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RESEARCH ARTICLE

Tearing Down Cytotoxic Agents and Ineffective Hypotensive Agents to Give Desperate Cancer and Cardiovascular Patients the Acces to Life Saving CDA Formulations

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Abstract

Health profession is dominated by inept authorities who are not only unable to provide solution but also to block the solution. The objective of this article is to urge powerful political figures to step in to call for the removal of DNA interaction agents and ineffective hypotensive drugs put up by the inept health establishments to block desperate cancer and cardiovascular patients the access to life saving CDA formulations. In 1987, President Reagan delivered a powerful historical speech at the Brandenburg Gate of Berlin to condemn the evil regime of Soviet Union to build Berlin Wall to limit east Berliners the access to freedom, and demanded Gorbachev to tear it down. Cytotoxic agents and ineffective hypotensive drugs are like the Berlin Wall built by the inept health establishments to limit desperate cancer and cardiovascular patients the access to life saving CDA formulations. King Charles and President Biden are powerful political figures who are suffering from advanced cancer that can only be helped by CDA formulations. We are hoping that they are willing to deliver equally powerful historical speeches at health head quarter to tear down cytotoxic agents and ineffective hypotensive drugs and to demand the approval of CDA formulations to save desperate patients struggling against fatal diseases evolving due to wound unhealing.

Cancer evolves due to wound unhealing. Creation of wounds is incorrect for the solution of cancer, but is favored by the cancer establishments to result in ever escalation of cancer mortalities. Apparently, cancer is not the only disease health authorities failed to provide the right solution. Cardiovascular diseases also evolve due to wound unhealing. The health authorities neglect the primary cause of wound unhealing to focus on the treatment of secondary buildup of vascular plagues, also to result in ever escalation of mortalities. The white lung of COVID-19 infection is obviously a fatal disease arising due to wound unhealing, which is neglected by the health authorities too busy to fight COVID-19 infection. There are other fatal diseases evolving due to wound unhealing that are not handled right by the health authorities. We hope King Charles and President Biden can also deliver powerful historical speeches to save a lot of patients.

Keywords: Berlin Wall, Cancer, Cardiovascular Diseases, CDA Formulations, President Reagan , Biden.

1. Introduction

Cancer therapy had a bad start to rely on toxic agents to kill cancer cells (CCs). Cytotoxic cancer therapy was a tragic byproduct of World War II. During the war, sulfur mustard gas bombs were used. Victims of toxic gas all displayed depletion of leukocytes in their blood specimens, which inspired oncologists to employ toxic chemicals to treat leukemia patients. Toxic chemicals were indeed very effective to eliminate leukemia cells, the most outstanding symptom of leukemia. Cytotoxic chemotherapy thus became not only the standard care of leukemia but also the solid cancer, and the shrinkage of tumor became a standard diagnosis for the evaluation of the success of cancer

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therapy. Both were wrong, because cancer evolved due to wound unhealing [1, 2], creation of wounds was definitely incorrect for cancer therapy [3, 4]. Since creation of wounds was wrong for cancer therapy, tumor shrinkage was also incorrect for the diagnosis of cancer therapy [5, 6]. Cytotoxic cancer therapies were the choice of cancer establishments when President Nixon declared War on Caner in 1971. The solution of top killing diseases is an important issue of national interest. Cardiovascular diseases (CVDs) were the top killer in the USA. But heart attack and stroke were too difficult to overcome. So, President Nixon picked the easier cancer, which was the next top killer, as his presidential project. The War on Cancer was not successful, which was a shameful record of health profession to fail a presidential project which did not require difficult technology. The solution of cancer did require the smart brains of Virchow and Liau et al. [1, 3-6], which were ignored. The previous two presidential projects were successful which required very difficult technology. Nuclear physicists achieved the Manhattan Project under President Roosevelt and rocket engineers achieved the Moonshot Project under President Kennedy. A presidential project carries a time limit of 5 years with unlimited support from national resources. When a therapy is drilled through as a presidential project and fails to achieve its objective, it is fair to conclude that the therapy is not good for cancer. Evidently cancer establishments agreed to the conclusion to start searching the replacements. Meanwhile they kept using failed cytotoxic therapies that was inappropriate. Failed drugs should be eliminated right away and replaced by other approved cancer drugs. Gene therapy was their first choice of replacement. They wasted 20 years from 1976-1996 to learn the difficult of gene therapy. Good thing that they were not successful in the development of gene therapy. If it was successful, we would be trapped in a difficult approach of cancer therapy like we are now trapped in unattainable cytotoxic cancer therapy. Anti-angiogenesis therapy was their second choice during 1996-2016, which was also unsuccessful. The development of anti-angiogenesis was successful, but the success of anti-angiogenesis therapy ended up to cause the deaths of patients due to internal bleeding, which echoed the failure of cytotoxic cancer therapy. The success of cytotoxic therapy often resulted in the deaths of patients due to adverse effects or recurrence. Now they are on the third choice of immunotherapy during 2016-2036. It is not promising despite the fact that immunotherapy was awarded Novel prize in 2025. It is halfway through, but the cancer mortalities are still on the trend to escalate at an annual rate of 0.2% according to the statistics of American Cancer Society [7]. Cancer is basically a problem of cell growth regulation going awry. Immunology has nothing to do with cell growth regulation. Up to now, cancer establishments do not have a successful record on cancer therapies. Yet, they are still in the commander's position to insist on pursuing wrong approaches of cancer therapy.

