Screening of Good Cancer Drugs via Myelodysplastic Syndromes

ABSTRACT

A right approach is essential to solve any illness. Cancer mortality remains at historic highand is still on the way to increase, indicating unsuccessful handling of cancer therapy in the past. The objective of this study is to find a right approach of cancer therapy to bring cancer mortality down. Myelodysplastic syndromes are diseases that can be used to screen good cancer drugs to bring down cancer mortality.

Cancer is caused due to wound unhealing. Wound triggers biological and immunological responses. Biological response leads to the production of prostaglandins (PGs) which are good for wound healing. Immunological response prompts the production of tumor necrosis factor (TNF) which is bad for wound healing. TNF causes apoptosis of stem cells, thus triggering the proliferation of progenitor stem cells (PSCs) to repair wound damages. TNF is also named cachectin after its effect to cause cachexia symptom. A manifestation of cachexia symptomis the excessive urinary excretion of low molecular weight metabolites resulting in the collapse of chemo-surveillance which is the nature's creation of allosteric regulation to keep a check on abnormal methylation enzymes (MEs).PSCs are cells with abnormal MEs.On wound healing, efficient terminal differentiation of PSCs is a critical mechanism to heal wound. If wound is not healed properly, PSCs may be forced to evolve into cancer stem cells (CSCs) through a single hit to silence TET-1 enzyme, and then to progress to faster growing cancer cells (CCs) through chromosomal abnormalities such as translocations or deletions to activate oncogenes or to inactivate suppressor genes. Myelodysplastic syndromes (MDS) are a classic case of cancer development at the stage of PSCs evolving to become CSCs.

Therapy of MDS requires the differentiation of pathological CSCs to become functional erythrocytes, platelets or neutrophils. So far, Vidaza, Decitabine and cell differentiation agent-2 (CDA-2) are the three drugs approved for the therapy of MDS.Vidaza and Decitabine inactivate abnormal MEs through covalent bone formation between DNA methyltransferase and 5-azacytosine base incorporated into DNA, whereas CDA-2 destabilizes abnormal MEs through elimination of telomerase. Obviously, inactivation of abnormal MEs is the only way to achieve therapy of MDS. Elimination of CSCs is very critical to the success of cancer therapy. Thus, MDS can be used to screen good cancer drugs to fulfill the wish of President Biden to reduce cancer mortality.

Keywords: Cancer drugs; CDA-2; CSCs; MDS; abnormal MEs; PSCs; wound healing.

1. INTRODUCTION

Cancer mortality remains at historic high, and is still on the way to increase.According to NCI experts, the cancer incidence was 19 million and the cancer mortality was 10 million worldwide in 2019, which were on the way to increase with an annual increment of 5% [1]. The high mortality is an indication that cancer therapy has not been handled well in the past. Cancer therapy got to a bad start. Cytotoxic chemotherapy was a tragic byproduct of World War II. During the war, toxic sulfur mustard bombs were used. Victims of toxic gas all displayed depletion of lymphocytes in their blood specimens, which inspired oncologists to employ toxic chemicals to treat leukemia patients.Cytotoxic chemotherapy thus became established as a standard therapy of cancer, and the disappearance of cancer cells or tumor became accepted criteria for the evaluation of therapeutic efficacy on hematological cancer or solid tumor. Cytotoxic chemotherapy and radiotherapy were the major drugs used to combat cancer during the War on Cancer declared by President Nixon in 1971-1976, which was not successful [2].If a treatment modality has been drilled through as a presidential project and failed to achieve its goal, it was fair to conclude that this treatment modality was not good forthe solution of cancer. Cancer establishments were, however, trapped in this failed modality, although they did actively searchalternatives such as gene and target therapies, agentsto induce apoptosis, anti-angiogenesis and immunotherapy [3].None could cause reduction of tumor mass as effective as cytotoxic drugs or radiation. They kept using these failed drugs to solve cancer to contribute to horrendous cancer mortality.

Perpetual proliferation of CCs is the most outstanding feature of cancer. Naturally, killing of CCs is the top choice of cancer establishments. Cancer is made up by CSCs and CCs, although CSCs are merelya small minority, usually less then 2% in most popular cancers. This small minority, however, contributes the most fatal effects of cancer that include metastasis, recurrence, drug resistance and angiogenesis. Therefore, elimination of CSCs is far more important than the elimination of CCs to prevent cancer fatality. CSCs are protected by drug resistance and anti-apoptosis mechanisms unresponsive to cytotoxic agents [4]. Inability to take out CSCs is a major factor to contribute to the failure of cytotoxic agents to put cancer away [5]. The contribution to the damage of chemo-surveillance by cytotoxic agents is another important factor to account for the failure of cytotoxic cancer therapies [6, 7].Cancer therapies based on the killing of CCs can only benefit a minority of early stage cancer patients whose chemo-surveillance has not yet been fatally damaged, allowing the recoveryof chemo-surveillance to subdue surviving CSCs, whereas a majority of advanced cancer patients whose chemo-surveillance has been fatally damaged cannot benefit from cytotoxic therapies. They are either wiped out as unresponsive patients, or fortunate enough to reach complete remission and then succumbed to recurrence [6, 7]. We characterize cytotoxic agents as bad cancer drugs which are able to kill CCs and to destroy chemo-surveillance, but are unable to affect CSCs to contribute to high cancer mortality.

