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Cancer Moonshot: Moonshot as a Magic Code to Guide Successful Solutions of Tough Challenges Such as Cancer

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ABSTRACT

Presidential projects deal with monumentally important issues. Moonshot and war on cancer were two unrelated presidential projects: the moonshot project was successful, but the war on cancer project was unsuccessful. President Biden brought up these two presidential projects on Sept. 12, 2022 apparently with an intention to urge the health profession to learn from the success of moonshot to come up solutions to save 50% of cancer patients in the following 25 years. The goal of cancer moonshot was modest. The health profession, however, must make a drastic change on the approach of cancer therapy to fulfill cancer moonshot.

Moonshot was an extremely difficult challenge. So far, the USA was the only nation able to achieve this difficult challenge. Evidently, the right approach to a difficult challenge was the magic code to the success of moonshot. On the other hand, a wrong approach to a simple matter might result in making simple problem unsolvable. Apparently, war on cancer was such a case. Cytotoxic chemotherapy and radiotherapy based on the killing of cancer cells were the choice of cancer establishments to wage the war on cancer. The approach was wrong, because cancer was a disease due to wound unhealing. Creating more wounds definitely was a wrong approach. The war on cancer was loomed to fail on the day of its declaration. The wrong approach continued to dominate cancer therapies with no hope in sight to successfully saving cancer patients. Cancer moonshot was in essence a protest of the failure to save cancer patients from the highest government official to the health profession.

A change of approach on cancer therapy is obviously needed to save cancer patients. Since cancer is caused by wound unhealing. Wound healing process is the most appropriate modality of cancer therapy. Wound healing comes naturally, because the nature creates chemo-surveillance to ensure perfection of wound healing. Wound healing requires the proliferation and the terminal differentiation of progenitor stem cells (PSCs). The success of wound healing depends on the efficient differentiation of PSCs to eliminate the symptom created by the wound. Chemo-surveillance plays such an important role to dictate the success of wound healing. Chemo-surveillance can be damaged under pathological conditions to produce tumor necrosis factor (TNF) to cause cachexia symptoms. Inability of PSCs to undergo terminal differentiation due to the collapse of chemo-surveillance then forces PSCs to evolve into cancer stem cells (CSCs) and then to progress to faster growing cancer cells (CCs). Obviously, cancer arises due to the collapse of chemo-surveillance. Restoration of chemo-surveillance with CDA formulations is, therefore, the right approach of cancer therapy. The wisdom of the nature beats the wisdom of cancer establishments on the issue of cancer.

Keywords

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

Introduction

Moonshot was a presidential project initiated by President Kennedy in 1962 to send an astronaut to the moon and back to the earth. War on cancer was a presidential project initiated by

President Nixon in 1971 to put cancer away [1]. A presidential project carries a 5 years limit to conclude with unlimited support of national resources. The Moonshot project was successful, but the war on cancer project was unsuccessful. Cancer moonshot initiative was brought up by President Biden on Sept 12, 2022, the 60th anniversary of moonshot speech of President Kennedy, apparently with an intention to urge the health profession to learn the success of moonshot to come up solutions to save 50% of cancer patients in the following 25 years. The goal of cancer moonshot was modest. The health profession, however, must make a drastic change of approach on cancer therapy to fulfill this modest goal, since it has failed miserably in the past on approaches based on killing of CCs to save cancer patients [2].

Commentaries and Discussions

Lessons to Learn from the Success of Moonshot

The moonshot project was an extremely difficult challenge. So far, the USA was the only nation able to achieve this difficult challenge. It required powerful rocket to boost a space craft from the earth to the moon, and from the moon back to the earth, a space craft tough enough to resist the friction during the flight between the earth and the moon, safe landing mechanisms onto the moon and back to the earth, and the life support in an environment unfit for astronaut to stay alive. In other words, it required a right approach to accomplish an extremely difficult challenge. A right approach to the difficult challenge is the magic code to the success of solving difficult challenge.

