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RESEARCH ARTICLE

Perfection of Wound Healing to the Rescue of Patients Struggling Against Fatal Diseases Evolving Due to Wound Unhealing

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Abstract

The object of this article is to correct the mistakes of health authorities on fatal diseases evolving due to wound unhealing. Health profession is an authoritarian profession. Policies are made by the top authorities for the profession to follow. Intelligent authorities can make good policies to enhance the reputation of health profession and to benefit patients. But inept authorities can make bad policies to damage the reputation of health profession and to hurt patients. Cancer and cardiovascular diseases (CVDs) are the top killers of humans for a very long time. Authorities in charge of cancer and cardiovascular diseases are apparently incompetent to let these diseases to become top killers for so long.

Cancer is a disease evolving due to wound unhealing, which was a valid concept of cancer introduced by Virchow in 1858. We unknowingly pursued cancer therapy following the guidance of Virchow to discover abnormal methylation enzymes (MEs), chemo-surveillance and the mechanism of wound healing to support the valid concept of cancer evolving due to wound unhealing. Obviously, perfection of wound healing is the only option for the solution of cancer correctly. Cancer authorities directed cancer therapies in opposition to the advice of Virchow by the employment of toxic agents to create wounds, thus, stirring up cancer as a giant killer. Cancer authorities are supposed to save cancer patients. But they function as the killers of advanced cancer patients instead. Cancer therapies based on the killing of cancer cells (CCs) can only benefit a small minority of cancer patients in the early stage. The survival of early stage cancer patients also critically depends on the restoration of chemo-surveillance to subdue surviving cancer stem cells (CSCs).

CVDs are also evolved due to wound unhealing. The damage to the inner lining of artery triggers the buildup of progenitor stem cells (PSCs) to heal the wound. Inability of PSCs to undergo terminal differentiation (TD) to heal the wound triggers the secondary responses of leukocyte infiltration and the deposit of light density lipoprotein to display the symptom of hypertension. CVDs authorities employ medications to reduce hypertension, which are not very effective to result in CVDs as the top killer of humans. Perfection of wound healing to remove the primary cause of wound unhealing is a more effective approach to the solution of CVDs.

Wound unhealing is the primary cause of fatal diseases such as the white lung of COVID-19 infection, liver cirrhosis, dementia and organ failures. Perfection of wound healing is the best approach for the solution of fatal diseases evolving due to wound unhealing.

Keywords: Cancer, CVDs, Health Profession, Wound Healing.

1. Introduction

Wound healing comes naturally. It is a very simple matter to attract attention. But if wound is not healed, it can lead to fatal diseases such as cancer and CVDs which are the top killers of humans, claiming 10 million cancer deaths and 20.5 million CVDs deat hs annually around the world [1]. The mortalities of cancer and CVDs keep on escalating ever

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since these diseases become known. Obviously, these diseases are not handled right by the health authorities to result in escalating mortalities. Health profession is an authoritarian profession very much like communist regimes. Policies are made by the big bosses for the profession to follow. If the big bosses are intelligent, they can make good policies such as vaccines and antibiotics to enhance the reputation of health profession and to benefit patients. But if the big bosses are inept, they can make bad policies such as toxic cancer drugs to damage the reputation of health profession and to hurt patients. Authorities of cancer and CVDs are inept bosses. 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 use toxic chemicals to treat leukemia patients. Indeed, toxic chemicals are very effective to eliminate leukemia cells. Perpetual proliferation of CCs is the most outstanding symptom of cancer. Toxic chemicals are very effective to eliminate CCs. Thus, cytotoxic chemotherapy became a standard care of cancer and the reduction of tumor became a standard diagnosis of the efficacy of the therapy of solid tumors. Both were wrong [2, 3]. Cancer evolving due to wound unhealing was a valid concept of cancer introduced by Virchow in 1858 [4]. Creation of wounds is a clear violation of his advice. His advice may be too ancient to remain in the memory of recent authorities. Virchow's concept of cancer evolving due to wound unhealing was brought up again by Dvorak in 1986 in the top medical journal that ought to catch the attention of recent authorities [5]. Obviously, the recent authorities preferred their wrong approach to block the correct cancer therapy [6] to result in ever escalation of cancer mortalities. Cancer authorities become the most difficult issue of cancer. Authorities of CVDs are not great either to insist on therapies to reduce hypertension not very effective for the therapy of CVDs, resulting in CVDs as the top killers of humans. It is necessary to drastically change the inept authorities of health profession to save patients evolving due to wound unhealing [7]. Perfection of wound healing is the most intelligent policy to put out fatal diseases evolving due to wound unhealing.