President Biden lost his very accomplished son congressman Beau to malignant brain tumor. He was genuinely concerned with high cancer mortality. On Sept. 12, 2022, the 60 anniversary of the moonshot speech of President Kenney, he delivered cancer moonshot speech to urge health profession to come up solutions to reduce cancer mortality by 50% in the following 25

years [8]. This is a more modest project than the presidential project of war on cancer to achieve total elimination of cancer.We cannot rely on bad cancer drugs to achieve this modest goal, which are causing cancer mortality to increase 5% a year. The modest goal of President Biden requires reduction of 2% a year. Now health profession must get serious to remove bad cancer drugs that are responsible for thehorrendous cancer mortality, particularly those reacting with DNA such as nucleoside analogs, platinum derivatives, intercalating agents and radiation, and to abandon tumor shrinkage as an exclusive criterion for the evaluation of cancer drugs, which was a darn mistake of cancer establishments to block development of good cancer drugs not based on the killing of CCs. The attention must also be shifted from the elimination of CCs to CSCs which contribute most fatal effects of cancer. MDS are an ideal case to guide searching of good cancer drugs capable of eliminating both CSCs and CCs through terminal differentiation.

MDS often start with a display of immunological disorder which prompts the production of inflammatory cytokines [9]. Among such cytokines, TNF is the critical element related to the development of MDS [10]. It causes excessive apoptosis of bone marrow stem cells, thus severely affecting the ability of the patient to produce hematopoietic cells such as erythrocytes, platelets and neutrophils. TNF also cause excessive urinary excretion of low molecular weight metabolites because of its effect to induce vascular hyperpermeability [11, 12]. Wound healing metabolites are among low molecular weight metabolites lost. Wound healing metabolites are metabolites active as differentiation inducers (DIs)capable of eliminating telomerase associated with abnormal MEs [13], and differentiation helper inducers (DHIs) which are inhibitors of MEs. DIs and DHIs can effectively induce PSCs to undergo terminal differentiation to heal wound. Failure to heal wound may force PSCs to evolve into CSCs to escape contact inhibition that limits the capacity of PSCs to proliferate. It takes a single hit to silence TET-1 enzyme for PSCs to become CSCs, which is within the reach of PSCs equipped with abnormally active MEs. The propagating pathological cells of MDS have been identified as CSCs [13]. MDS are diseases attributable entirely to the propagation of CSCs suitable for the search of good cancer drugs to eliminate CSCs. Elimination of CSCs is a top priority of cancer therapy since most fatal effects of cancer are the making of CSCs. The elimination of CSCs is far more important than the elimination of CCs to save cancer patients. We have a lot to catch up to reduce cancer mortality.

2. COMMENTARIES AND DISCUSSION

2-1. Abnormal MEs as the Most Critical Issue of Cancer

Perpetual proliferation of CCs is the most outstanding feature of cancer. Abnormal MEs blocking differentiation is an important factor, and the activation of oncogene or the inactivation of suppressor gene is another important factor to contribute to perpetual proliferation of cancer cells. We considered abnormal MEs as the most critical issue of cancer because this abnormality happened on PSCs, the precursors of CSCs,and passed on to CSCs and

then to CCs [13].Abnormal MEs are universal to all cancers [14], whereas oncogenes and suppressor genes are variable among different cancers, which happen late during the evolution of cancer. The elimination of abnormal MEs can also put to rest chromosomal abnormalities, but the correction of chromosomal abnormalities cannot affect abnormal MEs [15].

