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The health profession is an authoritarian profession. When the establishments at the very top of health professions make a mistake, there is no way to rectify the mistake, and the mistake carries on to hurt patients. It will depend on higher authorities to rectify the mistake. King Charles and Princess Kate are in such positions to force changes of current cancer therapies to save themselves and other cancer patients, many of them are in a hopeless situation created by the current therapies.

Keywords: cancer therapy, chemotherapy, differentiation therapy, immunotherapy, CDA, CSCs, DIs, DHIs, PSCs, Wound healing.

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ABSTRACT

The recent cancer diagnoses of King Charles and Princess Kate, while a misfortune no one wishes to happen, offer a supreme authority to rectify cancer therapies to save cancer patients. Cancer incidence and mortality continue to increase during the past 50 years. Obviously, cancer has not been eradicated. The health profession is an authoritarian profession. When the establishments at the very top of health professions make a mistake, there is no way to rectify the mistake, and the mistake carries on to hurt patients. It will depend on higher authorities to rectify the mistake. King Charles and Princess Kate are in such positions to force changes of current cancer therapies to save themselves and other cancer patients, many of them are in a hopeless situation created by the current therapies.

Cancer therapy has had a bad start by relying on toxic chemicals to kill cancer cells (CCs) and the disappearance of tumor as a criterion for the judgment of therapeutic efficacy. These were mistakes made by cancer establishments at a time when we did not have the complete understanding of cancer. Now we have better knowledge of cancer, but the cancer establishments are still trapped in the failed principle of killing of CCs and the disappearance of tumor to direct cancer therapies. Cancer evolves as a consequence of wound unhealing due to the collapse of chemo-surveillance. Wound healing requires the proliferation and the terminal differentiation of progenitor stem cells (PSCs). Chemo-surveillance is the nature's creation of allosteric regulation on abnormal methylation enzymes (MEs) to achieve terminal differentiation. Abnormal MEs are also the nature's creation to allow the buildup of PSCs to heal the wound. MEs of PSCs are abnormal due to association with telomerase. The buildup of PSCs is limited by contact inhibition. The nature does not create a mechanism to rectify the breakdown of chemo-surveillance. Inability to complete terminal differentiation of PSCs forces PSCs to evolve into cancer stem cells (CSCs) in order to escape contact inhibition. By a single hit to silence TET-1 enzyme, which is well within the reach of PSCs equipped with abnormally active MEs, PSCs can be easily turned to become CSCs.

The proliferation of CSCs still cannot heal the wound, because the problem is the breakdown of chemo-surveillance. CSCs are then forced to progress to faster growing CCs by chromosomal abnormalities such as translocations to activate oncogenes or deletions to inactivate suppressor genes. Evidently, cancer evolves due to wound unhealing. Therefore, the appropriate solution of cancer is to follow the wound healing process.

Pro-wound healing is the right approach of cancer therapy. Cancer establishments pursue the opposite approach by treating with toxic chemicals or agents that create more wounds to aggravate the already bad situation to result in horrendous cancer fatalities. Cancer establishments are responsible for the failure of cancer therapies. King Charles and Princess Kate are the supreme authorities to direct the right approach of cancer therapies to save themselves and other cancer patients in the same situation.

We have carried out extensive studies of natural and unnatural differentiation inducers (DIs) and differentiation helper inducers (DHIs) for the manufacturing of cell differentiation agent (CDA) formulations to save cancer patients. The development of CDA formulations was constantly blocked by cancer establishments,

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We have carried out extensive studies of natural and unnatural differentiation inducers (DIs) and differentiation helper inducers (DHIs) for the manufacturing of cell differentiation agent because CDA formulations ran against their wish on the claim of tumor shrinkage as a criterion of effective cancer drugs. Recent success of immunotherapy of cancer appears to support the cancer establishments' stance on cell killing as the commanding principle of cancer therapy. It is undeniable that immuno-surveillance plays an important role to prevent cancer evolution.

