cancer. MDSs offer a unique model for the development of drugs against CSCs. MDSs are diseases attributable entirely to the propagation of CSCs [17], which are ideal for the development of drugs against CSCs. MDSs often start with a display of immunological disorder [53], which prompts the production of inflammatory cytokines. Among cytokines produced, TNF is the critical factor related to the development of MDSs [54]. 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 wound unhealing to force the evolution of PSCs to become CSCs. MDSs are at the stage of establishing CSCs. Further progression of chromosomal abnormalities will lead to acute myeloid leukemia. Solution of MDSs requires the TD of PSCs and CSCs to produce functional erythrocytes, platelets or neutrophils. Therefore, inactivation of methyltransferase (MT) is the only option for the therapy of MDSs. Inactivation of MT to achieve induction of TD of PSCs and CSCs can be accomplished by CDA-2, which is a preparation of wound healing metabolites we produced [16], or by Vidaza and Decitabine to trap MT [55]. CDA-2 is specific to target the tumor factor telomerase of abnormal MEs, whereas Vidaza and Decitabine are non-specific drugs which can also affect normal unipotent stem cells (UPSCs). Professor Jun Ma, the Director of Harbin Institute of Hematology and Oncology, was instrumental in conducting clinical trials of all three MDSs 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 Professor Ma' assessments based on two cycles of treatment protocols each 14 days, CDA-2 had a noticeable better therapeutic efficacy

based on cytological evaluation, although slower to reach complete remission and a markedly better hematological improvement therapeutic efficacy, namely becoming independent on blood transfusion to stay healthy, as shown in Fig. 2, which is reproduced from the reference [56].

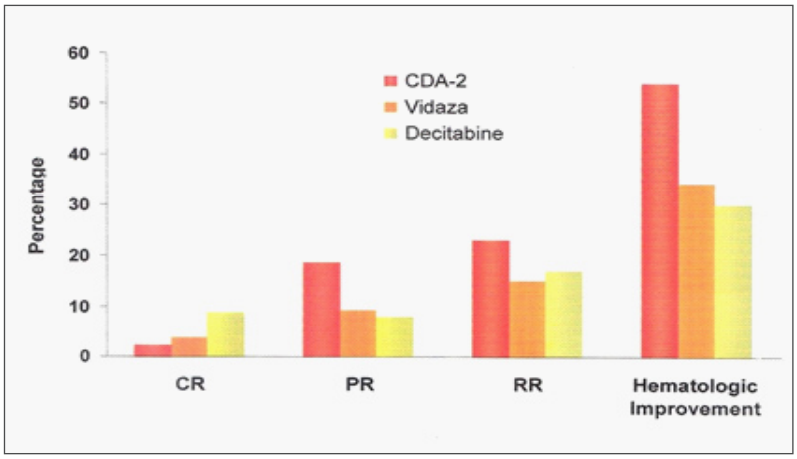

Figure 2. *CDA-2 as the Best Drug for the Therapy of MDSs*

Fig. 2 is a very impressive clinical datum produced by Professor Ma to support the validity of the concept of cancer evolving due to wound unhealing and the perfection of wound healing as the best drug for the solution of CSCs. Obviously, CDA-2 is the best drug for the therapy of CSCs with superior therapeutic efficacy and without adverse effects. Vidaza and Decitabine are not as good on the therapeutic efficacy but also to produce adverse effects as carcinogen [57, 58] and very toxic to DNA, particularly the cardiac cell DNA [59-61]. CDA-2 is apparently the drug of choice for the therapy of CSCs. We have predicted that the winner of the contest to eradicate CSCs won the contest of cancer therapies [62]. We were the clear winner. But our winner's status was denied by the cancer establishments who put up a rule of tumor shrinkage as a requirement of cancer drugs which was wrong [63]. Cancer establishments used an erroneous rule to deny our great contribution on the solution of CSCs that was a blatant violation of justice. They knew the solution of CSCs was extremely important to put up 1.4 billion to develop monoclonal antibodies unsuccessfully as the drugs for the therapy of CSCs. CDA-2 is obviously the best drug for the therapy of CSCs. They killed the drug worth more than 1.4 billion, that essentially blocked the solution of cancer.