MEs are a ternary enzyme complex consisting of methionine adenosyltransferase(MAT)-methyltransferase (MT)-S-adenosylhomocysteine hydrolase (SAHH), which plays a pivotal role on the regulation of cell replication and differentiation. Because of this pivotal role, these enzymes are exceptionally subject to double allosteric regulations: one on the individual enzymes and one on the enzyme complex [16]. On the individual enzymes, SAHH is under the allosteric regulation of steroid hormone or related allosteric regulators [17]. On the enzyme complex, MEs are under the allosteric regulation of telomerase and wound healing metabolites [18, 19].Enzymes playing important regulatory roles are often subject to delicate regulations. Allosteric regulation is the most pervasive mode of regulation. It is the regulation to maintain biological optimum to avoid hazardous extreme often to result in display of clinical symptoms. MEs enzymes are critical for the maintenance of optimal growth by virtue of the fact that DNA methylation controls the expression of tissue specific genes [20], and pre-rRNA methylation controls the production of ribosome [21], which in turn dictates the commitment of cell to initiate cell replication [23]. If enhanced production of ribosome is locked in place, it becomes a factor to drive carcinogenesis [24]. In most normal stem cells, MEs are under the allogenic regulation of steroid hormone or related allosteric regulatory factors to dictate optimal growth. In telomerase expressing stem cells, MEs are associated with telomerase to change kinetic properties of MEs to tilt the regulation in favor of growth. K_m values of the telomerase associated MAT-SAHH isozyme pair are 7-fold higher than the normal isozyme pair [17, 24]. The increased K_m values suggest that telomerase expressing cells have much larger pool sizes of S-adenosyl methionine (AdoMet) and S-adenosylhomocysteine (AdoHcy), which are important for the build up of cells with abnormal MEs. It has been shown by Prudova et al [25] that AdoMet could protect protein against protease digestion. Chiva et al. [26] found that the pool sizes of AdoMet and AdoHcy shrunk greatly when HL-60 cells were induced to undergo terminal differentiation, indicating larger pool sizes of AdoMet and AdoHcy were necessary for the build up of cells with abnormal MEs. Embryonic stem cells and PSCs express abnormal MEs.Abnormal MEs do not seem to cause problems for these cells, because there are safety mechanisms such as contact inhibition, TET-1 enzyme to direct lineage transitions and chemo-surveillance to destabilize abnormal MEs to keep a check on abnormal MEs from flaring into clinical problems. On the contrary, pre-mature interruption of the build up of cells with abnormal MEs may be detrimental for the normal function of abnormal MEs. Interruption of abnormal MEs during fetal development by thalidomide can cause malformation, notably limbs. Therefore, regulatory mechanisms created by the nature should be followed closely to avoid disastrous consequences. Dysfunction of safety mechanisms to keep a check on abnormal MEs can lead to various clinical problems.

Cancer therapies based on the killing of CCs is the choice of cancer establishments, which do not have to take into consideration factors thatcause cancer evolution. That was a big mistake of cancer establishments. They could only choose bad cancer drugs most effective to kill CCs,

which unfortunately were also responsible for causing the death of advanced cancer patients. Targeted cancer therapies are better choices to offer selectivity that can avoid adverse effects. Abnormal MEs are obviously the best cancer target, because abnormal MEs are the most critical issue of cancer [13], and the elimination of this critical issue can also put to rest other important cancer contribution factors such as chromosomal abnormalities which are otherwise very difficult to solve [15]. One may argue that since abnormal MEs are also expressed in normal embryonic cells and PSCs, they cannot be considered as a cancer target, the silence of TET-1 enzyme and the collapse of chemo-surveillance qualify abnormal MEs as a specific cancer target, which is obviously the best target for cancer therapy [15].

2-2. Chemo-surveillance as the Creation of the Nature of Allosteric Regulation to Keep A Check on Abnormal MEs

Whatever happens naturally is the nature's creation to benefit humans. Photosynthesis is a prime example. Immuno-surveillance is another example, which is well accepted. Chemo-surveillance can also be an example, but which was not accepted, because it ran against the wish of cancer establishments. The cancer establishments wanted the tumor to disappear, but chemo-surveillance could not make the tumor to go away. The bad cancer drugs they developed caused the destruction of chemo-surveillance. Naturally, they could not accept chemo-surveillance. If there is no such thing as chemo-surveillance, how can they explain wound healing that comes naturally.

Chemo-surveillance was our creation to describe a novel concept of natural mechanism against cancer [19]. The proposal of chemo-surveillance was based on the observation that healthy people were able to maintain a steady level of metabolites active as (DIs)and DHIs. DIs and DHIs are hydrophobic metabolites that can be retained by C18 and eluted with 80% methanol. Peptides share similar physical-chemicalproperties of DIs and DHIs, and, therefore, can be used as surrogate molecules to represent DIs and DHIs. On quantitative analysis of plasma and urinary peptide content, plasma as nmolepeptides/ml and urine as nmolepeptides/mg creatinine, of normal people and cancer patients, we found that normal people were able to maintain a steady plasma/urine ratioaround 0.8, whereas cancer patients tended to show such levels below 0.8 as shown in Figure 1. Data presented in Table 1 clearly show that the maintenance of cell differentiation agent (CDA), which is a term to indicate the content of DIs plus DHIs, at the level of 5 as the healthy people is important to avoid cancer, and cancer develops as a consequence of the decline of CDA levels, namely the collapse of chemo-surveillance. The decline of CDA levels of cancer patients is obviously due to excessive urinary excretion caused by TNF. Plasma and urinary peptide profiles are similar to the peptide profile