Health profession is an authoritarian profession like communist regimes. The bosses put up policies for the entire profession to follow. The intelligent bosses can put up good policies of immunization and antibiotics to enhance the reputation of health profession and to benefit patients. But the inept bosses can put up bad policies of cytotoxic agents and ineffective hypotensive drugs to damage the reputation of health profession and to hurt patients. CDA formulations are obviously the only intelligent solution for the fatal diseases evolving due to wound unhealing [8-15]. These excellent drugs were blocked by cancer establishments. Cancer establishments are not only unable to provide solution, but also to block the solution. This is a political issue which can only be resolved by political means. King Charles was an ardent supporter of alternative therapies and President Biden was an enthusiastic political leader to save cancer patients, who initiated a quasi-presidential project of Cancer Moonshot in 2022 when he was healthy [16, 17]. Both were suffering from advanced cancer. We are hopeful that they are willing to come out to deliver powerful historical speeches at health head quarter like the historical speech of President Reagan at Brandenburg Gate to condemn health profession as a dumb profession unable to solve a simple wound unhealing problem and to demand the approval of CDA formulations to save themselves and many patients in the same desperate situation.

2. Tearing Down the Cytotoxic Agents to Give Desperate Cancer Patients the access to Life Saving CDA Formulations and Discussion

2.1 Establishing a Valid Concept of Cancer to Confront Cancer Successfully

To successfully confront cancer, it is necessary to establish a valid concept of cancer [18]. Cancer evolving due to wound unhealing was a valid concept of cancer introduced by Virchow in 1858 [1]. He did not produce experimental data to advance his excellent

concept on cancer. We pursued cancer therapy unknowingly following his guidance to discover abnormal methylation enzymes [19-21], chemo-surveillance [22-24], and the mechanism of wound healing [25-28], which provided experimental data to strongly support the validity of Virchow's concept of cancer evolving due to wound unhealing. Thus, Virchow and Liau et al. form an alliance to promote the valid concept of cancer evolving due to wound unhealing [15].

Wound healing comes naturally. Since wound healing is such a simple matter, it is unable to attract attention. But if wound is not healed, it can lead to disastrous consequences that can be fatal. Actually, wound healing is a major health issue, so that the nature creates chemo-surveillance and immuno-surveillance to ensure perfection of wound healing, chemo-surveillance to take care of wounds caused by toxic chemicals or physical means and immuno-surveillance to take care of wounds caused by infectious agents. Chemo-surveillance and immuno-surveillance can act synergistically to heal wounds. Chemo-surveillance was a terminology we created to describe an observation that healthy people were able to maintain a steady level of metabolites active as 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 [22]. 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. DIs and DHIs are wound healing metabolites to promote terminal differentiation (TD) of cells expressing abnormal MEs. MEs are a ternary enzyme complex consisting of methionine adenosyltransferase (MAT)-methyltransferase (MT)-S-adenosylhomocysteine hydrolase (SAHH), which are critically involved in the regulation of cell growth and differentiation [29].