2. Perfection of Wound Healing to the Rescue of Patients Struggling against Fatal Diseases Evolving due to Wound Unhealing and Discussion

2.1 The Logic of Wound Unhealing to the Evolution of Fatal Diseases

Virchow was extremely talented to comprehend the logic of wound unhealing to the evolution of cancer at a time neither cancer nor wound healing was completely known [4]. He did not produce experimental data to convince people of his outstanding concept. We unknowingly pursued cancer therapy following his guidance. During our studies of hepatocarcinogenesis, we noticed the appearance of numerous tiny hyperplastic nodules displaying abnormal MEs we discovered earlier [8], which must represent the active healing of wounds created by hepato-carcinogens. Most of these tiny hyperplastic nodules disappeared shortly afterward, indicating the completion of wound healing. Only a few large size carcinomas appeared later from unhealed tiny nodules [9]. If Antineoplaston A10, namely phenylacetylglutamine, was given to the animals after the administration of hepatocarcinogen aflatoxin B_1, the appearance of carcinomas could be completely prevented as shown in Figure 1, which is reproduced from the reference [10].

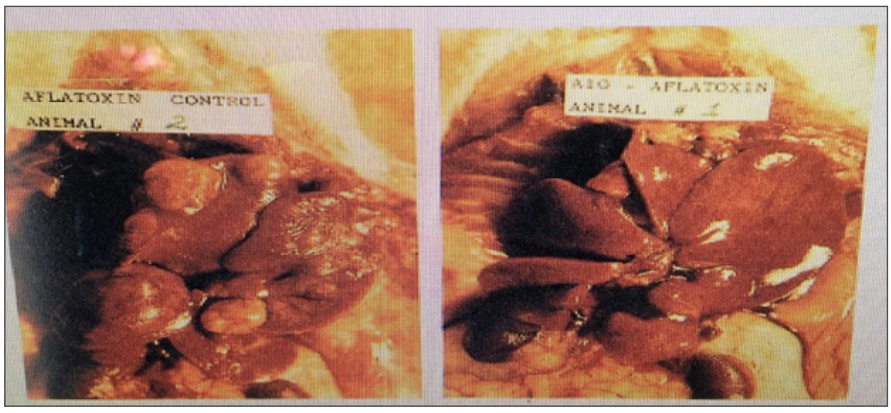

Figure 1. *Effective Prevention of Hepatocarcinogenesis by Antineoplaston A10.*

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

Antineoplaston A10 is biologically inactive chemical. But it can effectively antagonize tumor necrosis factor (TNF) to prevent the loss of wound healing metabolites [11]. By keeping the functionality of chemo-surveillance intact for the perfection of wound healing, Antineoplaston A10 could effectively prevent carcinogenesis induced by potent carcinogen. This is a very convincing experimental datum to support the validity of Virchow's concept of cancer evolving due to wound unhealing. Our studies of chemo-surveillance provide another experimental datum to support the validity of Virchow's concept of cancer evolving due to wound unhealing. Chemo-surveillance was a terminology we created to describe the 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 [11]. DIs are metabolites capable of eliminating telomerase from abnormal MEs, and DHIs are inhibitors of MEs capable of greatly potentiating the activity of DIs. Obviously wound healing is an important health issue, so that the nature creates chemo-surveillance to ensure perfection of wound healing to avoid disastrous consequences of wound unhealing such as the evolution of cancer or CVDs.