Table 1. Plasma/urine peptide ratios of cancer patients

Plasma/Urine Peptide Ratios	CDA Level	No. of Patients	% Distribution

	0.8-0.83 (Normal)	5.0	2	1.8
	0.6-0.8	4.3	7	6.5
	0.4-0.6	3.1	18	16.7
	0.2-0.4	1.8	38	35.2
0.1-0.2		0.9	24	22.2
	0.05-0.1	0.46	19	17.6

Plasma peptides: nmoles/ml; Urine peptides: nmoles/mhcreatinine.

of spleen extract, but dissimilar to the peptide profiles of other organ extracts. These findings suggest that plasma and urinary peptides are the degradative products of hemoglobins since spleen is known as an organ toprocess dead erythrocytes.Degradation of erythrocytes is very likely a major sourceof plasma DIs as acidic peptides, arachidonic acid (AA) and membrane fragments with phosphatidylinositol, and DHI as uroerythrin [25-28].Steroid metabolites are important DHIs which may be derived from organs involve in steroid metabolism [25, 29, 30]. Pregnenolone is an important DHI. According to Morley [30], the production of pregnenolone is bell shape with a peak of 50 mg a day produced by 20-25 year old. The very young and the very old people produce relatively smaller amounts of pregnenolone, and these are the two age groups most vulnerable to develop cancer.Evidently, chemo-surveillance is an important mechanism to protect healthy people from becoming cancer patients. Our carcinogenesis studies strongly support the importance of chemo-surveillance to ward off cancer evolution. During challenging with hepatocarcinogen, numerous tiny hyperplastic nodules appeared before the appearance of large size carcinomas [31], which displayed abnormal MEs. These tiny preneoplastic hyperplastic nodules must represent active repair by PSCs. Most of these tiny hyperplastic nodules disappeared, indicating completion of wound healing, and only a few large sized carcinomas appeared later, indicating only unhealed wounds caused by carcinogen later developed to become carcinomas. If Antineoplaston A10 was provided during the challenge with hepatocarcinogen, development of carcinomas could be prevented [32].Antineoplaston A10 is phenylacetylglutamine which is inactive as DI or DHI, neither as cytotoxic agent. It is an effective anti-cachexia agent to prevent the loss of DIs and DHIs [19]. An effective anti-cachexia agent can also be effective for the therapy of early stage cancer patients [19].Cachexia is a symptom commonly shared by inflammatory patients and cancer patients. The progression of cancercan cause CDA levels to decline. Cytotoxic agents create wound. Therefore, the administration of cytotoxic agents can accelerate the decline of CDA levels. The destruction of chemo-surveillance is definitely a factor to contribute to the failure of cytotoxic agents to put cancer away [33]. we strongly recommended restoration of chemo-surveillance through CDA formulations asa top priority to save cancer patients [7].

2.3 Wound Unhealing to Lead to the Evolution of Cancer

The concept of cancer due to wound unhealing was first introduced by the great German scientist Virchow in the 19th century [34]. It was again brought up by Dvorak in 1986 [35].The close relationship between cancer and wound healing was noticed by MacCarthy-Morrough and Martin [36]. We provided the most important details on this subject that included abnormal methylation enzymes to block differentiation [13-16, 18, 24]; chemo-surveillance as the nature's creation of allosteric regulation to keep a check on abnormal MEs [7, 19, 37, 38]; DIs and DHIs as wound healing metabolites and also as active players of chemo-surveillance [7, 19, 25-28, 37, 38];hypomethylation of nucleic acids as the most critical mechanism for the induction of terminal methylation of cells with abnormal MEs [39]; the mechanism of wound healing to involve the proliferation and the terminal differentiation of PSCs [40-42]; and the evolution of CSCs from PSCs due to wound unhealing [4, 43, 44]. Our studies are very convincing to show that cancer is the consequence of wound unhealing. Therefore, the most appropriate solution of cancer is to pursue perfection of wound healing [45].Wound healing is a simple matter that comes naturally without having to put up any effort. Cancer therapy should also be a simple matter if the therapy follows the process of wound healing. But cancer establishments prefercancer therapies opposite to wound healing to result in horrendous cancer mortality of more than 10 million a year worldwide.These cancer establishmentshave to be replaced to save cancer patients [46].