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 TD of progenitor stem cells (PSCs) [26]. PSCs are the most primitive stem cells to initiate the development of organ or tissue during the embryonic stage of fetal development. A small percentage, usually less than 2% of the organ or tissue mass, is preserved in the organ or tissue for future expansion or repair. Wound healing is actually an extension of the embryonic program of organ development. The primitive embryonic stem cells express telomerase. MEs of telomerase expressing cells are abnormal due to the association with telomerase. The association of telomerase with MEs changes kinetic properties of MEs and the regulation of MEs on cell growth greatly in favor of cell growth by promoting the stability of MEs. The K_m values of the telomerase associated MAT^{LT}-$SAHH^{LT}$ isozyme pair are 7-fold higher than the K_m values of normal MAT^{L}-$SAHH^{L}$ isozyme pair. The higher K_m values of MEs in cells expressing telomerase are an indication that MEs in cells expressing telomerase are more stable to promote cell growth, since the study of Prudova et al. showed that S-adenosylmethionine (AdoMet) could stabilize protein against protease digestion [30]. The higher K_m values of MAT^{LT}-$SAHH^{LT}$ isozyme pair of telomerase expressing cells are also an indication that cell expressing telomerase have larger pool sizes of AdoMet, S-adenosylhomocysteine (AdoHcy) and homocysteine (Hcy), which are important to promote the growth of cells expressing telomerase, since the study of Chiva et al. showed that when HL-60 cancer cells were induced to undergo TD, the pool sizes of AdoMet and AdoHcy shrank greatly [31]. Obviously, larger pool sizes of AdoMet and AdoHcy are needed to promote the growth of cells expressing telomerase. Telomerase is a recognized oncoprotein. The association with MEs to promote cell growth is the most critical factor to contribute to telomerase as an oncoprotein. Because of the important role of MEs in the regulation of cell growth and differentiation. MEs are exceptionally regulated by double allosteric regulations, one on individual enzymes by steroid

hormone and the other on enzyme complex by telomerase and chemo-surveillance [32]. Usually, enzymes involved in the important biological functions are subjected to delicate biological regulations. Allosteric regulation is the most pervasive biological regulation. Single regulation is very common. Double regulations are an exception to stress the exceptional role of MEs in growth regulation. The exceptional role of abnormal MEs is obviously needed for the development of fetus and for wound healing. The operation of abnormal MEs in the development of fetus and wound healing is strictly under the control of safety mechanisms such as contact inhibition, ten eleven translocator-1 (TET-1) enzyme and chemo-surveillance. Cells with abnormal MEs are allowed to proliferate when space is available. But when space is not available, the proliferation is terminated. The dormant stem cells can be induced to undergo lineage transitions through TET-1 enzyme. Replicating stem cells can be forced to undergo TD by chemo-surveillance to become terminally differentiated cells to performed specialized cellular function. Terminally differentiated cells are no longer capable of proliferation. Chemo-surveillance is the last defense mechanism created by the nature to halt the pathological buildup of cells with abnormal MEs. It appears that the seed of fatal diseases evolving due to wound unhealing is sown at the very beginning of life, namely the fertilization of egg with a sperm to activate the totipotent stem cell which expresses telomerase. The expression of telomerase spreads through primitive embryonic pluripotent stem cells, but secedes when pluripotent stem cells undergoing lineage transitions to reach unipotent stem cells (UPSCs). Cancer stem cells (CSCs) are derived from PSCs which express telomerase. Therefore, CSCs also express telomerase to display abnormal MEs. CCs are derived from CSCs. Therefore, CCs also express telomerase to display abnormal MEs. CSCs are PSCs without TET-1 enzyme [33, 34]. The cell feature, antigenicity and cell mission of CSCs are exactly the same as those of PSCs. PSCs are tolerable to the natural immune mechanisms, so are CSCs. Immunotherapy is effective against CCs marked with programed death antigen to be eliminated by immunotherapy. Both PSCs and CSCs are not marked with programmed death antigen to tolerate immuno-surveillance. PSCs and CSCs are protected by drug resistance and anti-apoptosis mechanisms to resist cytotoxic cancer therapies [35-40]. So, both cytotoxic cancer therapies and immunotherapy are ineffective against PSCs and CSCs. CDA formulations are the only option effective to eliminate PSCs and CSCs [8-15]

Data presented in Table 1 are the quantitative data of plasma and urinary peptides. Peptides are hydrophobic metabolites sharing chemical-physical 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 are the major DIs of Antineoplaston preparations purified from urine used by Burzynski for cancer therapy to achieve excellent cancer therapy during 1976-1990 [22, 41-43]. Majority of patients responded well to Antineoplaston therapy to show the restoration of CDA levels back to the normal level of 5.0. Non-responders continued to show the decline of CDA levels. Cancer cells are known to express a high level of degradative enzymes to salvage substrates for macromolecular syntheses to support their faster growth. Antineoplastons are natural metabolites which may be degraded in faster growing cancer cells to lose activity. Antineoplastons were blocked by cancer establishments around 1990, because these drugs were non-toxic unable to cause tumor to disappear. It was very unfortunate that cancer establishments put up a rule of tumor shrinkage as a condition of cancer drugs, which was the most grave mistake they have committed [44, 45]. The rule cancer establishments put up to block Antineoplastons as cancer drugs also blocked their mission to win the war on cancer, because wound healing metabolites are the only option for the solution of CSCs [8-15]. It is incredible that cancer establishments put up a rule to defeat themselves. Of course, cancer establishments knew that the solution of CSCs was critical 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 against CSCs invented by the scientists of Stanford University. They made big noise as if they had found the solution of cancer. Now the topics of CSCs and monoclonal antibodies totally disappear as if these topics never existed. They failed to develop monoclonal antibodies for the solution of CSCs, because killing was not an option to solve CSCs which were critically linked to wound unhealing. Induction of terminal differentiation (TD) is the only option for the solution of CSCs [8-15], which they blocked.