Chemo-surveillance and immuno-surveillance are both protection mechanisms created by the nature to ward off cancer, one against wounds created by toxic chemicals and the other against wounds created by infectious agents. Both protection mechanisms can be synergistic to eliminate cancer causing factors. But these two protection mechanisms can also be antagonistic to each other. Cachexia symptoms are triggered by immunological reactions, which is responsible for the collapse of chemo-surveillance. In this sense, immunological approach is harmful to cancer therapy. Immunotherapy is definitely a better version of cytotoxic cancer therapy than chemotherapy. But the outcome is the same to cause increasing cancer mortality, because immunotherapy is unable to solve the problem of CSCs. CDA formulations are the only viable solution of CSCs, and the solution of cancer depends on the solution of CSCs.

Keywords: cancer therapy, chemotherapy, differentiation therapy, immunotherapy, CDA, CSCs, DIs, DHIs, PSCs, Wound healing.

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I. INTRODUCTION

Cardiovascular diseases are the number one cause of death. Cancer is the second leading cause of death worldwide. Health profession is hapless to solve these two giant killers. Cardiovascular diseases may be difficult to overcome. Cancer is actually a simple matter, but is not handled right by the cancer establishments. Cancer can be solved if cancer establishments can be replcaed [1]. When leading health establishments continue to practice ineffective therapies, there is no mechanism to rectify the decision to continue with current ineffective therapies. This mistake is continuing to hurt patients. It will depend on authoritative figures higher than the current establishments to initiate change. The recent cancer diagnoses of King Charles and princess Kate, while unfortunate, could potentially bring attention to current practices to rectify cancer therapies to save themselves and other cancer patients. Many patients are in hopeless situation created by the current cancer therapies still used by top cancer establishments [2]. Cytotoxic drugs create damages to trigger the proliferation of CSCs to work on the repair of damages they created. In most primary cancer, the proportion of CSCs is usually less than 2% of the tumor mass.

CSCs are protected by drug resistance and anti-apoptosis mechanisms. They are not responsive to cytotoxic drugs or radiation. The proportion of CSCs will increase to reach a high level no longer responsive to further treatment. Primary brain cancer has a very high level of CSCs above 10% [3, 4], which is not responsive to cytotoxic cancer therapy. The ineffectiveness of cytotoxic drugs against CSCs and the contribution to the damage of chemo-surveillance are the reason for the horrendous cancer mortality caused by cytotoxic drugs and radiation.

According to NCI experts, the cancer incidence was 19 million and the cancer mortality was 10 million in 2019 worldwide, which were a 5% increment from the previous year [5]. They predicted a 5% yearly increment likewise in the following years. Drugs are developed to save patients, however, cytotoxic drugs contribute horrendous cancer fatalities, which must be eliminated to save cancer patients [6].

II. COMMENTARIES AND DISCUSSION

II.1 Abnormal MEs as the Most Critical Issue of Cancer

Cancer is basically a problem of growth regulation going awry. MEs are at the center of growth

regulation playing a pivotal role on the regulation of cell replication and differentiation, therefore these enzymes are critically involved with cancer.

MEs are a ternary enzyme complex consisting of methionine adenosyltransferase (MAT)- methyl-transferase (MT) - S-adenosylhomocysteine hydrolase (SAHH) [7]. In steroid hormone targeted organs, SAHH is the steroid hormone receptor.

SAHH requires steroid hormone to assume a stable configuration to form a dimeric complex with MT, which has a molecular size similar to MAT. MT-SAHH and MAT then form a ternary enzyme complex, which is the stable and active unit. Steroid hormone functions as an allosteric regulator to promote MEs to active ternary enzyme complex. Without steroid hormone, ternary enzyme complex dissociates to become inactive individual enzymes. MTs in the monomeric form have a tendency to be modified to become nucleases that can cause damages to result in cell apoptosis. MEs most important for the regulation of cell replication and differentiation are 2'O-ribose MEs of pre-rRNA which control the production of ribosome [8, 9] and DNA MEs which control the expression of tissue specific genes [10]. Because of the important regulatory role on cell growth, MEs are subjected to exceptional allosteric regulation [11].