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*

Wound healing requires the proliferation and the terminal differentiation (TD) of PSCs [12]. PSCs are the most primitive stem cells to initiate the development of organ or tissue during embryonic stage of fetal development. A small percentage of these cells, usually less than 2% of the organ or tissue mass, are preserved in the organ or tissue for future expansion or repair. PSCs express telomerase. MEs of cells expressing telomerase are abnormal due to association with telomerase, which changes the kinetic properties of MEs and the regulatory role of MEs greatly in favor of promoting cell growth. The exceptional growth promoted by abnormal MEs is needed for the development of fetus and the healing of wound. The operation of abnormal MEs in the development of fetus and the healing of wound is well guarded by safety mechanisms such as contact inhibition, ten-eleven translocator-1 (TET-1) enzyme and chemo-surveillance. If these safety mechanisms become dysfunctional, the operation of abnormal MEs becomes problematic to display clinical symptoms as shown in Table 1. Table 1 shows quantitative analyses of plasma and urinary peptides. Peptides share physical-chemical properties similar to DIs and DHIs. As a matter of fact, acidic peptides are the major DIs of Antineoplaston preparations purified from urine [13, 14]. Therefore, peptides can be used as surrogate molecules to represent DIs and DHIs. If the patients undergoing Antineoplaston therapy responded well, CDA levels would increase to restore to the level of healthy people [11, 15]. Not all cancer patients responded well to Antineoplaston therapy. Non-responders continued to show decline of CDA levels. CCs are known to express a high level of degradative enzymes to salvage substrates for the synthesis of macromolecules to support malignant growth. DIs and DHIs are natural metabolites which may be degraded in faster growing CCs to lose activity. The responders to Antineoplaston therapy were the majority. Cancer therapy by wound healing metabolites was initiated by Burzynski to demonstrate an excellent cancer therapy during 1976-1990. Unfortunately, this excellent cancer therapy was blocked by cancer authorities. Cancer authorities are the most difficult issue of cancer. They are unable to produce good cancer therapies. They also blocked the only option that could really put cancer away. They failed to win the War on Cancer during 1971-1976, to develop gene therapy during 1976-1996, to develop anti-angiogenesis therapy during 1996-2016, and very likely to develop immunotherapy during 2016-2036. Cancer is basically a problem of growth regulation going awry. Immunology has nothing to do with growth regulation. They must have run

out of choices to put the hope on immunotherapy. Immunotherapy is a better version of therapies based on killing of CCs to target on programmed death antigen. The discovery of programmed death antigen to mark the pathological cells for immunological elimination was a remarkable scientific achievement. Three scientists were awarded Nobel prizes in 2025. The excellent scientific achievements may not be translated into benefits to help patients, as the excellent scientific achievements of the discoveries of oncogenes and suppressor genes to receive Novel prizes did not yield drugs to benefit cancer patients. CSCs are PSCs without TET-1. The cell feature, antigenicity and cell mission of CSCs are exactly the same as those of PSCs. PSCs are tolerable to immune systems. CSCs are the most vicious pathological cells. Most fatal effects of cancer such as metastasis, drug resistance, anti-apoptosis, angiogenesis, unresponsiveness and recurrence are attributable to CSCs. But CSCs are not recognized as pathological cells by the natural immune systems. Ineffectiveness against CSCs and the contribution to damage chemo-surveillance are the reasons contributing to the failure of chemotherapy. Immunotherapy has the same problem as chemotherapy. Immunotherapy can spare adverse effects of chemotherapy, but cannot improve significantly mortality. It is half way through on the development of immunotherapy. The trend of mortality in the USA is still on the way to escalate. Perfection of wound healing is the only option to solve cancer to turn around cancer mortality from escalation to deceleration [16-20].

Evidently, CVDs are also caused due to wound unhealing. CVDs are caused by the damage to the artery's inner lining, which triggers the proliferation of PSCs in an attempt to heal the wound. Inability of PSCs to undergo TD triggers the secondary responses of the infiltration leukocytes and the deposit of light density lipoproteins to buildup the plague to display the symptom of hypertension. Aberrant DNA methylation displaying as global hypomethylation and regional hypermethylation is a hallmark of cancer, namely the cells with abnormal MEs [21-23]. Aberrant DNA methylation is implicated in the onset and progression of atherosclerosis, heart failure and cardiac arrythmia [24-26]. 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 metabolism of cells with abnormal MEs. Cells with abnormal MEs have larger pool sizes of S-adenosylmethionine (AdoMet) and S-adenosylhomocysteine(AdoHcy)[27],consequently higher level of homocysteine which is a risk factor of CVDs [26]. CpG of human atherosclerosis aortic samples were hypermethylated in many genomic loci versus non-atherosclerotic controls [24, 25] These are clear indication that the metabolism of PSCs during the process of wound healing plays important role on the pathological process of CVDs. Perfection of wound healing is a therapy based on the elimination of the cause of diseases, which is always superior than the therapy based on the elimination of symptom [28]. Cytotoxic cancer therapies and CVDs therapies are aimed to eliminate symptoms, which are not as effective as CDA formulations to eliminate causes of the diseases.