Our studies on chemo-surveillance selectively destroyed in cancer patients as presented in Table 1 strongly supported the validity of Virchow's

concept of cancer evolving due to wound unhealing. Chemo-surveillance is the creation of the nature for the perfection of wound healing. The alliance of Virchow and Liau et al. [15] has the blessing of the creator of nature as a valid concept of cancer. Cancer establishments can make mistakes, but the creator of nature will never make mistakes. We have produced additional experimental data to support the validity of cancer evolving due to wound unhealing. During our studies of animal hepato-carcinogenesis, we noticed the appearance of numerous tiny hyperplastic nodules soon after the application of hepatocarcinogens to animals, which displayed abnormal MEs we have discovered earlier [19]. These tiny hyperplastic nodules must represent the proliferation of PSCs In the process of active wound healing, most of which disappeared shortly afterward indicating the success of wound healing, and only a few large size carcinomas appeared later from the tiny hyperplastic nodules not healed [46]. If Antineoplaston A10, namely phenylacetylglutamine, was provided to the animals after the application of hepatocarcinogen aflatoxin B_1, the appearance of hepatocarcinomas could be effectively prevented as shown in Figure 1, which is reproduced from the reference [47]. Antineoplaston A10 is biologically inactive chemical. Nevertheless, it can effectively antagonize tumor necrosis factor (TNF) to prevent the loss of wound healing metabolites to keep the functioning of chemo-surveillance intact [22]. TNF is another well recognized oncogenic protein beside telomerase due to its ability to create wounds as a toxic protein, and to induce hyperpermeability of blood vessels [48, 49] to cause excessive excretion of low molecular weight metabolites, wound healing metabolites are among low molecular weight metabolites excreted to result in the collapse of chemo-surveillance to cause wound unhealing. TNF is also named cachectin after its effect to cause cachexia symptoms.

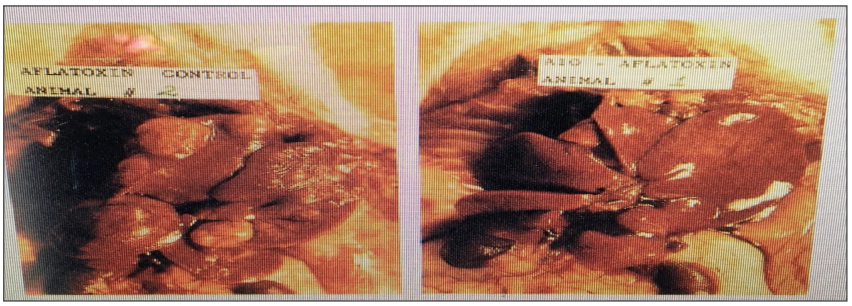

Figure 1. *Effective Prevention of Hepatocarcinogenesis by Antineoplaston A10*

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

A manifestation of cachexia symptoms is the excessive excretion of low molecular weight metabolites due to the effect of TNF to cause hyperpermeability of blood vessels above mentioned. Figure 1 is a very persuasive experimental datum to support the validity of Virchow's cancer evolving due to wound unhealing. Oriental medicine stresses the importance of drugs that can prevent diseases from taking place [11]. Drugs that can prevent diseases from taking place are considered the best drugs. Thus, phenylacetylglutamine belongs to the category of best cancer drugs. Phenylacetylglutamine is a major chemical component of CDA-2 we purified from urine for cancer therapy [50].

Cancer evolving due to wound unhealing is a valid concept of cancer [1. 2. 15]. Study of wound healing should be an important medical issue. Yet it is totally neglected. No wonder, health profession is unable to solve diseases evolving due to wound unhealing to allow these diseases to become the top killers of humans [13]. Wound healing requires the proliferation and the TD of PSCs [26]. Wound usually triggers biological and immunological responses. The biological response involves the release of arachidonic acid (AA) from membrane bound phosphatidyl-inositol by phospholipase A2 for the synthesis of prostaglandins (PGs) by cyclooxygenases and PG synthases [51, 52]. Although AA and PGs are active DIs [53, 54], 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 [51] is responsible for the increase of membrane permeability to facilitate the extravasation of plasma proteins and regulatory factors into the wound area resulting in edema response, which 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 must be released for PSCs to proliferate to produce