Lessons to Learn from the Failure of War on Cancer

Perpetual replication of cancer cells is the most outstanding feature of cancer. Naturally, killing of cancer cells becomes the choice of cancer establishments to combat cancer. Cytotoxic chemotherapy and radiotherapy were the choice of cancer establishments when the war on cancer was declared in 1971, although other therapies such as gene therapy, targeted therapy, differentiation therapy, and hormonal therapy were also available at that time. Disappearance of cancer cells or tumor became the standard criteria for the evaluation of cancer therapy. Cytotoxic agents including radiation were good to kill cancer cells and to cause the tumor to shrink, but were not good to save cancer patients [3]. Rocket was obviously the most important element in the success of moonshot. However, rocket alone could not accomplish the mission of moonshot. Landing mechanisms and life support also played important roles. Cancer establishments neglected to take into consideration of other issues that also played important roles on the development of cancer to end up failing to save cancer patients. Cancer is caused by multiple factors: wound, cachexia, membrane permeability, chemo-surveillance, evolution of CSCs from PSCs, and the activation of oncogenes and/or inactivation of suppressor genes all play important roles on the development of cancer [4]. A right approach of cancer therapy must take care of all these factors involved. The failure to reduce cancer mortality was a fair indication that killing of cancer cells alone was not good enough to accomplish the mission to win the war on cancer.

After the failure to win the war on cancer, the emphasis of cancer therapy was shifted from cytotoxic agents to gene and targeted therapies during 1976-1996, and to anti-angiogenesis therapy during 1996-2016, and now to immunotherapy from 2016 [5]. During the emphasis on gene therapy, the entire human genomes were sequenced in a preparation to develop gene therapy. The plan did not materialize, simply because it was too difficult and too expansive to develop drugs for gene therapy. Targeted therapy was a right approach. It did produce many excellent cancer drugs, which were primarily used for the therapy of hematological cancers. Targeted therapeutic agents are excellent DHIs [6]. The therapeutic end point of DHIs ia the terminal differentiation of cancer cells. The tumor will not disappear. These excellent cancer drugs were not used for the treatment of solid tumors because they could not compete with cytotoxic drugs to cause the tumor to disappear. The disappearance of tumor was a darn mistake of cancer establishments to block the development of good cancer drugs not based on the killing of cancer cells. Cancer establishments were trapped in the unwinnable killing of cancer cells and the disappearance of tumor to combat cancer. They did not seem to learn the lessons from the failure of the war on cancer.

Cancer Arises as a Consequence of Wound not Healing Properly

Wound healing and cancer evolution are closely related to involve PSCs as the critical common elements. The concept of cancer as unhealing wound was first introduced by the great German scientist Virchow in the 19th century [7]. It was again brought up by Dvorak in 1986 [8]. The close relationship between cancer and wound healing was noticed by MacCarthy-Morrough and Martin [9]. We provided the most important details on this subject that included abnormal methylation enzymes (MEs) to block differentiation [10-12]; chemo-surveillance as a natural mechanism to ensure perfection of wound healing to avoid cancer [13-16]; differentiation inducers (DIs), which are chemicals capable of eliminating telomerase from abnormal MEs, and differentiation helper inducers (DHIs), which are inhibitors of MEs, as the wound healing metabolites and also as the active players of chemo-surveillance [14-16]; hypomethylation of nucleic acids as the most critical mechanism to achieve terminal differentiation of cells with abnormal MEs [17]; the mechanism of wound healing to involve the proliferation and the terminal differentiation of PSCs [18-20]; and the evolution of CSCs from PSCs due to wound unhealing [21-23]. Our studies clearly establish that wound healing is a very important health issue, so that the nature creates chemo-surveillance to ensure perfection of wound healing to avoid bad consequences such as tissue fibrosis, dementia, and the worst cancer [5,20,24]. Wound causes the patient to produce biological response and immunological response. The biological response involves the release of arachidonic acid from membrane bound phosphatidylinositol for the synthesis of prostaglandins (PGs) [25]. PGs are excellent DIs [26], but they are also excellent inflammatory agents. They are unstable metabolites produced at the early stage of wound, so that the function of PGs is believed to trigger local inflammation for the release of regulatory inhibitors from inside of PSCs in order for PSCs to proliferate to repair the wound. Healthy people produce enough wound healing metabolites to prevent the build up of PSCs. But under the pathological condition of wound, it