Diseases attributable to wound unhealing happen frequently. White lung of COVID-19 infection is a famous example, which is caused by the buildup of PSCs unable to undergo TD because of the collapse of chemo-surveillance during the initial phase of viral infection [29]. White lung is as fatal as heart attack. CDA formulations are the only drugs to the rescue of these fatal diseases. There is an urgent need for the development of CDA formulations. Liver cirrhosis is a symptom similar to the white lung of COVID-19 infection, which is caused by the infection of hepatitis B and C. Liver cirrhosis is not as acute as the white lung of COVID-19. But if untreated, liver cirrhosis can progress to become hepatoma. Dementia is potential a disease of wound unhealing. Neurological cells destroyed by toxic proteins beta-amyloid and tau trigger the wound healing process. Inability to complete wound healing may be the reason for dementia to progress to become fatal symptom of Alzheimer's disease. Inability to complete wound healing may be due to the insufficiency of stem cells or the collapse of chemo-surveillance. Kidney failure is clearly a disease of wound unhealing. But this case of wound unhealing is unique. Collapse of chemo-surveillance is a common cause of wound unhealing as shown in Table 1. Wound happens to kidney causes the buildup of wound healing metabolites to result in premature induction of TD of PSCs very much like the malformation of the body parts of the fetus caused by thalidomide. Inability to heal the wound of kidney failure is too much DIs and DHIs, exactly the opposite to other cases of wound unhealing. Growth factor such as erythropoietin or prostaglandis (PGs) to promote proliferation of PSCs is the right solution of kidney failure.

2.2 On the Mechanism of Wound Healing

Wound unhealing is a major killer of humans. We ought to pay more attention to wound healing process

to avoid wound unhealing. Wound healing requires the proliferation and the TD of PSCs [12]. Wound usually triggers biological and immunological responses. The biological response involves the release of arachidonic acid (AA) from membrane bound phosphatidyl-inositol through phospholipase A2 for the synthesis of PGs by cyclooxygenases and PG synthases [30, 31]. Although AA and PGs are active DIs [32, 33], 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 [30] 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 mediate through DIs and DHIs normally function 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 [30]. 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 [32].

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 produced 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. Acute wounds in general favor wound healing, whereas chronic wounds are most likely to result in wound unhealing. CDA formulations are the best solution of diseases evolving due to wound unhealing. kidney failure is an exception, which must be treated differently.

Wound unhealing can produce symptoms that are fatal or non-fatal. If it is a fatal symptom such as the white lung of COVID-19 infection or heart attack of CVDs, fatality is the end point. If it is non-fatal, there is a good possibility that unhealed wound will be forced to evolve into cancer. PSCs are at the center of wound healing. Wound unhealing in most instances is due the collapse of chemo-surveillance to fail the completion of TD of PSCs. Chemo-surveillance is always operating at the maximum capacity. There is no mechanism to replenish the collapsed chemo-surveillance. The body responds by forcing PSCs to proliferate. The proliferation of PSCs is limited by contact inhibition. PSCs are then forced to evolve into CSCs to escape contact inhibition. It takes a single hit to silence TET-1 enzyme to convert PSCs to become CSCs [34, 35]. This is a task very easy for CSCs to accomplish, since these cells are equipped with exceptionally active MEs [12]. The evolution of PSCs to become CSCs still cannot solve the problem of wound unhealing, because the problem is the collapse of chemo-surveillance, not the insufficiency of PSCs. The proliferation of CSCs still cannot solve the problem of wound unhealing. The slow proliferating CSCs are then forced to progress into faster growing CCs by chromosomal translocations to activate oncogenes or deletions to inactivate suppressor genes.

This is the valid concept of cancer evolution established by the alliance of Virchow and Liau et-al. [36]. It is essential to establish a valid concept of cancer to confront cancer successfully [18, 19]. Piecemeal solutions to eliminate symptoms get nowhere.