In telomerase expressing cells, MEs are associated with telomerase [12]. The association with telomerase changes kinetic properties of MAT-SAHH isozyme pair, and the regulation greatly in favor of cell growth. K_m values of telomerase associated MAT-SAHH isozyme pair are 7-fold higher than those of normal isozyme pair [7, 12, 13]. The higher K_m is an indication that MEs of telomerase expression cells are much more stable than normal MEs, since Prudova et al. found S-denosylmethionine (AdoMet) could protect protein against protease digestion [14].

Larger pool sizes of AdoMet and S-adenosylmohocysteine (AdoHcy) are evidently important for the maintenance of cell growth of cells expressing telomerase, since Chiba et al. found greatly shrunk pool sizes of AdoMet and AdoHcy when HL-60 cells were induced to undergo terminal differentiation [15]. Apparently, abnormal MEs play a critical role on the buildup of cells expressing telomerase, such cells include CSCs, CCs, embryonic stem cells (ESCs) and PSCs.

Evidently, the buildup of ESCs and PSCs is a normal process in the development of fetus and in the process of wound healing. Abnormal MEs do not cause problems in the execution of such normal processes. On the contrary, if the buildup of stem cells is prematurely interrupted by speeding up terminal differentiation, e.g. by the administration of thalidomide, normal development will be affected, resulting in malformation of body parts notably limbs. The nature creates safety mechanisms such as contact inhibition, TET-1 enzyme to direct lineage transitions and chemo-surveillance to prevent unwanted buildup of stem cells with abnormal MEs. Only when such safety mechanisms become dysfunctional or damaged, cells with abnormal MEs evolve to become CSCs and CCs to create clinical symptoms.

PSCs are ESCs to initiate the development of specific organs or tissues. A small fraction, usually less than 2% of the organ or tissue mass is reserved for the future expansion or repair, which requires the proliferation and the terminal differentiation of PSCs [16]. On wound healing, wound triggers biological and immunological responses. The biological response involves the release of arachidonic acid (AA) from membrane bound phosphatidylinositol through phospho-lipase A2 for the synthesis of prostaglandins (PGs) by cyclooxygenases and PG synthases [17, 18].

Although AA and PGs are active DIs [19], which are chemicals capable of eliminating telomerase from abnormal MEs, the induction of terminal differentiation of PSCs at the initial stage of wound is not the primary objective of PGs.

Rather, the localized inflammation caused by PGs [20] is responsible for the increase of membrane permeability to facilitate the extravasation of plasma proteins and regulatory factors into the wound resulting in edema response, which is the primary objective of PGs to orchestrate the

healing process. Chemo-surveillance mediated through DIs and DHIs, which are inhibitors of MEs capable of potentiating the activity of DIs, normally functions as a brake to prevent the buildup of PSCs. This brake must be released in order for PSCs to proliferate to produce enough cells to heal the wound. PGs are metabolically unstable [17]. 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 terminal differentiation of PSCs at the final stage of wound healing is accomplished by DIs and DHIs of chemo-surveillance. The stable end products of PGs, namely dicycloPGs, are also active as DIs, although not as active as PGs [19], which may get involved in the promotion of terminal differentia tion of PSCs at the final stage of wound healing. Destabilization of abnormal MEs through chemo-surveillance is the critical mechanism of wound healing, which dictates the success of wound healing as well as cancer therapy [21, 22]. Consequently, restoration of chemo-surveillance, which is destroyed in order for cancer to show up [23], is a top priority of cancer therapy [24]. The biological response of the wound producing PGs is good for wound healing. The immunological response producing cytokines is not good for wound healing. Tumor necrosis factor (TNF) among cytokines produced is particularly bad for wound healing [25, 26]. On one hand, it causes the apoptosis of stem cells to trigger proliferation of PSCs, and, on the other hand, it causes cachexia symptoms to result in the collapse of chemo-surveillance. The collapse of chemo-surveillance removes the brake to promote the proliferation of PSCs. The expansion of normal stem cells is limited by contact inhibition.

If wound cannot be healed due to the collapse of chemo-surveillance, which the nature does not have a mechanism to rectify, PSCs will be forced to evolve into CSCs in order to escape contact inhibition. It takes a single hit to silence TET-1 enzyme to turn PSCs to become CSCs [27, 28], which is within the reach of PSCs equipped with abnormally active MEs. The propagation of CSCs still cannot heal the wound, because the problem is the collapse of chemo-surveillance. The slow replicating CSCs will be forced to progress to faster growing CCs by chromosomal abnormalities such as translocations to activate oncogenes, or deletions to inactivate suppressor genes.

