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Winning Formulas to Fulfill Cancer Moonshot

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ABSTRACT

The objective of this study was to develop winning formulas to fulfill cancer moonshot declared by President Biden on Sept. 12, 2022, the 60th anniversary of the moonshot speech of President Kennedy. The intention of President Biden was to use the spirit of successful moonshot project to salvage the failure of war on cancer project declared by President Nixon in 1971 [1]. Cancer therapies based on killing of cancer cells were the choice of cancer establishments in the past. The choice of killing cancer cells is understandable because the perpetual replication of cancer cells constitutes the most outstanding feature of cancer. Cancer is contributed by multiple factors. Factors other than replication of cancer cells also play essential roles on the development of cancer. Cancer arises as a consequence of wound not healing properly due to the collapse of chemo-surveillance, thus allowing Progenitor Stem Cells (PSCs) to evolve into Cancer Stem Cells (CSCs), and then to progress to faster growing Cancer Cells (CCs) through activation of oncogenes and/or inactivation suppressor genes. Cell killing creates more wounds to aggravate the already bad situation on the functionality of chemo-surveillance, which is an important mechanism to suppress the build-up of cells with abnormal Methylation Enzymes (MEs) that include PSCs, CSCs, and CCs. PSCs and their immediate derivatives CSCs are protected by drug resistant and anti-apoptosis mechanisms. Cytotoxic agents can wipe out CCs but cannot affect CSCs. The damage to chemo-surveillance contributed by cell killing agents allows CSCs to become dominant cells to cause he failure of cancer therapy, thus losing the war on cancer.

Cell Differentiation Agent (CDA) formulations are the preparations consisting of Differentiation Inducers (DIs) and Differentiation Helper Inducers (DHIs), plus phenylacetylglutamine as an anti-cachexia agent. Such preparations are perfect cancer drugs to take out both CCs and CSCs by the induction of terminal differentiation through destabilization of abnormal MEs, and to restore the functionality of chemo-surveillance. Cancer therapies mediated by CDA formulations are the nature's choice to combat cancer that can fulfill the goal of President Biden's cancer moonshot. CDA formulations, however, cannot make the tumor to disappear, which can be easily accomplished by therapies based on cell killing.

President Biden's goal is very modest, requiring reduction of cancer mortality 50% in 25 years. That goal can be easily accomplished by winning formulas that include CDA formulations and therapies to eliminate or to kill CCs. We offer the following winning formulas:

1. *Therapy with CDA-CSC, a preparation made up by an approved DI and an approved DHI, to eradicate CSCs and CCs by the induction of terminal differentiation and to restore the functionality of chemo-surveillance, followed by the surgical removal of the residual tumor.*
2. *Surgical removal of the primary tumor, followed by the administration of CDA-CSC to prevent recurrence and metastasis, and to restore the functionality of chemo-surveillance.*
3. *Radiotherapy, immunotherapy, or chemotherapy to kill CCs, followed by the administration of CDA-CSC to eradicate CSCs and to restore the functionality of chemo-surveillance.*

Keywords
Cancer moonshot, CDA, Chemo-surveillance, Differentiation inducers, Differentiation helper inducers, Wound healing.

Introduction
President Biden declared cancer moonshot initiative on Sept. 12, 2022, the 60th anniversary of the moonshot speech of President Kennedy. The intention of President Biden was to use the spirit of successful moonshot to salvage the failure of the war on cancer project declared by President Nixon in 1971 [1]. President Biden had a strong motivation to defeat cancer because he lost his very accomplished son Veau to malignant brain tumor. This is a golden opportunity for the health profession to make-up for the previous failed attempt of war on cancer. The moon shot and the war on cancer were two entirely different presidential projects. The moonshot project succeeded, but the war on cancer project failed. Technologically, the moonshot project was far more difficult than the war on cancer project. It is time to reflect why technologically far more difficult moonshot project succeeded, whereas technologically not so difficult war on cancer project failed. The message of President Biden was very clear that the health profession must succeed in the following 25 years to find solutions for 50% cancer patients to stay alive. We offer a cell differentiation agent (CDA) formulation to supplement surgery or therapies based on cell killing as winning formulas to fulfill President Biden's cancer moonshot.