Wound healing and cancer are closely related to involve PSCs as the common elements. Wound healing requires the proliferation and the terminal differentiation of PSCs [40]. PSCs are the most primitive stem cells to initiate the development of particular organs or tissues during the embryonic development of fetus. They are pluripotent stem cells capable of differentiation into various component cells of the organ or tissue, such as parenchyma cells, epithelial cells, connective tissue and blood vessels to repair the wound. A small percentage of these cells, usually less than 2%, are reserved for the need to expand or repair. Wound triggers biological and immunological responses [47]. Biological response involves the release of AA from membrane bound phosphatidylinositol for the synthesis of PGs, which are unstable metabolites. The function of PGs is believed to cause edema for the extravasation of inhibitors such as DIs and DHIs for PSCs to proliferate. The promotion of terminal differentiation of PSCs at the final stage of wound healing is accomplished by CDA above described. Wound healing comes naturallywithout having to put up any effort since healthy people can maintain CDA at healthy level of 5. Take treatment of surgical wound for example, suture and antibiotic treatment are subsidiary to speed up and to prevent infection. The integrity of chemo-surveillance dictates the success of wound healing [37, 38].If chemo-surveillance has been damaged by wounds due to accidents, surgeries, toxic chemicals or infections, wound healing will be affected to result in disastrous consequences to display clinical symptoms such as tissue fibrosis, dementia, organ failures, and cancer. Management of wound healing is an important matter. That is why the nature creates chemo-surveillance to ensure perfection of wound healing. Cancer can be solved as easy as wound healing, if the therapy fallows pro-wound healing process [45].

2.4. Screening of Good Cancer Drugs via MDS

MDS are intermediate diseases ofcancer at the stage of CSCs as above described. These diseases are ideal for the evaluation of drugs effective against CSCs, which is the most important issue of cancer, because CSCs contribute the most fatal effects of cancer. Therapy of MDS requires the conversion of pathological CSCs to become functional erythrocytes, platelets or neutrophils, which requires terminal differentiation of CSCs, precisely the critical mechanism of wound healing.Killing of CSCs cannot cure MDS. Besides, CSCs cannot be easily killed. So far, Vidaza, Decitabine and CDA-2 are three drugs approved for the therapy of MDS by China and the US. CDA-2 is a drug approved only by China, which was a drug of wound healing metabolites purified from freshly collected urine of our creation [48]. Professor Jun Ma, Director of Harbin Institute of Hematology and Oncology, was instrumental to conductclinical trials for the approval of these three MDS drugs in China [49]. Based on two cycles of treatment protocols, each 14 days, Professor Ma found CDA-2had a slightly better therapeutic efficacy based on cytological evaluation and a marked better therapeutic efficacy based on hematological improvement evaluation as shown in Figure 1. Hematological improvement was an indication of dependency on blood transfusion to stay healthy.

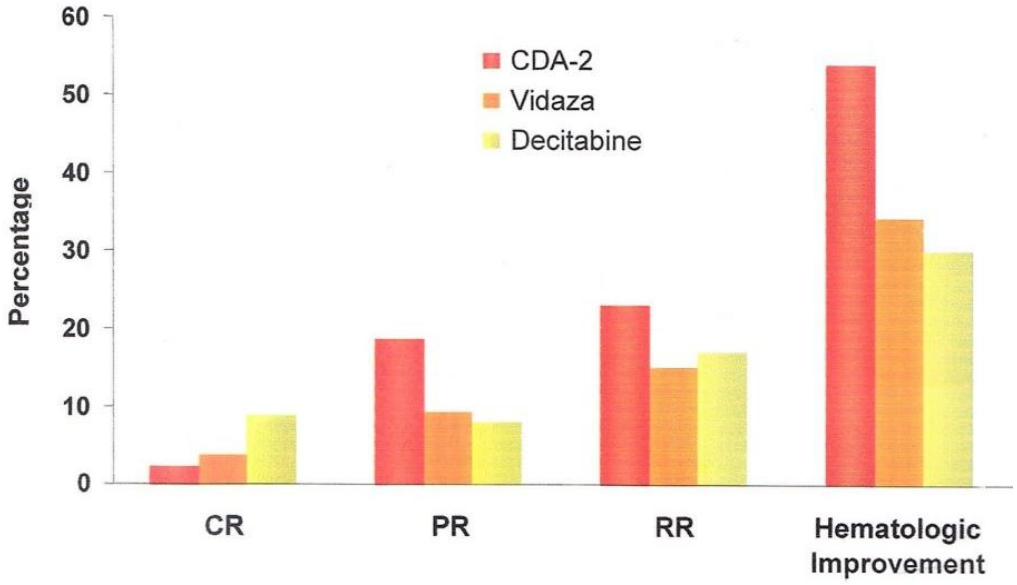

Figure 1. A Comparison of Therapeutic Efficacy of CDA-2, Vidaza and Decitabine on MDS