is necessary to release inhibitory wound healing metabolites for the proliferation of PSCs. PGs produced at the early stage of wound function to promote the proliferation of PSCs. At the final stage of wound healing, the promotion of terminal differentiation of PSCs relies on stable wound healing metabolites, which dictate the effectiveness of wound healing [15,16,18-20]. Cell differentiation agents (CDAs) are terms to include wound healing metabolites active as DIs and DHIs. Healthy people can maintain CDA with a score of 5 [5], only 2% of cancer patients can manage to show this high score [13]. Evidently, the collapse of chemo-surveillance is necessary for cancer to emerge, and the progression of cancer further causes chemo-surveillance to deteriorate.

The immunological response triggered by the wound prompts the patient to produce cytokines. TNF among such cytokines is particularly damaging to chemo-surveillance. TNF has another name as cachectin after its effect to cause cachexia. A manifestation of cachexia is the excessive urinary excretion of low molecular weight metabolites because of membrane hyperpermeability induced by TNF [27,28]. Wound heading metabolites are among such low molecular weight metabolites excreted resulting in the collapse of chemo-surveillance to affect the efficient induction of terminal differentiation of PSCs. The symptom created by the wound, e.g. anemia of myelodysplastic syndrome (MDS) or white lung of COVID-19, then forces PSCs to keep on dividing. PSCs are after all normal stem cells. The proliferation of normal stem cells is limited by contact inhibition. They are then forced to evolve into CSCs through a single hit to silence TET-1 enzyme in order to escape contact inhibition [21-23], and then to progress to faster growing CCs by the activation of oncogenes and/or inactivation of suppressor genes. So, the evolution of CSCs and the progression of CSCs to faster growing CCs are caused by the collapse of chemo-surveillance to efficiently induce PSCs to undergo terminal differentiation in order to eliminate the symptom caused by the wound. It is obvious, the right approach of cancer therapy should be the efficient differentiation of PSCs, CSCs, and CCs to eliminate the symptom caused by the wound. Destabilization of abnormal MEs is, therefore, the most appropriate modality of cancer therapy [4,5,14,16-19,21,29-31]. Cancer therapy based on destabilization of abnormal MEs displays the features as pro-wound healing and the right indication of cancer therapy, whereas cancer therapies based on killing of CCs display the features exactly opposite as anti-wound healing and contra-indication of cancer therapy, which are not the right approach of cancer therapy.

Abnormal MEs as the Bullseye of Cancer Target

Targeted therapies are a better choice, because they offer selectivity to avoid adverse effects. Abnormal MEs are due to the association of telomerase with MEs [12]. MEs are a ternary enzyme complex consisting of methionine adenosyltransferase (MAT)-methyltrasferase(MT)-S-adenosylhomocysteine hydrolase (SAHH) [32]. The association with telomerase changes the kinetic properties and the regulation of MEs. The Km values of the telomerase associated isozyme pair MAT-SAHH are 7-fold higher than the normal isozyme pair. The increased Km values is important for the cancer enzymes to have greater stability and cancer cells to display larger pool sizes needed to carry on malignant growth. It has been shown by Prudova et al. [33] that the association with S-adenosylmethionine (AdoMet) protects the protein against protease digestion. Chiva et al. [34] showed that the induction of terminal differentiation of HL-60 cells resulted in great shrinkage of the pool sizes of AdoMet and S-adenosylhomocysteine (AdoHcy). Thus, abnormal MEs play an essential role to promote malignant growth. Consequently, they are a good cancer target for cancer therapy. One may argue that abnormal MEs cannot be considered as specific cancer target since normal stem cells such as PSCs and embryonic stem cells have the same abnormal MEs. The silencing of TET-1 enzyme qualifies abnormal MEs as a specific cancer target [21-23]. Differentiation of primitive stem cells is blocked like cancer cells. However, they are still able to carry on lineage transitions by means of TET-1. The silencing of TET-1 totally eliminate the capability of cancer cells to undergo differentiation. CSCs and CCs can only keep on dividing when the functionality of chemo-surveillance is damaged. Destabilization of abnormal MEs is, therefore, a good approach of cancer therapy. Evidently, this is the critical mechanism to achieve induction of terminal differentiation of PSCs and CSCs, which are protected by drug resistance and anti-apoptosis mechanisms. CSCs are a very difficult problem of cancer. Metastasis, recurrence, drug resistance, and angiogenesis that contribute to treatment failures can all be attributed to CSCs. Cytotoxic agents and radiation cannot affect these cells. The antigenicity of these cells is the same as PSCs. PSCs are tolerable to human immune systems. Therefore, immunotherapy is unlikely able to get rid of these cells. Wound healing metabolites are the natural partners of their biological function to repair the wound. Therefore, wound healing metabolites are the best medicines to eliminate CSCs.