Commentaries and Discussions
Wound Healing as a Critical Issue of Cancer
Cancer and wound healing are closely related. The concept of cancer as a non-healing wound was first introduced by the great German scientist Virchow in the 19th century [2]. It was again brought up by Dvorak in 1986 [3]. The close relationship between cancer and wound healing was noticed by MacCarthy-Morrough and Martin [4]. We provided the most important details on this subject that included abnormal MEs to block differentiation [5-7]; chemo-surveillance as a natural mechanism to ensure perfection of wound healing to avoid cancer [8-11]; DIs and DHIs as the wound healing metabolites and also as the active players of chemo-Surveillance [9-11]; hypomethylation of nucleic acids as the most critical mechanism to achieve terminal differentiation of cells with abnormal MEs [12]; the mechanism of wound healing [13-15]; and the evolution of CSCs from PSCs [16]. Our studies clearly established that cancer arose as a consequence of wound not healing properly due to the collapse of chemo-surveillance, thus allowing PSCs to evolve into CSCs, and then to progress to faster growing CCs through activation of oncogenes and/or inactivation of suppressor genes. The occurrence of human cancer fits this progressing pattern. Wound triggers the patient to produce biological and immunological responses. The biological response involves the release of arachidonic acid from membrane bound phosphatidylinositol for the synthesis of prostaglandins [17], which promote the proliferation of PSCs [13]. Efficient induction of the terminal differentiation of PSCs is required to complete wound healing, which is accomplished by wound healing metabolites active as DIs and DHIs. DIs are chemicals capable of eliminating telomerase from abnormal MEs and DHIs are inhibitors of MEs that can greatly potentiate the activity of DIs. The mixtures of DIs and DHIs are collectively named CDAs. Arachidonic acid and its metabolites are active as DIs [18,19]. They are good for wound healing. The immunological response prompts the patient to produce tumor necrosis factor, which is also named cachectin after its effect to cause cachexia symptoms. A manifestation of cachexia symptoms is the excessive excretion of low molecular weight metabolites. DIs and DHIs are among such metabolites excreted. By causing the loss of DIs and DHIs, tumor necrosis factor is bad for wound healing. In general, acute wound usually benefits wound healing and chronic wound hurts wound healing. Chemo-surveillance plays a pivotal role to protect healthy people from becoming cancer patients. Chemo-surveillance is the creation of the nature to benefit human being, It is as important as immuno-surveillance. It ensures perfection of wound healing to avoid diseases arising due to the failure to heal wound that include dementia, tissue fibrosis and cancer [20,21]. It is very convincing that the protection of the functionality of chemo-surveillance is extremely important to dictate the success of wound healing and cancer therapy [10].

Cancer Therapies Based On the Destabilization of Abnormal MEs
Induction of the terminal differentiation of PSCs is a critical mechanism of wound healing [13], which is accomplished by DIs and DHIs to destabilize abnormal MEs [12]. Cancer therapies based on the destabilization of abnormal MEs display the features as pro-wound healing and the right indication of cancer therapy. These are the nature's choice of cancer therapies that include differentiation therapy, hormone therapy, and targeted therapy. The therapeutic endpoint of pro-wound healing is the terminal differentiation of cancer cells. The tumor will not disappear. However, it will stop increase in size. Cancer establishments setup the disappearance of tumor as a criterion of effectiveness on cancer therapy. These therapies were excluded as alternative therapies.