PSCs are at the center of wound healing issue. MEs of PSCs are abnormal, thus abnormal MEs are also at the center of wound healing issue. MEs are a ternary enzyme complex consisting of methionine adenosyltransferase (MAT)-methyltransferase (MT)-S-adenosylhomocysteine hydrolase (SAHH) [37]. MEs play a pivotal role on the regulation of cell growth, differentiation and apoptosis by virtue of the fact that these enzymes control the expression tissue specific genes [38] and the production of ribosome [39] which in turn dictates the cell to enter cell cycle [40]. If enhanced ribosome production is locked in place, it becomes a driving force to promote carcinogenesis [41]. Because of their important regulatory roles on cell replication and differentiation, these enzymes are subjected to exceptional double allosteric regulations [42], one on the individual enzymes and the other on the enzyme complex. On the individual enzymes, MEs are under the regulation of steroid hormone. SAHH is a steroid hormone receptor subjected to regulation by steroid hormone or related regulatory

factors. In cells expressing telomerase, MEs become associated with telomerase. The association with telomerase changes kinetic properties of MEs and the regulatory roles of MEs greatly in favor of promoting cell growth [43, 44]. K_m values of telomerase associated MAT^{LT}-$SAHH^{LT}$ isozyme pair are 7-fold higher than the normal MAT^{L}-$SAHH^{L}$ isozyme pair. The increased K_m values of abnormal MEs suggest that cells expressing telomerase produce larger pool sizes of AdoMet, AdoHcy and homocysteine which are important to promote exceptional growth of cells expressing telomerase. The study of Prudova et al. indicated that AdoMet could stabilize protein against protease digestion [45]. Therefore, MEs are far more stable in cells expressing telomerase. The study of Chiba et al. indicated when cancer cells were induced to undergo TD, the pool sizes of AdoMet and AdoHcy shranked greatly [27]. Thus, the expanded pool sizes of AdoMet, AdoHcy and homocysteine are important to promote the exception growth of cells expressing telomerase. It appears that the seed of diseases evolving due to wound unhealing 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, but secedes when pluripotent stem cells undergoing lineage transitions to reach unipotent stem cells. The function of abnormal MEs is required for the development of fetus. Attempt to disrupt the function of abnormal MEs is detrimental as demonstrated by the malformation of limbs caused by thalidomide. Wound healing is an extension of embryonic program involving PSCs, which also relies on the function of abnormal MEs. The normal functions of abnormal MEs are guarded by safety mechanisms of contact inhibition, TET-1 enzyme and chemo-surveillance. If these safety mechanisms become dysfunctional, the buildup of cells with abnormal MEs become problematic to display clinical symptoms to cause major medical problems. Perfection of wound healing can be easily accomplished to limit the damages of wound unhealing which are often fatal.

2.3 CDA Formulations as the Only Option to Achieve Perfection of Wound Healing

Myelodysplastic syndromes (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 cause the production of inflammatory cytokines [46]. TNF among cytokines produced is the critical factor related to the development of MDSs [47-49]. 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 result in the conversion of PSCs to become CSCs. The propagating pathological cells of MDSs have been identified as human CSCs [50]. So, MDSs are diseases attributable entirely to CSCs. CSCs are PSCs without 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 [51-57]. These cells express chemokine receptor to display a great ability to promote metastasis [58, 59]. Obviously, CSCs are the 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 to be marked with programmed death antigen for the elimination by the natural immune system. CSCs can be eliminated by artificially created monoclonal antibodies. Cancer establishments were aware the importance of the elimination of CSCs to the success of cancer therapy. Approximately 19 years ago, the pharmaceutical giant GSK put up an outrageous 1.4 billion, the most expensive investment on a cancer drug, to develop monoclonal antibodies invented by the scientists of Stanford University, which was apparently not successful because killing of CSCs was not an option to solve the issue of CSCs which are critically linked to wound unhealing. Induction of TD of CSCs is the only option to solve the issue of CSCs. Therefore, drugs that can inactivate abnormal MEs to induce TD of CSCs are the only drugs good for the therapy of MDSs. Vidaza, Decitabine and CDA-2 were the three drugs approved by the Chinese FDA for the therapy of MDSs. Vidaza and Decitabine were also approved by the US FDA for the therapy of MDSs. CDA-2 was a preparation of wound healing metabolites purified from urine we developed [60]. Professor Ma, Director of Harbin Institute of Hematology and Oncology, was instrumental in carrying out clinical trials of these three MDSs drugs in China. According to his assessments based on two cycles of treatment protocols, each l4 days, CDDA-2 had a noticeable better therapeutic efficacy based on cytological evaluation, although

slower to reach complete remission and a markedly better therapeutical efficacy based on hematological improvement evaluation, namely becoming independent of blood transfusion to stay healthy as shown in Figure 2, which is reproduced from the reference [61]. CDA-2 destabilize abnormal MEs by targeting on telomerase, the tumor factor of abnormal MEs [44, 60], whereas Vidaza and Decitabine inactivate MT by the formation of covalent bond between MT and DNA containing 5-azacytosine [62].