Obviously, CDA-2 is a better drug for the therapy of MDS based on therapeutic efficacy. Better yet, it is a drug without serious adverse effects, whereas Vidaza and Decitabine are known carcinogens [50, 51] and very toxic to DNA [52-54].Apparently, abnormal MEs are the target of MDS drugs, which supportsthe validity of our claim of abnormal MEs as the most critical issue of cancer [13]. CDA-2 destabilize abnormal MEs by the elimination of telomerase from abnormal MEs, which is a specific cancer target, and Vidaza and Decitabine inactivate abnormal MEs through covalent bond formation between methyltransferase and 5-azacytosine base incorporated into DNA, which is not s specific event limited to cancer cells [54].Although Vidaza

and Decitabine can be classified as good cancer drugs because of its effectiveness to induce terminal differentiation of CSCs, they also belong to bad cancer drugs as nucleoside analogs. Therefore, CDA-2 is the only good cancer drug. CDA-2 is only available in China. The rest of the world do not have good cancer drugs to combat cancer. That is why the cancer mortality remains so horrendously high. Development of CDA formulations made up by DIs and DHIs is urgent to reduce cancer mortality [3-8, 45, 56].

3. CONCLUSION

A right approach is essential for the solution of any illness. Cancer arises due to the failure of wound healing. Perfection of wound healing is the right approach of cancer therapy. Creation of wound is the wrong approach of cancer therapy. The right approach relies on good cancer drugs that can promote terminal differentiation of CSCs and CCs, and to restore chemo-surveillance to the healthy CDA5. The wrong approach is the making of bad cancer drugs that can kill CCs and destroy chemo-surveillance, but are unable to affect CSCs to result in horrendous high cancer mortality. MDS are disease attributable entirely to CSCs, which are ideal for the screening of good cancer drugs that can reduce cancer mortality to fulfill the wish of President Biden who has called for the reduction of cancer mortality by 50% in the following 25 years.

4. REFERENCES

1. Google search on cancer statistics-NCI.
2. Liau MC, Fruehauf JP. It has been half a century since President Nixon declared war on cancer: Destabilization of anormal methylation enzymes has the blessing of the nature to win the war on cancer. Adv Complement Alt Med. 2020; 6(1): 538-539.
3. Liau MC, Craig CL. Wound healing metabolites to heal cancer and unhealed wounds. Intl Res J Oncol. 2022; 6(3): 8-20.
4. Liau MC, Kim JH, Fruehauf JP. Destabilization of abnormal methylation enzymes: Nature's way to eradicate cancer stem cells. Online J Complement Alt Med. 2019; DOI: 10.33552/OJCAM.02.000546.
5. Liau MC, Baker LL. Cancer patients' lives matter. Adv. Complement Alt Med. 2021; 6(1): 638-640.
6. Liau MC, Craig CL, Baker LL. CDA formulations to fulfill cancer moonshot and to win the war on cancer. Intl J Res Oncol. 2023; 2(2): 1-8.
7. Liau MC, Craig CL, Baker LL.Restoration of chemo-surveillance as a top priority to save cancer patients. Intl Res J Oncol. 2023; 6(2): 227-237.
8. Liau MC, Fruehauf JP. Cancer moonshot: Moonshot as a magic code to guide successful solutions of tough challenges such as cancer. Intl J Res Oncol. 2023; 2(1): 1-5.
9. Williamson PJ, Kruger AR, Reynolds PJ, Hamlin TJ, Oscier DG. Establishing the incidence of myelodysplastic syndromes. Br J Haemato. 1994; 87(4): 743-745.