MEs play a critical role on the regulation of cell replication, differentiation and apoptosis by virtue of the fact that DNA MEs control the expression of tissue specific genes [22], and pre-rRNA MEs control the production of ribosome [23], which in turn dictates the commitment of cells to initiate replication [24]. If enhanced production of ribosome is locked in place, it becomes a factor to drive carcinogenesis [25]. Biological methylation is mediated by a ternary enzyme complex consisting of Methionine AdenosylTransferase (MAT)-MethylTransferase (MT)-S-Adenosyl- Homocysteine Hydrolase (SAHH) [26,27]. SAHH is the target for the regulation of MEs' stability and activity in normal cells. MEs become associated with telomerase in the cells expressing telomerase. The association with telomerase changes the kinetic properties and the regulatory mechanisms of MEs. The Km values of the telomerase associated MAT-SAHH isozyme pair are 7-fold higher than the Km values of the normal isozyme pair. The increased Km values offer greater stability and activity of the abnormal MEs. It has been shown by Prudova et al. that S-AdenosylMethionine (AdoMet) could protect protein against

protease digestion [28]. The increased Km vakues of the tumor MEs mean tumor has increased pool sizes of S-adenosylmethionine and S-AdenosylHomocysteine (AdoHcy) which are obviously needed to maintain malignant growth. Chiba et al. showed that the induction of terminal differentiation of HL-60 cells resulted in great shrinkage of the pool sizes of AdoMet and AdoHcy [29]. These studies support our findings of abnormal MEs as a very important issue of cancer. Consequently, abnormal MEs are a good target for cancer therapy [30]. One may argue that abnormal MEs cannot be considered as a cancer target since normal stem cells such as PSCs and embryonic stem cells also express abnormal MEs. The silencing of the TET-1 enzyme, which is expressed in normal stem cells to undergo lineage transitions, qualifies abnormal MEs as a selective cancer target. By inducing terminal differentiation, the cancer therapies based on destabilization of abnormal MEs can also put to rest the issues of oncogenes and suppressor genes. Oncogenes and suppressor genes are cell cycle regulatory genes. They have important roles to play when cells are in cell cycle replicating. But if cells exit cell cycle to undergo terminal differentiation, they have no role to play. Therefore, induction of terminal differentiation is an easy solution of gene abnormalities, which are otherwise very difficult to solve. Killing cancer cells is another easy way to solve difficult problems of gene abnormalities. That has been put to test and failed. Untested destabilization of abnormal MEs is a good option to assume the duty to fulfill cancer moonshot.

Cancer Therpies Based on Cell Killing

Perpetual replication of CCs is the most outstanding feature of cancer. Naturally, killing of CCs became the choice of cancer establishments to combat cancer. These therapies, however, failed the challenge to win the war on cancer [1], and fared poorly to save lives of cancer patients [31,32]. The contribution of these therapies to damage chemo-surveillance and the ineffectiveness of these therapies against CSCs are responsible for the failure to win the war on cancer and to save the lives of cancer patients. So even the patient is lucky to achieve complete remission, such lucky patient is eventually loss to inevitable recurrence.

The deleterious effects of cell killing can be remedied by CDA formulations. A combination of therapies based on cell killing and CDA formulations may be winning formulas of cancer moonshot, relying on cell killing strategy to eliminate tumor, and destabilization abnormal MEs strategy to eliminate CSCs and to restore the functionality of chemo-surveillance.

Winning Formulas to Fulfill Cancer Moonshot

Curing cancer can be as easy as healing wound, done without having to put up any effort [13-15]. To cure cancer definitely we have to put up some efforts, efforts such as CDA formulations, because the functionality of chemo-surveillance of cancer patients has been damaged for the symptoms of cancer to show up. CDA formulations made up by DIs and DHIs are very appropriate drugs for the treatment of cancer. DIs and DHIs are excellent cancer drugs. All trans retinoic acid, a DI, is the standard care of acute promyelocytic leukemia. Imatinib mesylate, a DHI, is the standard care of chronic myeloid leukemia. Phenylbutyrate, the first DHI of our discovery which was only moderately active [33], has been dexterously employed by Burzynski to cure malignant brain cancer [34,35]. Malignant brain tumors are untreatable by therapies based on cell killing because these tumors are enriched with CSCs [36]. President Biden lost his very accomplished son Beau, and the US senate lost very distinguished senators Kennedy and McCain to malignant brain tumors. Surprisingly untreatable malignant brain tumors respond well to inconspicuous phenylbutyrate, which is only a moderately active DHI. The brain compartment is full of lipid materials. It may have fatty acids with functions similar to arachidonic acid, which is a moderately active DI [19]. Therefore, a moderately active DHI can have remarkable therapeutic effect to cure untreatable malignant brain tumors. The eradication of CSCs is essential for the success of cancer therapy [16,18,37-40]. We are in a unique position to have the ability to eradicate CSCs. This position gives us the edge to fulfill cancer moonshot.