Evidently, abnormal MEs and chromosomal abnormalities to cause activation of oncogenes or inactivation of suppressor genes are very critical issues of cancer, responsible for perpetual proliferation of CCs which is the most outstanding feature of cancer. Abnormal MEs and the collapse of chemo-surveillance are responsible for the blockade of differentiation, and chromosomal abnormalities are responsible for the promotion of cell replication. Chromosomal abnormalities received a lot of attention. Cancer establishments devoted exclusive attention to develop gene therapy during the 20 years period between 1976-1996 right after the unsuccessful attempt to win the war on cancer declared by President Nixon in 1971 [29]. Entire human genomes were sequenced in a preparation to develop gene therapy. They gave up, because it was simply too difficult and too expensive to develop gene therapy. Additionally, it was not feasible to develop gene therapy due to the difficulty to control chromosomal abnormality consecutively throughout. Abnormal MEs are the most critical issue of cancer [30], which show up in PSCs, the precursors of CSCs, and pass on to CSCs and CCs.

The abnormal MEs are commonly shared by all human cancers [31]. A stroke to eliminate abnormal MEs can also resolve problems attributable to chromosomal abnormalities. After all, oncogenes and suppressor genes are cell cycle regulatory genes. These genes have important roles to play when cells are in cell cycle replication, though if replicating cells exit the cell cycle to undergo terminal differentiation, these genes have no roles to play. It appears that the solution of abnormal MEs can also achieve the effects of gene therapy which is otherwise very difficult to accomplish. Killing of CCs can also resolve issues attributable to abnormal MEs and chromosomal abnormalities. It has been tested, but failed. Abnormal MEs are definitely the bullseye of cancer target [32]. Cancer

establishments were very close to the establishment of cancer therapy to target abnormal MEs. Aberrant tRNA methylation was aggressively pursued during a few years span around 1966, and aberrant DNA methylation was aggressively pursued during a few years span around 1985.

They looked into the wrong directions to analyze methylated nucleic acids. Had they focused the attention on abnormal MEs, cancer would have possibly been solved in these two periods.

II.2 Cancer Evolves as a Consequence of Wound Failed to Heal

In the previous section, we have briefly described the evolution of cancer due to wound unhealing, resulting in the evolution of PSCs to CSCs, and then the progression to faster growing CCs. The concept of cancer evolving due to wound unhealing was first introduced by the great German scientist Virchow in the 19th century [33]. It was again brought up by Dvorak in 1986 [34]. The close relationship between cancer and wound healing was noticed by MacCarthy-Morrough and Martin [35]. We provided the most important details on this subject which included abnormal MEs to promote perpetual replication of CCs [8, 11-13, 31]; chemo-surveillance as the nature's creation of allosteric regulation to ensure perfection of wound healing [21-24]; DIs and DHIs as wound healing metabolites and as active players of chemo-surveillance [21-24]; hypomethylation of nucleic acids as a critical mechanism on the induction of terminal differentiation of cells with abnormal MEs [36]; mechanism of wound healing to involve the proliferation and the terminal differentiation of PSCs [16, 29, 37, 38]; and the evolution of CSCs from PSCs through a single hit to silence TET-1 enzyme [27,28,39]. These studies strongly support the concept that cancer evolves as a consequence of wound failed to heal. Our carcinogenesis studies confirmed the validity of this concept. During the challenges with hepatocarcinogens, we noticed numerous tiny hyperplastic nodules appeared before the appearance of large size carcinomas [40]. These preneoplastic hyperplastic nodules must represent proliferation of PSCs in the process of active wound healing, most of which disappeared shortly afterward, which was an indication of the completion of wound healing. Only the tiny hyperplastic nodules which was not healed later developed to become large size carcinomas. If Antineoplaston A10 was administered during the challenge with potent hepatocarcinogen aflatoxin B_1, the development of carcinomas could be effectively prevented. Antineoplaston A10 is phenylacetylglutamine, which is an effective anti-cachexia chemical to protect the integrity of chemo-surveillance [23]. So, wound healing and cancer are closely related.