enough cells to heal the wound. PGs are metabolically unstable [51]. 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 [54]. 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 proteins will create wounds to aggravate the already bad situation. TNF among cytokines is particularly bad for wound healing as above described. Thus, immunological response can act antagonistically to chemo-surveillance. It is the balance of biological response and immuno-logical response to dictate the outcome of wound healing. If biological response prevails, wound is healed. But if immunological response prevails, wound is not healed to produce clinical symptoms. If clinical symptoms are fatal such as the white lung of COVID-19 infection [55] or the heart attack of CVDs, fatality is the end point. If clinical symptoms are not fatal such as those caused by carcinogens, there is a good possibility that unhealed wound will be forced to evolve into cancer. Wound unhealing in most cases is caused by the collapse of chemo-surveillance. Chemo-surveillance is always operating at the maximum capacity. There is no mechanism to boost the production of DIs and DHIs. Wound unhealing will produce pressure to force the proliferation of PSCs. The contact inhibition limits the extent that PSCs can proliferate. PSCs are then forced to evolve into CSCs to escape the limit of contact inhibition. It takes a single hit to silence TET-1 enzyme to turn PSCs to become CSCs [33, 34] that is an easy task for PSCs to accomplish, since these cells are equipped with exceptionally active MEs. The appearance of CSCs in the primary tumor is critically linked to wound unhealing. But the metastasis of CSCs is not linked to wound unhealing. The evolution of CSCs still cannot heal the wound, because the problem is the collapse of chemo-surveillance. CSCs are then forced to progress to faster growing CCs by chromosomal abnormalities of translocations to activate oncogenes or deletions to inactivate suppressor genes to become full blown cancer. CCs are the dominant cells to attract most attention. CSCs constitute only a small subpopulation, which, however, are the most vicious cancer cells to cause fatal effects of cancer, fatal effects of cancer such as metastasis, drug resistance, anti-apoptosis, unresponsiveness and recurrence are all the making of CSCs [8-15, 35-40]. Therefore, the solution of CSCs is far more important than the solution of CCs. Cancer establishments only tried to develop monoclonal antibodies against CSCs, but failed. That was the only effort they put up trying to solve the most important issue of cancer. 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 [1]. Cancer establishments are extremely dumb not able to understand the logic of wound unhealing to the evolution of cancer at a time both cancer and wound healing become known completely. A drastic change of cancer leaderships is necessary to save cancer patients [56]

2.2 Decoding CSCs: A Game Change in Oncology Therapeutics

Solution of CSCs is the utmost important issue of cancer, because CSCs contribute the most fatal effects of cancer [8-15]. Myelodysplastic syndromes (MDSs) are diseases attributable entirely to CSCs [57], therefore, these diseases can be used to evaluate cancer drugs effective against CSCs. MDSs often start with a display of immunological disorder prompting the production of cytokines [58]. TNF among cytokines produced is most critically related to the development of MDSs, since antibody of TNF was effective to halt the progression of MDSs [59]. TNF causes the apoptosis of bone marrow stem cells, thus severely affecting the productions of hematopoietic cells such as erythrocytes, platelets or neutrophils. TNF is also responsible for the collapse of chemo-surveillance as above described to force the evolution of CSCs from PSCs. Induction of TD of CSCs is the only option to solve MDSs [14, 60-62]. Vidaza, Decitabine and CDA-2 were the three drugs approved by the Chinese FDA for the therapy of MDSs. CDA-2 was a preparation of wound healing metabolites purified from urine we produced [50]. Vidaza and Decitabine were also approved by the US FDA for the therapy of MDSs. Professor Jun Ma, the Director of Harbin Institute of Hematology and Oncology, was instrumental in carrying out clinical trials of all three MDSs drugs in China. 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 markedly better therapeutic efficacy based on hematological improvement, namely becoming independent on blood transfusion to stay healthy, as shown in Figure 2, which is reproduced from the reference [63].

