SRYAHWA PUBLICATIONS

Archives of Oncology and Cancer Therapy
ISSN: 2638-5074 | Volume 6, Issue 1, 2026
https://doi.org/10.22259/2638-5074.0601002

RESEARCH ARTICLE

The Alliance of Virchow and Liau et al. To Offer the Only Intelligent Solution to Win the War on Cancer, on Cardiovascular Diseases, and on a Series of Fatal Diseases Evolving due to Wound Unhealing

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Received: 10 February 2026 Accepted: 24 February 2026 Published: 23 February 2026

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Abstract

The objective of this article is to offer an intelligent solution to win the war on cancer, on cardiovascular diseases (CVDs) and on a series of fatal diseases evolving due to wound unhealing, which remain unsolved for a very long time. Health profession is an authoritarian profession very much like communist regimes often dominated by very powerful bosses to put up policies for the entire profession to follow. Intelligent bosses can put up good policies to enhance the reputation of health profession and to benefit patients. But inept bosses can put up bad policies to damage the reputation of health profession and to hurt patients. Apparently, health authorities are unable to handle diseases evolving due to wound unhealing, since the mortalities of diseases due to wound unhealing keep on escalating. Solution of top killing diseases is a national priority to every country. Cancer and CVDs are the two top killers of humans, cancer claiming 10 million casualties and CVDs claiming 20.5 million casualties annually worldwide. Saving patients should not be a battle of ideologies. It should be a choice of intelligent solutions.

Virchow was extremely talented to comprehend the logic of wound unhealing to the evolution of cancer at a time neither cancer nor wound healing was completely known. Liau et al. were also extremely talented to decode the logic of wound unhealing to the evolution of cancer by the discoveries of abnormal methylation enzymes, chemo-surveillance and the mechanism of wound healing to support the validity of Virchow's concept of cancer evolving due to wound unhealing. It is very disappointing that cancer establishments are unable to understand the valid concept of cancer evolving due to wound unhealing when cancer and wound healing have become completely known. This is the problem of health profession. Once the bad policy is adopted by the big bosses, the bad policy carries on to damage the reputation of health profession as a profession unable to solve a simple wound healing problem and to hurt patients. This is a political issue. We have to find a political solution to resolve the impasse. A congressional hearing to discuss the issue is appropriate to find a political solution, since solution of top killing diseases is an important issue of national interest.

Keywords: Cancer, CVDs, Health Authorities, Liau et al., Virchow, Wound Healing.

1. Introduction

Solution of top killing diseases is a very important issue of national interest. President Nixon brought up War on Cancer as a presidential project in 1971 [1], and President Biden brought up Cancer Moonshot as a quasi-presidential project in 2022 [2]. War on Cancer was a total failure, and Cancer Moonshot is not appearing to head in the winning way to fulfill the demand of President Biden who modestly requested the health profession to reduce cancer mortality by 50% in 25 years in 2022. The health profession should achieve an annual reduction of 2% of cancer mortality from 2023 onward, but the actual cancer mortalities were still on the trend to escalate at a rate of 0.2%

Citation: Ming C. Liau, Christine L. Craig, Linda L. Baker.The Alliance of Virchow and Liau et al. To Offer the Only Intelligent Solution to Win the War on Cancer, on Cardiovascular Diseases, and on a Series of Fatal Diseases Evolving due to Wound Unhealing. Archives of Oncology and Cancer Therapy. 2026; 6(1): 13-26.

annually up to 2025 [3]. It is very disappointing that the health profession could not fulfill the requests of their commander-in-chief. CVDs are a top killer in the USA, claiming 0.92 million casualties annually, and cancer is the next to the top, claiming 0.61 million casualties annually [3]. CVDs are the top killer. But heart attack and stroke are too difficult to overcome. So, President Nixon picked the easier cancer which is the second top killer as his presidential project. The previous two presidential projects were technically very difficult projects. Nuclear physicists achieved the Manhattan Project of President Roosevelt, and rocket engineers achieved the Moonshot Project of President Kennedy. The health profession failed the War on Cancer project that did not require difficult technology. It was indeed a very shameful record of health profession. As long as the health profession is unable to solve cancer, this profession will be marked as a dumb profession. Actually, the health profession had a very intelligent fellow to win the War on Cancer. Virchow introduced the concept of cancer evolving due to wound unhealing in 1858 [4]. Had we followed his advice, cancer was solved in 1858. His advice may be too ancient to remain in the memory of recent authorities. His concept of cancer evolving due to wound unhealing was brought up again by Dvorak in 1986 in the very prestige medical journal [5] that ought to catch the attention of current authorities. Apparently, the current authorities are unmoved by the advice of Virchow to insist on their failed approaches of cancer therapies. The health profession is dominated by arrogant and inept authorities refusing to change the course to solve the problem. That is a political issue that can only be resolved by political means. A congressional hearing to discuss the issue is appropriate to find a political solution, since the solution of top killing diseases is a national interest.

2. The Alliance of Virchow and Liau et al. Offers the Only Intelligent Solution to Win the War on Cancer, on CVDs and on a Series of Fatal Diseases Evolving due to Wound Unhealing and Discussion.

2.1 The Alliance of Virchow and Liau et al. to Promote Perfection of Wound Healing as the only Intelligent Solution of Cancer

Virchow was extremely talented to comprehend the logic of wound unhealing to the evolution of cancer at a time neither cancer nor wound healing was completely known [4]. Virchow did not produce experimental data to advance his excellent concept of cancer evolving due to wound unhealing. We provided the experimental data unknowingly to support his excellent concept of cancer evolving due to wound unhealing. During our studies of hepato-carcinogenesis, we noticed the appearance of numerous tiny hyperplastic nodules in the liver soon after the application of hepatocarcinogens to animals, which displayed abnormal methylation enzymes (MEs) we have discovered earlier [6], which must represent the proliferation of progenitor stem cells (PSCs) in the process of active healing of wounds created by hepatocarcinogens. Most of these tiny hyperplastic nodules disappeared shortly afterward, indicating the completion of wound healing.