Wound healing is a simple matter, which comes naturally without having to put up any effort. Take surgical wound for example, suture and application of antibiotics are subsidiary to speed up and to prevent infection. The nature creates chemo-surveillance and immuno-surveillance to ensure perfection of wound healing. Chemo-surveillance is to heal wounds caused by toxic chemicals including carcinogens or physical means and immuno-surveillance is to heal wounds caused by infectious agents. Chemo-surveillance and immuno-surveillance can be synergistic to heal wounds by eliminating different origins of wounds, but can also be antagonistic. Immunological response tends to trigger the production of cytokines to cause the collapse of chemo-surveillance. immuno-surveillance can hurt chemo-surveillance, but chemo-surveillance cannot hurt immuno-surveillance. White lung observed during COVID-19 infection is the buildup of PSCs in the process of wound healing unable to undergo terminal differentiation because of the collapse of chemo-surveillance following active immuno-logical response to COVID-19 infection.

Wound healing is a simple matter. Likewise, cancer therapy can also be a simple matter, if the therapy follows the process of wound healing. Obviously, the functionality of chemo-surveillance is very critical to dictate the success of wound healing [21-24]. Chemo-surveillance has to be

damaged for cancer to set in. The progress of cancer further contributes to the damage of chemo-surveillance. The progress of cancer invites immunological response that yields TNF to cause cachexia symptoms leading to the damage of chemo-surveillance. Cytotoxic agents and immunologic agents cause the acceleration of the damage to chemo-surveillance. Ineffectiveness against CSCs and the contribution to the damage of chemo-surveillance are the reason cytotoxic chemotherapy failed to win the war on cancer.

Cancer therapy following the process of wound healing displays the feature as pro-wound healing, which is the right indication of cancer therapy because cancer evolves due to wound unhealing.

Cancer therapy mediated through cytotoxic agents and immunological agents display the feature as anti-wound healing, clearly the contra-indication of cancer therapy. A right approach is the magic code to the success of solving tough challenges [42], but a wrong approach cannot solve a simple matter as cancer and supported as a presidential project [43].

II.3 CDA Formulations as Persuasive Good Cancer Drugs

Cytotoxic chemotherapy of cancer was a tragic by product of World War II. During the war toxic 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 chemotherapy became the standard care of cancer, and the disappearance of cancer cells or tumor became the standard criteria for the evaluation of therapeutic efficacy. These were tragic mistakes made at a time when we did not have complete knowledge of cancer.

Chemotherapy and radiotherapy were the major therapeutic modalities employed to combat cancer when President Nixon declared war on cancer in 1971. But this presidential project was not successful [43]. If a treatment modality was drilled through as a presidential project and failed, it was fair to conclude that the treatment modality was not good. Apparently, cancer establishments agreed to such conclusion, and immediately shifted the development of cancer therapies from cytotoxic chemotherapy to gene and targeted therapies during 1976-1996, to anti-angiogenesis during 1996-2016, and then to immunotherapy from 2016 onward [29]. They did not develop acceptable therapy good enough to replace chemotherapy, as the commanding principle was still based on cell killing and the disappearance of tumor. Cytotoxic drugs and radiation remain the dominant cancer drugs to contribute to ever increasing cancer mortality to more than 10 million annual deaths worldwide [5]. Immunotherapy is definitely better than chemotherapy. It is selective against cancer cell surface antigens. Hopefully, it can replace DNA interacting drugs to reduce toxicity. But it still has the same problem of chemotherapy to create damage to chemo-surveillance and to show ineffectiveness against CSCs. The antigenicity of CSCs is exactly the same as that of PSCs, which is tolerable to human immune systems.