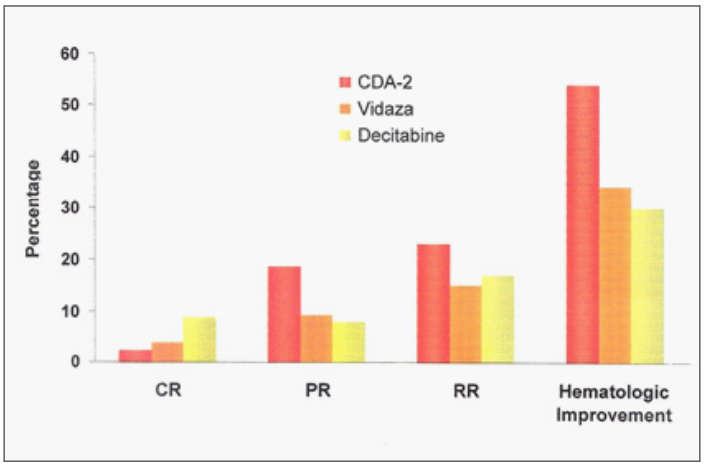

Figure 2. *CDA-2 as the Best Drug for the Therapy of MDSs*

Figure 2 is a very valuable datum produced by Professor Ma to support the validity of Virchow's concept of cancer evolving due to wound unhealing. CDA-2 achieves destabilization of abnormal MEs by targeting on the tumor factor telomerase [21], whereas Vidaza and Decitabine achieve inactivation of MT by the covalent bond formation between MT and 5-azacytosine incorporated into DNA [64]. CDA-2 was without adverse effects, whereas Vidaza and Decitabine were proven carcinogens [65, 66] and very toxic to DNA [67-69]. CDA-2 is clearly the drug of choice for the therapy of MDSs with a 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 [70]. We were the clear winner, but our winner's status was blocked by the cancer establishments who put up shrinkage of tumor as a condition of cancer drugs. The same rule cancer establishments put up to block our winner's status also block their mission to win the war on cancer, because elimination of CSCs is essential to win the war on cancer [6, 14-18].

2.3 Cytotoxic Agents Can Only Benefit Cancer Patients in the Early Stage

Oncologists always urge people to be alert to detect cancer early, because they can only help cancer patients in the early stage. But cancer in the early stage is not easy to be detected. King Charles' cancer was a metastatic cancer. His primary cancer is still unknown. President Biden's prostate cancer when first diagnosed in 2025 was an advanced cancer with Gleason score of 9 and distant bone metastasis. Both of their cancers are beyond the help of cytotoxic cancer therapies. Cytotoxic cancer therapies kill CCs, but cannot affect CSCs because CSCs are resistant to cytotoxic assaults, including immunological assaults as above described [35-40]. The killing of CCs creates wounds to trigger the proliferation of CSCs to heal the wounds created by cytotoxic agents [71]. CSCs are not responsive to cytotoxic agents neither immunological agents, so, the percentage of CSCs in the tumor will increase. When the percentage of CSCs reaches the threshold above 3%, the tumor becomes unresponsive to further therapies [72]. Therefore, cytotoxic cancer therapies and immunotherapy can only help cancer patients with CSCs count below 1% [72], stage I and II cancer patients without metastasis, prostate cancer patients with Gleason scores below 7 and cancer patients with CDA levels above 2.5 as described in Table 1, which are only a minor population of cancer patients around 25%. Cancer establishments are unable to save 75% of cancer patients in advanced state. The reason that cytotoxic cancer therapies can only benefit early stage cancer patients is because chemo-surveillance in the early stage is not yet fatally destroyed beyond recovering to the functional state to subdue the surviving CSCs. The success of cytotoxic cancer therapies is not entirely the credit of killing CCs. The recovery of chemo-surveillance to the functional state plays a decisive role. Killing CCs by DNA interacting agents is a dangerous attempt. It can kill CCs, but it can also kill UPSCs to cause the deaths of cancer patients [73]. Besides, alteration of gene structure may produce monstrous cells nobody can handle. The cancer establishments put up DNA interacting agents to kill CCs, and the results are cancer mortalities keep on escalating. Immunotherapy is a better choice, although it is also not able to win the war on cancer. The combination therapies involving immunotherapy

and CDA formulations may be a perfect solution, immunotherapy to satisfy cancer establishments of tumor shrinkage, and CDA formulations to eliminate CSCs to save cancer patients.

2.4 Wound Unhealing is also the Cause of CVDs and Many Fatal Diseases

CVDs are the top killer of humans, claiming 20.5 million casualties around the world and 0.92 million in the USA annually [7]. CVDs are also the diseases evolving due to wound unhealing [13]. CVDs are caused by the damages to the artery's inner lining that trigger the build up of PSCs to heal the wound. Aberrant DNA methylation detected in atherosclerotic aortic samples [74-76] and elevated Hcy as risk factor of CVDs [75] are an indication of active metabolism of cells with abnormal MEs, most likely the buildup of PSCs unable to undergo TD. Inability of PSCs to undergo TD triggers infiltration of leukocytes and the deposit of light density lipoproteins to create the secondary buildup of plagues to display symptom of hypertension, which is the most outstanding symptom of CVDs. Treatment of CVDs are primarily focused on the reduction of hypertension. Drugs targeting symptoms to produce immediate effects are the favorite of western medicine, which are not as effective as the drugs to target the cause of the disease [11]. CDA formulations are the drugs to target the primary cause of wound unhealing to produce more effective therapy. Drugs to target the cause of the disease are considered the next best drugs after the drugs that can prevent diseases from taking place [11]. Vital Reds is a food supplement produced by the famed cardiologist Steven Gundry to clear blocked blood vessels [77]. Polyphenols are the active ingredients of Vital Reds. Our studies indicated that polyphenols were very active DHIs [78]. Therefore, the effect of Vital Reds to clear blocked blood vessels is attributable to the induction of TD of PSCs, the initial cause of CVDs. So, Gundry has found an intelligent solution of CVDs to ally with Virchow and Liau et al. [15].