One more advantage of destabilization of abnormal MEs is to put away problems caused by chromosome abnormalities. These are the objective of gene therapy very difficult to achieve. Oncogenes and suppressor genes are cell cycle regulatory genes, which have important roles to play when cells are in cell cycle replicating. However, when cells exist cell cycle to undergo terminal differentiation, these genes have no roles to play. Thus, induction of terminal differentiation is a simple way to achieve gene therapy, which is otherwise very difficult to accomplish. Thus, destabilization of abnormal MEs is an excellent modality of cancer therapy, which is also effective to eliminate very difficult problems attributable to CSCs and gene abnormalities.

Therapeutic end of the destabilization of abnormal MEs is the terminal differentiation of CSCs and CCs. The tumor will not disappear. The residual tumor is actually harmless, albeit annoying. Since the functionality of chemo-surveillance has been restored through the application of CDA formulations [31], the residual tumor can be surgically removed without complication. Surgical wound will heal naturally. We have to develop different criteria such as disappearance of tumor markers or disappearance of circulating CSCs to evaluate efficacy of cancer therapy employing CDAs.

CDAs as the Right Medicines to Target Abnormal MEs

Abnormal MEs are an excellent cancer target. They are also the target for wound healing. Wound healing metabolites are obviously the best medicines to put away abnormal MEs to cure cancer and to repair wound. CDA-2 was a preparation of wound healing metabolites of our creation [35], which has been approved by the Chinese FDA for the therapy of MDS and cancer. Apparently, it was the drug of choice for the therapy of MDS [5,31]. MDS is a disease attributable entirely to CSCs. CDAs are definitely effective to take out both CSCs and CCs by inducing these cells to undergo terminal differentiation. In the process, CDAs can also restore the functionality of chemo-surveillance. Therefore, when the cancer is cured, the remission lasts life long. Cytotoxic agents and immunotherapy kill CCs, but contribute to the destruction of chemo-surveillance and show ineffectiveness against CSCs. The treatments create the ground for inevitable recurrence and fatality to take place. So, even the few patients fortunate to achieve complete remission. The remission can only last a limited time.

CDAs can be made by DIs and DHIs according to the formula previously established [37]. We have carried out extensive studies of natural and synthetic DIs and DHIs for the formulations of CDAs to fulfill cancer moonshot [5,6,26,29-31,37-39].

Conclusion

The right approach to a difficult challenge is the magic code to success. Cancer therapy is obviously not successful because cancer mortalities remain at historical high. President Biden urged the health profession to learn the success of moonshot to find solutions to save 50% of cancer patients in the following 25 years. The health profession must make a drastic change to fulfill cancer moonshot. Cancer therapies based on killing of CCs in the past were wrong to result in failure to save cancer patients. Cancer arises due to wound unhealing. Wound healing requires the proliferation and the terminal differentiation of PSCs. Wound if not healed properly, the symptom created by the wound can force PSCs to evolve into CSCs, and then to progress to faster growing CCs. Creating more wounds is definitely wrong for cancer therapy. The right approach of cancer therapy is to heal wound to eliminate the symptom created by the wound. Destabilization of abnormal MEs is the critical mechanism of wound healing. Abnormal MEs are an excellent cancer target, because the elimination of this target can also put to rest difficult problems of chromosomal abnormalities. CDAs are the best medicines to target abnormal MEs to achieve cancer therapy. The therapy can also restore the functionality of chemo-surveillance, therefore, the remission achieved by this therapy can last lifelong. CDA formulations are the best hope to fulfill President Biden's cancer moonshot initiative.

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