10. Boula A, Vougarelis M, Giannouli S, Katrinakis G, Psyllaki M, Pontikoglou C, et al. Effect of CA2 of antitumor necrosis factor-alpha antibody therapy on hematopoiesis of patients with myelodysplastic syndromes. Clin Cancer Res. 2006; 12(10): 3099-3108.
11. Itkin T, Rafii S. Leukemia cells “gas up” leaky bone marrow blood vessels. Cancer Cell. 2017; 32(3): 276-278.
12. Passaro D, Di Tullo A, Abarrategi A, Rousault-Pierre K, Foster K, Ariza-McNaughton L, et al. Increased vascular permeability in the bone marrow microenvironment contributes to disease progression and drug response in acute myeloid leukemia. Cancer Cell. 2017; 32(3): 324-341.
13. Liau MC, Craig CL, Liau LL. Abnormal methylation enzymes as the most critical issue of cancer. Intl Res J Oncol. 2023; 6(2): 168-176.
14. Liau MC, Chang CF, Giovanella BC. Demosstration of an altered S-adenosylmethionine synthetase in human malignant tumors xenografted into athymic nude mice. J Natl Cancer Inst. 1980; 64(5): 1071-1075.
15. Liau MC, Baker LL. Abnormal methylation enzymes as the bullseye of targeted cancer therapy. Nov Res Sci. 2021; 7(4): 1-3.
16. Liau MC, Craig CL, Baker LL. Exceptional allosteric regulation of methylation enzymes. In: Saraydin SU (ed): Novel Research Aspects in Medicine and Medical Science. 2023; Vol. 4: 39-56. DOI: 10.9734/bpi/nramms/v4/19881D.
17. Liau MC, Chang CF, Saunder GF, Tsai YH. S-adenosylhomocysteine hydrolases as the primary target enzymes in androgen regulation of methylation complexes. Arch BiochemBiophys. 1981; 208(1): 261-272.
18. Liau MC, Zhuang P, Chiou GCY. Identification of the tumor factor of abnormal methylation enzymes as the catalytic subunit of telomerase. Clin Oncol Cancer Res. 2010; 7(2): 86-96.
19. Liau MC, Szopa M, Burzynski B, Burzynski SR. Chemo-surveillance: A novel concept of the natural defense mechanism against cancer. Drug Exptl Clin Res. 1989; 13(Suppl. 1): 72-82.
20. Racanelli AC, Turner FB, Xie LY, Taylor SM, Meran RG. A mouse gene that coordinate epigenetic controls and transcriptional interference to achieve tissue specific expression. Mol Cell Biol. 2008; 28(2): 836-848.
21. Liau MC, Hunt ME, Hurlbert RB.Role of ribosomal RNA methylases in the regulation of ribosome production. Biochemistry. 1976; 15(14): 3158-3164.
22. Bernstein KA, Bleichert F, Bean JM, Cross FR, Baserga SJ.Ribosome biogenesis is sensed at the start cell cycle check point. Mol Biol Cell. 2007; 18(3): 953-964.
23. Justilien Y, Ali SA, Jamieson L, Yin N, Cox AD, Der CJ, et al. ECT2-dependent rRNA synthesis is required for KRAS-TRP53-driven lung adenocarcinoma. Cancer Cell. 2017; 31(2): 256-269.
24. Liau MC, Lin GW, Hulbert RB. Partial purification and characterization of tumor and liver S-adenosylmethionine synthetases. Cancer Res. 1977; 37(2): 427-435.
25. Liau MC, Fruehauf PA, Zheng ZH, Fruehauf JP. Development of synthetic cell differentiation agent formulations for the prevention and therapy of cancer via targeting of cancer stem cells. Cancer Stu Ther. 2019; 4(1): 1-15.
26. Liau MC, Kim JH, Fruehauf JP. In pursuance of differentiation inducers to combat cancer via targeting of abnormal methylation enzymes. J Cancer Tumor Intl. 2020; 10(2): 39-47.

27. Liau MC, Kim JH, Fruehauf JP. Arachidonic acid and its metabolites as the surveillance differentiation inducers to protect healthy people from becoming cancer patients. Clin PharmacolToxicol Res. 2021; 4(1): 7-10.
28. Liau MC, Liau CP. Methyltransferase inhibitors as excellent differentiation helper inducers for differentiation therapy of cancer. Bull Chin cancer. 2002; 11: 166-168.
29. Liau MC, Kim JH, Fruehauf JP. Potentiation of ATRA activity in HL-60 cells by targeting methylation enzymes. J PharmacolPharmaceutPharmacovig. 2019; 3: 009. DOI: 10.24966/PPP-5649/100009.
30. Morley JE. Hormone, aging, and endocrines in the elderly. In: Felig P, Frohman LA, "Endocrinology and Metabolism, 4th edn, 2001, McGrow-Hill, Inc., Medical Publishing Division, New York, pages 1455-1482.
31. Liau MC, Chang CF, Becker FF. Alteration of S-adenosylmethionine synthetases during chemical hepatocarcinogenesis and in resulting carcinomas. Cancer Res. 1979; 39(6): 2113-2119.
32. Kamparath BN, Liau MC, Burzynski B, Burzynski SR. Protective effect of Antineoplaston A10 in hepatocarcinogenesis induced by aflatoxin B1. Intl J Tiss React. 1990; 12 (Suppl.): 43-50.
33. Liau MC, Baker LL. Destruction promotes the proliferation of progenitor stem cells. Therefore, non-destruction is a better strategy for cancer therapy: A commentary. J PharmacolPharmaceutPharmacovig. 2020; 4:029. ROI:10.24966/PPP-5649/100029.
34. Virchow R. Die Cellular Pathologie in Ihrer Begrundung auf Physiologische und Pathologische Gewebelehve. Hirschwald. 1858; 16: 440.
35. Dvorak HF. Tumors: Wounds that do not heal. N Engl J Med. 1986; 315(26): 1650-1659.
36. MacDcarthy-Morrough L, Martin P. The hallmarks of cancer are also the hallmarks of wound healing. Science Signaling. 2020; 13: 648.
37. Liau MC, Baker LL. The functionality of chemo-surveillance dictates the success of wound healing as well as cancer therapy. Nov Res Sci. 2021; 7(2): 1-3.
38. Liau MB Craig CL. Chemo-surveillance as a natural mechanism to ensure perfection of wound healing to avoid cancer evolution and to cure cancer. In: New Horrizons in Medicine and Medical Research. 2022; Vol. 6, Chapter 3. Print ISBN: 978-93-5547-607-4.
39. Liau MC, Lee SS, Burzynski SR. Hypomethylation of nucleic acids: A key to the induction of terminal differentiation. Intl J Exptl Clin Chemother. 1989; 2: 187-199.
40. Liau MC, Craig CL. On the mechanism of wound healing and the impact of wound on cancer evolution and cancer therapy. Intl Res J Oncol. 2021; 5(3): 25-31.
41. Liau Craig CL. On scar as an indication of perfect wound healing, ugly scar as imperfect wound healing and cancer as failed wound healing. J Cancer Tumor Intl. 2022; 12(1): 29-34.
42. Liau MC, Craig CL, Baker LL.Wound unhealing as a grave issue of cancer. Intl Res J Oncol. 2023; 6(1): 97-103.
43. Kudo Y, Tateishe K, Yamamoto K, Yamamoto S, Asaoka Y, Ijichi H, et al. Loss of 5-hydroxymethylcytosine is accompanied with malignant cellular transformation. Cancer Sci 2012; 103(4): 670-678.
44. Ficz GM, Gibben JG. Loss of 5-hydroxymethylcytosine in cancer: Cause or consequence? Genomics. 2014; 104(5): 352-357.
45. Liau MC, Craig CL, Baker LL. Wound healing process as the most appropriate modality of cancer therapy. Eur J Applied Sci. 2023; 11(1): 463-471.