A perfect cancer drug must be able to take out both CCs and CSCs, and to restore the functionality of chemo-surveillance [44]. Although CSCs constitute only a small sub-population less than 2% of the mass of most primary cancers, CSCs actually contribute the major fatal effects of cancer. Fatal effects of cancer such as metastasis, recurrence, drug resistance, and angiogenesis are the making of CSCs. Thus, elimination of CSCs is essential to save cancer patients [45]. Cancer drugs put up by cancer establishments cannot access CSCs which are protected by drug resistance and anti-apoptosis mechanisms. These drugs can only benefit early stage cancer patients whose chemo-surveillance has not yet been fatally damaged, relying on the recovery of chemo-surveillance to subdue surviving CSCs. Chemo-surveillance of advanced patients is often badly damaged beyond recovery. CSCs population of advanced patients, particularly the patients undergoing long term chemotherapy, is much higher than early stage patients. Such patients cannot respond to cytotoxic drugs. If still responsive to reach complete remission, these patients are very likely

to recur and become unresponsive to further treatment. CSCs are a dominant issue of metastatic, unresponsive and recurrent cancer patients. CSCs like PSCs are closely linked to wound healing which is a major biological mission of these cells. Induction of terminal differentiation is the only option to eliminate CSCs [45]. Killing cannot solve the problem related to CSCs. Therefore, CDA formulations made up by DIs and DHIs are the best drugs to handle CSCs [39, 45].

Myelodysplastic syndromes (MDS) are unique diseases caused by the propagation of CSCs [46]. These diseases are a show case to demonstrate the evolution of CSCs due to immunological disorder to trigger production of TNF resulting in the collapse of chemo-surveillance [25, 26]. Antibody to TNF can prevent the progression of the disease. Thus, TNF is responsible for the development of MDS. On one hand, it causes excessive apoptosis of bone marrow stem cells, thus severely affect the ability of the patient to produce hematopoietic cells such as erythrocytes, platelets or neutrophils.

On the other hand, it increases vascular permeability to result in excessive excretion of low molecular weight metabolites [47, 48]. DIs and DHIs of wound healing metabolites are among low molecular weight metabolites excreted to result in wound unhealing that forces evolution of CSCs from PSCs. The propagating pathological cells have been identified as human CSCs [46].

Therapy of MDS requires the induction of the terminal differentiation of CSCs to become functional erythrocytes, platelets or neutrophils. Killing of CSCs cannot heal MDS. So far, Vidaza, Decitabine and cell differentiation agent-2 (CDA-2) are the three drugs approved for MDS therapy by the Chinese FDA. CDA-2 is our creation, which was wound healing metabolites purified from freshly collected urine [49]. Vidaza and Decitabine are also approved for MDS therapy by the US FDA. Professor Jun Ma, Director of Harbin Institute of Hematology and Oncology, was instrumental to conduct clinical trials of all three MDS drugs in China. According to his assessments based on two cycles of treatment protocols, each cycle lasting 14 days, CDA-2 had a noticeably better therapeutic efficacy based on cytological evaluation, and a markedly better therapeutic efficacy based on hematological improvement evaluation, which was an evaluation based on the dependence of blood transfusion [50]. All three drugs achieve MDS therapy by inactivation of abnormal MEs, Vidaza and Decitabine by the covalent bond formation between DNA methyltransferase and 5-aza-cytosine base incorporated into DNA to eliminate MT [51], whereas CDA-2 destabilizes abnormal MEs by the elimination of telomerase [12]. The action of CDA-2 is selective on the cancer target of abnormal MEs, whereas the action of Vidaza and Decitabine is non-selective that can also eliminate MT of normal stem cells. CDA-2 is devoid of adverse effects, whereas Vidaza and Decitabine are proven carcinogens [52, 53] and very toxic to DNA [54-56]. CDA-2 is obviously a drug of choice for the therapy of MDS with better therapeutic efficacy and devoid of adverse effects. It appears that CDA-2 is the only drug that can be characterized as a perfect cancer drug. The development of perfect cancer drugs should follow the hints revealed by CDA-2. CDA-2 contains DIs and DHIs as major ingredients to fight cancer. DIs are most like the degradation products of erythrocytes in the forms of liposomal complexes, which we assigned the name as OA-0.79, containing active DIs as fatty acids such as AA, dicycloPGs in association with pregnenolone [57, 58], and membrane fragments, which we assigned the name as PP-0, containing OA-0.79 in association with membrane fragments [57, 58].