The white lung of COVID-19 infection is obviously a case of wound unhealing [55]. It is caused by the buildup of PSCs unable to undergo TD because of the collapse of chemo-surveillance during the initial stage of COVID-19 infection. Health authorities are too busy to fight viral infection to neglect the symptom it causes. White lung is an acute symptom, more fatal than heart attack or stroke. If this fatal symptom can be effectively solved, COVID-19 infection may not be a fearful disease. Influenza virus also causes damage to the lung. The damage is not fatal. So, influenza virus is not a feared disease. CDA formulations are the right solution of the white lung symptom. Kidney failure is apparently a case of wound unhealing. Kidney failure is caused by the damage to the glomerulus resulting in the failure of filtration process to cause the accumulation of low molecular weight metabolites that include waste metabolites designated to be excreted and good wound healing metabolites active as DIs and DHIs. The accumulation of DIs and DHIs can cause premature TD of PSCs to interfere with the process of wound healing very much like the malformation of body part by thalidomide to induce premature TD of stem cells during the process of organ development. Therefore, the intelligent solution of kidney failure is to promote the proliferation of PSCs to produce enough stem cells for the healing of the damage to glomerulus. Application of growth factors such as PGs or erythropoietin is the right solution. CDA formulations in the case of kidney failure is contra-indication. Dementia is caused by the damage of memory cells by toxic proteins beta-amyloid and tau. Wound healing metabolites are hydrophobic metabolites very likely to be enriched in the brain compartment. The situation is like kidney failure with too many wound healing DIs and DHIs to cause premature TD of PSCs during wound healing process. The solution of dementia may also require the application of growth promotion instead of CDA formulations. Dementia if not solved effectively can lead to Alzheimer's disease that is fatal. The best way to solve fatal diseases is to prevent them from taking place. Perfection of wound healing is the only intelligent solution. The enrichment of DIs and DHIs in the brain compartment may also explain that most malignant brain tumors have elevated levels of CSCs [72], because only malignant tumors with elevated levels above 3% can prevail in the brain compartment. Astrocytoma is an exception with CSCs count less than 1% [72]. Brain compartment is also enriched in growth hormone produced by the pituitary gland, which can promote the growth of astrocytoma and benign tumors.

2.5 Development of CDA Formulation for the Therapy of Diseases Evolving due to Wound Unhealing

Majority of diseases evolving due to wound unhealing are caused by the collapse of chemo-surveillance. Therefore, Restoration of chemo-surveillance is a top priority to save patients evolving due to the collapse of chemo-surveillance [9, 79, 80]. Perfection of wound healing is apparently the best strategy to win the war

on cancer [10, 12, 13, 15, 81, 82]. Chemo-surveillance is the nature's creation to destabilize abnormal MEs, which are obviously the most critical issue of cancer [8, 32, 62]. Destabilization of abnormal MEs becomes the most effective strategy to solve fatal diseases evolving due to wound unhealing [13, 15, 60, 62, 83].

We have carried out extensive studies of natural and ono-natural DIs and DHIs for the manufacture of CDA formulations [11-16, 42, 43, 50, 53, 54, 60, 84, 85]. Active DIs and DHIs are presented in Table 2 and 3, which are summarized from references above cited. $ED_{25,\ 50,\ and\ 75}$ of DIs and reductive index 0.5 ($RI_{0.5}$) of DHIs are included to facilitate manufacturing of CDA formulations. $RI_{0.5}$ of DHI is equivalent to ED_{25} of DI, which can be determined by the procedure previously reported [84]. DIs and DHIs can be excellent cancer drugs. ATRA, a DI, is the standard care of acute promyelocytic leukemia [86] and gleebec, a DHI, is the standard care of chronic myeloid leukemia [87]. It has to demonstrate an excellent therapeutic efficacy to be designated as a standard care of particular cancer. ATRA requires the expression of the receptor of ATRA, namely RAR, to achieve the therapeutic efficacy.