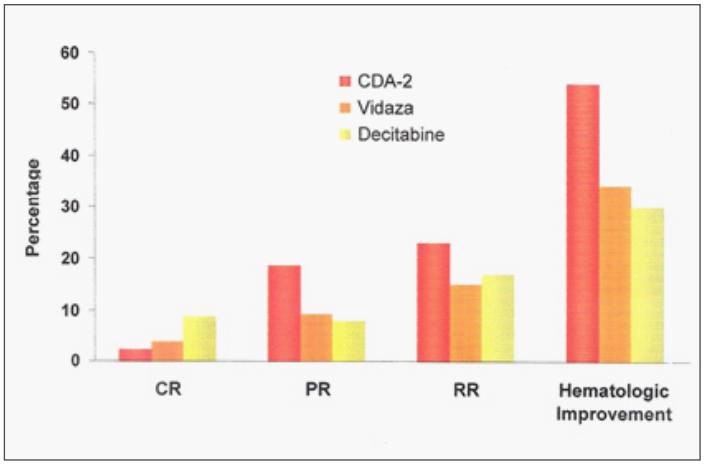

Figure 2. *CDA-2 as the Best Drug for the Therapy of MDSs.*

CDA-2 is devoid of adverse effects, whereas Vidaza and Decitabine are proven carcinogens [63, 64], and very toxic to DNA [65-67]. Apparently, CDA-2 is the drug of choice for the therapy of MDSs with superior therapeutic efficacy and without adverse effects. We have predicted that the winner of the contest to eradicate CSCs won the contest of cancer therapies [68]. Clearly, we are the winner to develop a superb cancer drug. Our winner's status was denied by the cancer establishments who put up a rule of tumor shrinkage as a condition of cancer drugs which was apparently wrong [3]. The same rule they put up to deny CDA formulations as cancer drugs also blocks their mission to win the war on cancer [6], since CDA formulations are the only option to solve the issue of CSCs [16]. Elimination of CSCs is essential to the success of cancer therapy [16, 18 , 69]. CDA formulations are effective drugs to the rescue of patients struggling against fatal diseases evolving due to wound unhealing.

2.4 Development of CDA Formulations to the Rescue of Patients Struggling against Fatal Diseases Evolving due to Wound Unhealing

We have carried out extensive studies of natural and ono-natural DIs and DHIs for the manufacture of CDA formulations [13, 14, 17, 19, 20, 29, 32, 33, 60, 70. 71]. Acrtive DIs and DHIs are presented in Table 2 and 3. $ED_{25,\ 50\ and\ 75}$ of DIs and reductive $index_{0.5}$ ($RI_{0.5}$) of DHIs are included to facilitate manufacturing of CDA formulations. $RI_{0.5}$ of a DHI is equivalent to ED_{25} of a DI, which can be determined by the procedure presented in the reference [70].

Table 2. *Active DIs*

DIs	ED25 (μM)	ED50 (μM)	ED75 (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

DIs and DHIs can be excellent cancer drugs, which are not regarded highly by the cancer establishments, because these drugs cannot make tumor to disappear. These excellent cancer drugs are primarily used in the treatment of hematological cancers. ATRA, a DI is the standard care of acute promyelocytic leukemia [72] and gleebec, a DHI, is the standard care of chromic myeloid leukemia [73]. ATRA requires the expression of the receptor of ATRA, namely RAR, to achieve the therapeutic efficacy. RAR is the repressor of the gene to code for oligoisoadenylate synthetase. The association of RAR with ATRA activates this

gene to produce oligoisoadenylate synthetase. The product of this enzyme, oligoisoadenylate, is the actual DI to act on abnormal MEs. Therefore, ATRA is an indirect DI. The rest of DIs presented in Table 2 are direct DIs to act on abnormal MEs. AA and PG derivatives are natural DIs to participate in chemo-survallance. BIBR1532 and boldine are non-natural DIs, which have been sproved for cancer therapy as telomerase inhibitors. PGJ2 and PGE2 have also been approved for delivery. Change of indication of the approved drugs does not take long clinical trials as the new drugs which usually take 10 years to complete clinical trials for the approval.