Cancer is a disease evolving due to wound unhealing. Drugs to target on the unhealed wound by inactivation of abnormal MEs to induce TD of PSCs and CSCs are the only option to solve wound unhealing. The solution of CSCs is a critical requirement for the success of cancer therapy. Therefore, healing of unhealed wound is an essential requirement for the success of cancer therapy. Proliferation of CCs is caused by wound unhealing, but is not critically linked to unhealed wounds as CSCs. CCs can be removed by killing or induction of TD. Killing is incorrect [15], because it promotes the proliferation of CSCs to increase the content of CSCs in the tumor to become unresponsive to cytotoxic cancer therapy [3, 39]. That makes healing the unhealed wounds as the only option for the success of cancer therapy [4-9, 12, 35, 36, 47, 49-51, 62]. Thus, drugs targeting on the elimination of CCs, namely the symptom of the disease, are poor choices. CVDs are also caused by wound unhealing to display large pool size of homocysteine related to the metabolic activity of cells expressing abnormal MEs [64]. The buildup of PSCs which express abnormal MEs at the unhealed vessels is responsible for the display of large pool size of homocysteine. The buildup of PSCs cause blood vessels to become hardened, which also trigger the infiltration of leukocytes and the deposit of low density lipoproteins to form plugs at the site of unhealed wounds to cause the blood pressure to increase. The hardening of the blood vessels to lose elasticity due to wound unhealing is the reason blood vessels becoming easy to burst. Therapy targeting on the unhealed wounds by the induction of TD of PSCs with Vital Reds introduced by the famed cardiologist Steven Gundry is the most intelligent solution of CVDs [65]. Vital Reds are polyphenols, which are excellent DHIs as signal transduction inhibitors and MT inhibitors [4- 9]. Obviously, perfection of wound healing is the most intelligent solution of CVDs. But hypotensive drugs are the choice of cardiovascular establishments to stir up CVDs as the top killer of humans. Negligence on unhealed wounds is the mistake of cardiovascular establishments resulting in the failure to solve CVDs [8, 9]. CVDs kill 0.92

million in the USA and 20.5 million around the world annually, which are much higher than cancer mortalities.

Wound unhealing in most instances is due to the collapse of chemo-surveillance caused by the pathological production of TNF. CDA formulations are the right solution for the diseases due to the collapse of chemo-surveillance such as cancer and CVDs. But wound unhealing can also be caused by too much wound healing metabolites that cause premature induction of TD of PSCs.. Maternal wound healing metabolites can affect the development of the fetus. Obviously, placenta serves as a barrier to block the entry of maternal wound healing metabolites into the fetal blood circulation to interfere with fetal development. Maternal wound healing metabolites are hydrophobic that can be excluded by placenta. Thalidomide can also interfere with the function of fetal MEs, which is hydrophilic allowing to pass through placenta. Thalidomide can cause malformation of body part due to the premature induction of TD of stem cells, noticeably limbs. Malformation of limbs is non-lethal. Baby can survive. But malformation can also happen to the vital organs such as heart and brain to cause still birth. Kidney failure is caused by the damage of glomerulus to destroy the function of filtration. Wound healing metabolites are also retained in the body to cause premature TD of PSCs in the process of healing glomerulus. Inability to heal wound is the shortage of PSCs. Therefore, handling of kidney failure must be done differently by boosting the supply of renal PSCs instead of CDA formulations. Likewise, healing of damaged brain cells may encounter the same problem as kidney failure due to too many wound healing metabolites to cause premature TD of PSCs to fail the healing of wounds. Wound healing metabolites are hydrophobic metabolites which tend to accumulate in the brain compartment. So, brain compartment is enriched in wound healing metabolites to cause premature TD of PSCs in the process of wound healing. In the handling of dementia and Alzheimer's diseases, boosting the supply of neurological PSCs may be a more appropriate approach. Malignant brain tumors are either astrocytoma with very low CSCs count or glioma with very high CSCs count [39]. Brain compartment is also enriched in growth hormone which is produced in the pituitary gland located in the brain compartment that can promote the growth of benign tumor and astrocytoma with very low CSCs count. Malignant brain tumors must have unusual high CSCs to prevail in the environment enriched in wound healing metabolites. That is why most malignant brain tumors have unusual high CSCs count.