46. Liau MC, Craig CL, Baker LL. A drastic change of cancer leaderships to save desperate cancer patients. In: Gurunathan R (ed), New Advances in Medicine and Medical Science, 2023; Vol. 7, Chapter 6: 61-69. DOI: 10.9734/bpi/namms/v7/19537D.
47. Ho ATV, Palla AR, Blake MR, Yual ND, Wang ND, Magnusson KEG, et al. Prostaglandin E2 is essential for efficacious skeletal muscle stem function, augmenting regeneration and strength. Proc Natl Acad Sci USA. 2017; 114(26): 6675-6634.
48. Liau MC. Pharmaceutical composition inducing cancer cell differentiation and the use for treatment and prevention of cancer thereof. US Patent 7232578 B2, 2007.
49. Ma J. Differentiation therapy of malignant tumor and leukemia. CSCO Treaties on the Education of Clinical Oncology. 2007; pages 480-486.
50. Prassana P, Shack S, Wilson VL. Samid D. Phenylacetate in chemoprevention of 5-aza-2'-deoxycytidine-induced carcinogensis. Clin Cancer Res. 1995; 1(18): 865-871.
51. Gaudet F, Hodgson JG, Eden A. Jackson-Grusby L, Dausman J, Gray JW, et al. Induction of tumor in mice by genomic hypomethylation. Science. 2003; 300(5618): 489-492.
52. Palii SS, van Emburgh BO, Sankpal UT, Brown KD, Robertson KD, DAN methylation inhibitor 5-aza-2'-deoxycytidine-induces reversible DAN damage that is distinctly influenced by DAN-methyltransferase 1 and 3B. Mol Cell Biol. 2008; 28(2): 752-771.
53. Kizietepe T, Hideshima T, Catley L, Raje N, Yasui H, Shirishi N, et al. 5-Azacytidine, a methyltransferase inhibitor, induces ATR-mediated DNA-double strand break responses, apoptosis and synergistic cytotoxicity with doxorubicine and bortezomib against multiple myeloma cells. Mol Cancer Ther. 2007; 6(6): 1718-1727.
54. Yang Q, Wu F, Wang F, Cai K, Zhang Y, Sun Q, et al. Impact of DNA methyltransferase inhibitor 5-azacytidine on cardiac development of zebrafish in vivo and cardiomyocyte proliferation, apoptosis, and homeostasis of gene expression in vitro. J Cell Biochem. 2019; 120(10): 17459-17471.
55. Santi DV, Norment A, Garrett CE. Covalent bond formation between a DNA-cytosine methyltransferase and DNA containing 5-azacytosine. Proc NatlAcadSci USA. 1984; 81(22): 6993-6997.
56. Liau MC, Kim JH, Fruehauf JP. Destabilization of abnormal methylation enzymes to combat cancer: The nature's choice to win the war on cancer. Lambert Academic Publishing. 2020;978-620-2-66889-7.