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
		Genisteine	2.19
MAT Inhibitor	RI0.5 (μM)	Pyrogallol	3.18
		Silibinine	3.80
Indol Acetic Acid	220	Caffeic Acid	3.87
Phenylacetylvaline	500	Ferulic Acid	7.41
Phenylbutyric Acid	970	Ellagoc Acid	4.45
Phenylacetylleucine	780	Gallic Acid	5.35
Butyric Acid	850	Phloroglucinol	38.82

DHIs listed in Table 3 show inhibitors of SAHH and MTs are better DHIs, effective at much lower dosages. The stability of three MEs is proportional to the mass [37]. SAHH is the smallest of the three enzymes and is the most unstable enzyme requiring steroid hormone to assume a stable configuration for the formation of MT-SAHH dimer to become stable. MAT has a mass similar as the MT-SAHH dimer to form ternary enzyme complex. MAT does not have affinity to form dimeric complex with MT or SAHH. 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 amount of inhibitor to shake loose of the stability of MAT. Inhibitors of MT and SAHH are better DHIs. Although pregnenolone is not the best DHI, we consider it a very valuable DHI. It is the master substrate of all biologically active steroids. It is also a single metabolite to have a profound influence on the development of cancer. According to Morley, the production of pregnenolone is bell shape in relation to ages with a peak daily production of around 50 mg at the ages of 20-25 [74]. The youngest and the oldest people produce the least amounts of pregnenolone, and these two age groups are the most vulnerable to develop cancer. It is our choice to make CDA-CSC formulations.

DIs are more important than DHIs to promote 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 therapy of acute promyelocytic leukemia with ATRA is excellent, but the majority of patients recur within a

year [72]. The inclusion of SAHH or MT inhibitors can keep MT-SAHH dimer intact to prevent modification of monomeric MT to become nuclease to disrupt differentiation process.

The finding of signal transduction inhibitors (STIs) as excellent DHIs is expected, since ST always produce effects to promote the activity of MEs. STIs can reduce the activity of MEs to promote TD. STIs are tyrosine kinase inhibitors. Inhibition of tyrosine kinase leads to the inhibition of MEs. STIs become the synonyms of inhibitors of MEs. The finding of polyphenols as excellent DHIs is a surprise. Epigallocatechin-3-gallate (EGCG) has been found as a good STI to inhibit MEs [75, 76]. It is possible that all polyphenols are potent STIs. Vital reds is a food supplement produced by the famed cardiologist Steven Gundry which is effective to clear blocked blood vessel [77]. It appears that Gundry has found an effective solution of CVDs, but he did not interpret it correctly. The correct interpretation is the perfection of wound healing to clear blocked blood vessel.

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 {78}. We recommend to make two sets of CDA formulations: one set CDA-CSC consisting of AA as the DI + pregnenolone as the DHI to access CSCs and PSCs, and another set CDA-CC consisting of BIBR + pyriminium panoate to resist enzymatic degradation of natural active ingredients by faster growing CCs. The application of phenylacetylglutamine is also recommended to antagonize TNF, which can be administered independently as a capsule preparation and monitored independently through quantitative assay of plasma and urinary peptides as shown in Table 1. The therapeutic endpoint of cancer can be the drop of carcino-embroynic antigens within the normal values and the therapeutic endpoint of CVDs can be the drop of blood pressure to the normal values. Other diseases can set at the disappearance of clinical symptoms.

3. Conclusion

Wound unhealing is a major medical issue to produce many fatal diseases to account for the major loss of humans. Perfection of wound healing provides the best and the only solution to the rescue of patients struggling against fatal diseases evolving due to wound unhealing. Health profession is dominated by arrogant and inept authorities who are not only unable to solve the problems but also to block the solution. That is a political issue beyond our reach.

Consent and Ethical Approval

It is not applicable

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Competing Interests

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