We have carried out extensive studies on DIs and DHIs, and reported our findings of excellent DIs and DHIs [18-20,33,37-41]. We will use the formula [37] previously described to establish effective CDA formulations to fulfill cancer moonshot. The establishment of effective CDA formulations is based on the evaluation of chemical and metabolic stabilities of DIs and DHIs, and the effectiveness to induce differentiation of HL-60 cells. Toxicities of DIs and DHIs are of course an important consideration. FDA must approve a newly created CDA formulation after clinical trial, which takes time. For immediate application, we can pick already approved DIs and DHIs to create CDA formulations.

The functionality of chemo-surveillance plays an important role to dictate the success of wound healing and cancer therapy [10]. The damage to the functionality of chemo-surveillance is caused by tumor necrosis factor to induce membrane hyperpermeability [13], which can be effectively antagonized byphenylacetylglutamine [8]. By protecting the functionality of chemo-surveillance, phenylacetylglutamine is strikingly effective to prevent hepatocarcinogenesis induced by potent hepatocarcinogen aflatoxin B1 [42] and to show effectiveness on the therapy of early stage cancer [8]. Phenylacetylglutamine can be administered as a capsule preparation independently from CDA formulation, and the effect to protect the functionality of chemo-surveillance can be monitored independently by the quantitative assay of plasma and urinary peptides [8].

The therapeutic endpoint of CDA formulations is the terminal differentiation of CCs and CSCs. For the therapy of hematological cancers, the disappearance of CCs for the assessment of therapies based on cell killing is applicable to CDA formulations. However, the disappearance of tumor on the therapy of solid tumors is inappropriate. We have to set up different criteria for the evaluation of therapeutic efficacy of CDA formulations. Disappearance of cancer markers, or disappearance of circulation CSCs are appropriate criteria for the evaluation of therapeutic efficacy of CDA formulations.

Cancer establishments set up the rule that the disappearance of

tumor is the ultimate judgement of the effectiveness of cancer therapy. We have to abide by the rule; even it is not a correct rule on the therapies not based on cell killing. A compromise is a combination of the right indication based on the destabilization of abnormal methylation enzymes and the contra-indication based on cell killing. The combinations may be the winning formulas to achieve the perfect therapy of cancer to take out both CCs, CSCs, and to restore the functionality of chemo-surveillance.

Conclusion

Cancer moonshot was the second challenge to the health profession to solve cancer declared by President Biden recently. Cancer establishments failed the first challenge of war on cancer declared by President Nixon half a century ago. Cancer therapies based on cell killing were the choice of cancer establishments to combat cancer in the past. These therapies are difficult to cure cancer because cancer is caused by wounds not healing properly. Creation of more wounds is contra-indication. The contribution to the damage of chemo-surveillance and the inability to eradicate CSCs are responsible for the failure of therapies based on cell killing to put cancer away.

Therapies based on the destabilization of abnormal methylation enzymes are a better solution of cancer, which display the features as pro-wound healing and the right indication of cancer therapy. CDA formulations are the perfect cancer drugs made up by DIs and DHIs to eliminate CCs and CSCs through induction of terminal differentiation. The supplementation of phenylacetylglutamine is helpful to restore the damaged chemo-surveillance. We offer the following winning formulas to fulfill cancer moonshot:

- Therapy with CDA-CSC, a preparation made up by an approved DI and an approved DHI, to eradicate CSCs and CCs by induction of terminal differentiation and to restore the functionality of chemo-surveillance, followed by surgical removal of the residual tumor.
- Surgical removal of the primary tumor, followed by the administration of CDA-CSC to prevent recurrence and metastasis, and to restore the functionality of chemo-surveillance.
- Radiotherapy, immunotherapy, or chemotherapy to kill CCs, followed by the administration of CDA-CSC to eradicate CSCs and to restore the functionality of chemo-Surveillance.

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