Since the profile of plasma peptides and the profile of peptides extracted from the spleen were similar, we believed that plasma peptides were the degradative products of erythrocytes since the spleen was the organ known to process dead erythrocytes [59]. Uroerythrin is an important active DHI component of CDA-2 [49], which is definitely a degradation product of heme from hemoglobins. So, we believe catabolism of erythrocytes is an important source of active components of chemo-surveillance. Steroid metabolites are other important DHIs of CDA-2,

which must come from organs involved in steroid metabolism. Human body produces important metabolites to heal wound, which are also the best cancer drugs, showing effectiveness and without adverse effects as demonstrated by the therapy of MDS with CDA-2 above described.

II.4 Development of CDA Formulations to Save Cancer Patients

Cancer evolves due to wound unhealing. Accordingly, the wound healing process provides the most appropriate modality of cancer therapy [60]. Indeed, wound healing process is the best strategy to cure cancer patients [61]. Cancer establishments may not be concerned with how many cancer patients die [6]. They think cancer patients are bound to die if untreated, they are happy to extent cancer patients' life a few years if the tumor disappear. Cancer establishments are focused on how to eradicate tumor to extent patients' life. The drugs used in therapies to eradicate tumor are also the drugs to kill cancer patients. Therefore, cancer mortalities continue to increase. It takes authorities above cancer establishments to save cancer patients. We rely on the Royal Family's supreme authorities to rectify cancer therapies to save cancer patients. CDA formulations are the only drugs that can take care of CSCs because induction of terminal differentiation of CSCs is the only option to solve CSCs [39, 44, 58, 62]. Vidaza and Decitabine can also solve CSCs, but these two drugs have to be incorporated into DNA to be effective [51]. They also damage DNA of normal stem cells to create destruction. Cancer establishments choose to continue to use drugs that damage the DNA of cancer cells to kill cancer cells, but these drugs also kill normal stem cells resulting in the death of cancer patients. Cancer establishments are the bosses. It takes authorities higher than the bosses of health profession to rectify the mistakes of bosses of health profession. The mistakes of cancer establishments are very likely to create damages to royal family's cancer. They have the authority to rectify damaging therapies. The right therapy of cancer is to eliminate CSCs by CDA formulations, which is tightly linked to wound healing. The elimination of CCs can be done by CDA formulations or cell killings, which is not so closely linked to wound healing. CDA formulations have an issue of residual tumor to deal with, albeit a harmless issue. If it is a worry concern, surgical removal of the residual tumor mass can solve the concern without having to worry on cancer metastasis because patients have the chemo-surveillance restored to prevent that from happening. Cell killings have adverse effects to deal with, which are often fatal, such as unresponsiveness and recurrence. Obviously, CDA formulations have the advantage over cell killings to save cancer patients.

We have carried out extensive studies of natural and unnatural DIs and DHIs for the establishment of CDA formulations for cancer therapy [19, 49, 57, 58, 63-68]. Our findings of effective DIs and DHIs are summarized in Table 1 and 2. On effective DIs, ATRA is the standard therapeutic drug of acute promyelocytic leukemia [69]. It requires the expression of the receptor of ATRA, namely RAR, to activate oligoisoadenylate synthetase to produce oligoisoadenylate as DI to achieve the therapeutic effect [70]. Other DIs listed in Table 1 work directly on abnormal MEs.

AA and its metabolites PG derivatives are natural DIs involved in chemo-surveillance. PG derivatives are approved drugs for the delivery. BIBR-1532 and boldine are approved cancer drugs as telomerase inhibitors. Development of CDA formulations is an application of new drugs which may take more than 10 years of clinical trial to get approval to save cancer patients. Change of indication does not take as long as new drug to the rescue of cancer patients. There are many approved drugs as DIs and DHIs, which can be used to establish CDA formulations right away to save cancer patients.