2.3 Abnormal MEs as the Central Issue of Wound Unhealing

Wound unhealing is caused by the inability to induce TD of PSCs due to the collapse of chemo-surveillance or the premature induction of TD of PSCs due to too much wound healing metabolites [20]. MEs in cells expressing telomerase are abnormal due to association with telomerase [30]. MEs are a ternary enzyme complex consisting methionine adenosyl-transferase (MAT)-MT-S-adenosylhomocysteine hydrolase (SAHH), which play a pivotal role on the regulation of cell replication and differentiation [66]. Because of this important role, MEs are exceptionally under double allosteric regulations [67]. Enzymes involved in important biological regulation are subjected to delicate regulation. Allosteric regulation is a pervasive biological regulation. Single regulation is very common. Double regulations are exceptional. In cells without expression of telomerase, MEs are allosterically regulated by steroid hormone or related factors. SAHH is the receptor of steroid hormone. In cells expressing telomerase, MEs are additionally regulated by telomerase. The association of MEs with telomerase change the kinetic properties of MAT-SAHH and the regulation greatly in favor of promoting 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. The higher K_m values suggest that abnormal MEs are far more stable since the study of Prudova et al. indicated that association with S-adenosylmethionine (AdoMet) could protect protein against protease digestion [68]. The higher K_m values also suggest that cells expressing abnormal MEs have larger pool sizes of AdoMet, S-adenosylhomo-cysteine (AdoHcy) and homocysteine (Hcy) 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 [69]. Therefore, larger pool sizes are needed to support the growth of cells expressing abnormal MEs. SAHH is the enzyme to carry out reversible reaction. Larger pool size of AdoHcy also mean larger pool size of Hcy which is a risk factor of CVDs. Obviously, the metabolical activity of cells with abnormal MEs is the cause of CVDs [64]. Thus, abnormal MEs are critically related to the issue of wound unhealing. Health profession in the USA was unable to handle the issue of wound unhealing, because the only scientists, Ming C. Liau and Robert B. Hurlbert of MD Anderson Cancer

Center, able to handle the issue of wound unhealing were destroyed by the American Cancer Society. We were actively involved in the study of MEs since 1968 inspired by the aggressive studies of aberrant tRNA methylation at that time. Cancer establishments were able to identify the important issues of cancer. They identified aberrant tRNA methylation around 1966 and aberrant DNA methylation around 1985 as very important issues of cancer, and launched aggressive studies. Most studies were focused on methylated tRNA and DNA. We were the small minority to focus on the studies of MEs. Our studies included rRNA MEs to get involved in the disputes on the arrangement of 18S and 28S rRNA in the 45S precursor molecule. The President of American Cancer Society assigned 28S rRNA at the 5'-end. But there were reports to assign 18S rRNA at the 5'-end. We had a plan that could resolve the controversy. Methylated dinucleotide profiles of 18S and 28S rRNA were distinctly different. Methylation of rRNA took place right after the nascent chain was generated. Thus, the analysis of methylated dinucleotide profiles of shorter nascent rRNA and longer nascent rRNA could resolve the controversy. We labeled nascent rRNA chains by incubation of isolated nucleoli in RNA synthesizing medium with H^3-methyl-AdoMet, and analyzed H^3-methyl-dinucleotide profiles of shorter and longer nascent rRNA chains to compare with the dinucleotide profiles of 18S and 28S. Our experimental results clearly showed 18S rRNA at the 5'-end to contradict the assignment of the President of the American Cancer Society [70]. The American Cancer Society was not happy and terminated the grant to Professor Hurlbert which supported our study. The grant to Professor Hulbert was a lifetime grant to award his contribution on the establishment of pyrimidine pathway. Without support, Professor Hulbert was forced to retire early and his associated Liau was dismissed from MD Anderson Cancer Center. American Cancer Society punished scientists for doing the right thing to correct the mistake of the President of American Cancer Society. That was a blatant violation of justice. Blatant violation of justice took place frequently in authoritarian organizations. On June 4, 1989, the Chinese communist regime sent tanks to kill unarmed college students gathering at Tienanmen Square of Beijing to demand democracy. That was also a display of blatant violation of justice to punish the right action. It happened that we were the only scientists to explore abnormal MEs which were critically related to the issues of wound unhealing and CSCs. The American Cancer Society destroyed the careers of Hurlbert and Liau who were the only scientists able to solve the issues of wound unhealing and CSCs. The American Cancer Society also destroyed its mission to win the war on cancer, because the solution of cancer required the solution of PSCs and CSCs which could only be accomplished by CDA formulations [7-9, 12, 16, 23, 31-33, 35, 36, 49-52, 56].

3. Conclusion

Wound unhealing is often neglected by health profession, which is a grave mistake. Diseases evolving due to wound unhealing can only by cured by the healing of unhealed wounds. Health profession is trapped in pursuing the elimination of symptoms to cure diseases which are either incorrect for the therapy of cancer or ineffective for the therapy of CVDs. Wound healing is a simple matter that can be easily accomplished with CDA formulations. Health profession ought to switch to healing the unhealed wounds to solve long unsolved diseases evolving due to wound unhealing.

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Competing Interests

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