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

RAR is the repressor of the gene coding for oligoisoadenylate synthetase. The association of RAR with ATRA activates the transcription of oligoisoadenylate synthetase gene to produce oligoisoadenylate synthetase. The product of this enzyme, oligoisoadenylate, is the active DI to destabilize MEs [88]. ATRA is actually an indirect DI. Oligoisoadenylate has to be synthesized inside the cell to function. The triphosphate structure of oligoisoadenylate prevents it from entering into cells from outside. The rest of DIs listed in Table 2 are direct DIs to act on abnormal MEs to achieve induction of TD of cells with abnormal MEs. PGs are drugs approved for the delivery. BIBR1352 and boldine are telomerase inhibitors approved for cancer therapy. Change of indication does not take long clinical trial as the application of new drug which usually requires 10 years. Effective CDA formulations can be developed quickly with approved drugs active as DIs and DHIs.

As listed in Table 3, inhibitors of SAHH and MT are better DHIs than inhibitors of MAT. The stability of three MEs is proportional to the mass [29]. 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 of MT-SAHH dimer to become stable. MAT has a mass similar to the MT-SAHH dimer. MAT can form a ternary complex with MT-SAHH dimer, but cannot form dimeric complex with MT or SAHH. MAT is the most stable enzyme.

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 Inhibitors	RI0.5 (μM)	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

The association with telomerase further increases its stability. Therefore, it requires very large amounts of inhibitors to function as DHIs. Inhibitors of SAHH and MTs are better DHIs.

Although pregnenolone is not the most active DHI, we consider it a very valuable DHI. It is the master substrate of 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 relation to ages with a peak daily production of around 50 mg at the ages of 20-25 [89]. The youngest and the oldest people produce the least amounts of pregnenolone, and these are the two age groups most vulnerable to develop cancer. It is our top choice of DHI 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 [86]. 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 STs always produce factors to enhance 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 unexpected. Epigallocatechin-3-gallet (EGCG) has been found as a good STI to inhibit MT [90-91]. 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 Gundry [77], which contains polyphenols as the active ingredients. Vital Reds is effective to clear blocked blood vessels. So, Gundry has found an intelligent solution of CVDs through perfection of wound healing. Polyphenols are generally considered healthy food. The finding of polyphenols as excellent DHIs adds the credibility of polyphenols as healthy food.

The manufacture of CDA formulations can be the following formulas 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 [60]. We recommend 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 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 [22]. The therapeutic endpoint of phenylacetylglutamine can be the restoration of CDA level to reach the healthy level of 5.0 of the Table 1. The therapeutic endpoint of cancer can be the drop of carcino-embryonic antigens to reach the normal levels. The therapeutic endpoint of CVDs can be set at blood pressure of normal value.

2.6 A Plead for King Charles and President Biden to Deliver Historical Speeches to Demand the Approval of CDA Formulations to Save Desperate Patients Struggling against Fatal Disease Evolving due to Wound Unhealing

Speeches from political figures can be very effective to solve difficult problems. In 1987, President Reagan delivered a powerful historical speech at Brandenburg Gate of Berlin to condemn Soviet Union as an evil regime to build up Berlin wall to limit east Berliners the access to freedom and demanded Gorbachev to tear it down. Berlin wall tumbled down two years later, followed by the dissolution of Soviet Union in the December of 1991. Historical speeches from King Charles and President Biden may also produce magic solution of difficult diseases. Both King Charles and President Biden are suffering from advanced cancer that can only be helped by CDA formulations which were blocked by cancer establishments [6, 92]. We are hopeful that they are willing to go to the health head quarter to deliver historical speeches condemning health profession as a dumb profession to put up cytotoxic agents and ineffective hypotensive drugs to cause enormous casualties, 10 million of cancer patients and 20.5 million of CVDs patients around the world annually [7], and to block desperate patients the access to life saving CDA formulations. Ask health authorities to tear down cytotoxic agents and hypotensive drugs and to approve CDA formulations to save desperate patients struggling against fatal diseases evolving due to wound unhealing.

3. Conclusion

Wound unhealing is a major medical issue. Health authorities handled this issue very poorly to result in diseases evolving due to wound unhealing to become the top killers of humans. Health authorities are not only unable to solve the problem, but also to block the solution. Inability to solve wound unhealing is a political issue that can only be resolved by political means. We plead King Charles and President Biden, who are suffering advanced cancer, to deliver historical speeches to demand the approval of CDA formulations to save desperate patients struggling against fatal diseases evolving due to wound unhealing.

Consent and Ethical Approval

It is not applicable.

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Competing Interest

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