Table 1: Effective DIs

DIs	ED_{25} (μM)	ED_{50} (μM)	ED_{75} (μM)
ATRA	0.18	0.36	0.75
PGJ2	7.9	13.8	20.5
PGE2	20.6	32.0	46.5
AA	21.0	42.0	-
Dicyclo-PGE2	21.0	43.5	-
BIBR1532	32.3	43.7	55.1
Boldine	80.1	78.7	94.2

Table 2: Effective DHIs

SAHH Inhibitors	$RI_{0.5}$ (μM)
Pyrvinium Pamoate	0.012
Vitamin D_3	0.61
Dexamethasone	0.75
Beta-sitosterol	1.72
Dihydroepiandrosterone	1.79
Prenisolone	2.22
HYdrocortisone	4.59
Pregnenolone	7.16
MT Inhibitors	**$RI_{0.5}$ (μM)**
Uroerythrin	1.9
Hycanthone	2.1
Riboflavin	2.9
MAT Inhibitors	**$RI_{0.5}$ (μM)**
Indol Acetic Acid	220
Phenylacetylvaline	500
Phenylacetylleucine	780
Butyric Acid	850
Phenybutyric Acid	970

Signal Transduction Inhibitors	$RI_{0.5}$ (μM)
Sutent	0.28
Berberine	1.62
Votrient	10.1
Gleevec	11.9
Selenite	19.7
Polyphenols	**$RI_{0.5}$ (μM)**
Tannic Acid	0.37
EGCG	0.62
Resveratrol	1.16
Curcumin	1.24
Kuromanin	1.43
Coumestrol	1.95
Genisteine	2.16
Pterostilbene	2.19
Pyrogallol	3.18
Silibinin	3.80
Caffeic Acid	3.87
Ellagic Acid	4.45
Gallic Acid	5.35

As shown in Table 2, SAHH inhibitors and MT inhibitors are better DHIs than MAT inhibitors.

MAT happens to be the largest molecule of MEs and the most stable enzyme of the three MEs. The association with telomerase further increases its stability. Therefore, it is relatively difficult to shake loose of this enzyme to help terminal differentiation of cells with abnormal MEs to achieve wound healing or cancer therapy. Signal transduction inhibitors as good DHIs are expected, since signal transductions tend to produce products to stimulate growth.

Polyphenols as good DHIs are a surprise, but is a good surprise. Polyphenols are regarded as good chemicals to maintain health, and promoted as healthy food. The activity of polyphenols as effective DHIs endorses the claim of polyphenols as healthy food. The breakdown of chemo-surveillance is due to the loss of DIs and DHIs the body produced. Supplement of effective DIs and DHIs is a good measure to restore the functionality of chemo-surveillance.

Pregnenolone is a major DHI of CDA-2 [58]. Apparently, pregnenolone is a major player of chemo-surveillance. It is the master substrate of

steroid metabolites to have a great influence on growth regulation. The production of pregnenolone is bell shape in relation to ages with a peak daily production of around 50 mg at 20-25 years old [71]. The younger and the older people produce relatively little amount of pregnenolone, and these are two age groups most vulnerable to develop cancer. Pregnenolone is a single metabolite to greatly influence the evolution of cancer. It is our top choice of DHI to make CDA formulations.

Effective CDA formulations are made up by DIs and DHIs [19, 49, 57, 58, 63-68]. Effective CDA formulations can be ED_{25} of a DI + 3x $RI_{0.5}$ of a DHI, or ED_{50} of a DI + 2x $RI_{0.5}$ of a DHI, or ED_{75} of a DI + $RI_{0.5}$ of a DHI [58]. In the design of CDA formulations, we must take into consideration of non-cancer issues such as blood brain barrier of brain cancer, collagen envelop of pancreatic cancer and hypoxia of melanoma to select DIs and DHIs to overcome non-cancer issues. A lot of work remains to be done.

III. CONCLUSION

Cancer evolves due to wound unhealing. Pro-wound healing is the right approach of cancer therapy. Cancer establishments prefer anti-wound healing approach of cancer therapy to result in horrendous cancer mortality. Cancer establishments are obviously wrong to handle cancer issue. It takes authority higher than cancer establishments to rectify the mistake of cancer establishments. Recent cancer diagnoses of English royal family members, while a misfortune no body wishes to happen, offer a supreme authority to rectify cancer therapies to save cancer patients. CDA formulations are the correct solution of cancer.

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Conflict of Interest

The authors declare no conflict of interest.

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