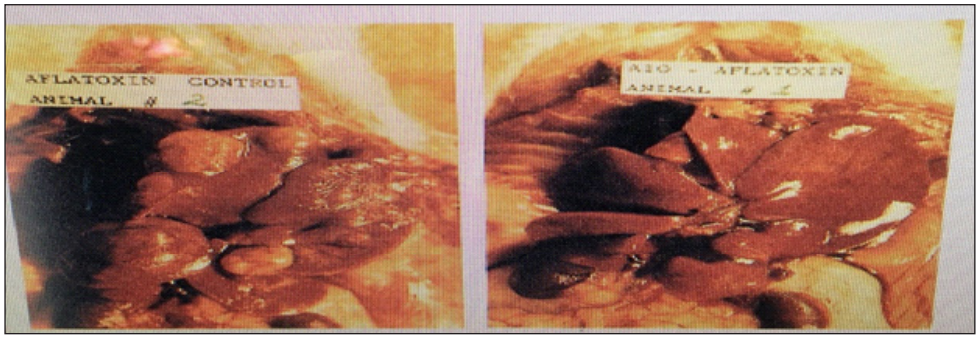


Figure 1. *Effective Prevention of Hepatocarcinogenesis by Antineoplaston A10.*
The figure on the left is the conrol liver receiving aflatoxin B1 only, and the figure on the right is the liver receiving Antineoplaston A10 after the administration of aflatoxin B1.

Only a few large size carcinomas appeared later from unhealed tiny hyperplastic nodules [7]. If Antineoplaston A10, namely phenylacetylglutamine, was given to animals after the administration of hepatocarcinogen, the appearance of carcinomas could be effectively prevented as shown in Fig. 1, which is reproduced from the reference [8]. Antineoplaston A10 is biologically inactive chemical. But it was effective toantagonize the effect of tumor necrosis factor (TNF) to prevent the loss of wound healing metabolites to keep the functioning of chemo-surveillance intact [9]. TNF is a cytokine produced by immune competent cells. It is also named cachectin after its effect to cause cachexia symptoms. A

manifestation of cachexia symptoms is the excessive excretion of low molecular wight metabolites because of membrane hyperpermeability caused by TNF [10, 11]. Wound healing metabolites are among low molecular weight metabolites excreted. Loss of wound healing metabolites is very damaging to chemo-surveillance, which is a natural defense mechanism against cancer [9]. TNF is also capable of inducing the production of oncogenic protein [12]. TNF by the destruction of cancer protection mechanism and the production of oncogenic protein is responsible for the induction of myelodysplastic syndromes (MDSs) [13-15]. By antagonizing TNF to keep the wound healing capability intact, Antineoplaston A10 can effectively prevent cancer from taking place, even challenged with potent carcinogen. Fig. 1 is a remarkable experimental datum we produced to support the validity of Virchow's concept of cancer evolving due to wound unhealing. Drugs that can prevent diseases from taking place are considered the best drugs by the standard of oriental medicine [16]. Phenylacetylglutamine belongs to the category of best drugs.

Table 1. *Chemo-surveillance Selectively Destroyed in Cancer Patients*

Plasma/Urine Peptide Ratios	CDA Levels	Number of Patients	% Distribution
0.83 – 0.80 (Normal)	5.0	2	1.8
0.80 – 0.60	4.3	7	6.5
0.60 – 0.40 (Responsive)	3.1	18	16.7
0.40 – 0.20	1.8	38	35.2
0.20 – 0.10	0.9	24	22.2
0.10 – 0.02 (Unresponsive)	0.37	19	17.6

Plasma Peptides : *nmoles/ml ; Urinary Peptides : nmoles/mg creatinine*

DIs are metabolites capable of eliminating telomerase from abnormal MEs [17], and DHIs are inhibitors of MEs capable of potentiating the activity of DIs [18]. DIs and DHIs are produced by the body, which are very critically involved in wound healing. Wound healing requires the proliferation and the terminal differentiation (TD) of PSCs, which are the most primitive stem cells to initiate the development of organ or tissue during embryonic stage of fetal development [19]. A small percentage of these cells, usually less 2% of the organ or tissue mass, are reserved in the organ or tissue for future expansion or repair. Wound healing is actually an extension of embryonic program of organ or tissue development. MEs are a ternary enzyme complex consisting of methionine adenosyltransferase (MAT)-methyltransferase (MT)-S-adenosylhomocysteine hydrolase (SAHH) [20]. MEs play a pivotal role on the regulation of cell growth and differentiation by virtue of the fact that DNA MEs control the expression of tissue specific genes [21], and rRNA MEs control the production of ribosome [22], which in turn dictates the cell to enter cell cycle [23]. Because of the important role of MEs in the regulation of cell growth and differentiation, these enzymes are exceptionally subjected to double allosteric regulations: one on the individual enzymes and the other on the enzyme complex [24]. On the individual enzymes, MEs are regulated by steroid hormones in steroid hormone targeted tissues. It is very likely that MEs of other tissues are under the regulation of factors closely related to steroid hormones. SAHH is a steroid hormone receptor [20]. In telomerase expressing cells, MEs become associated with telomerase. The association of MEs with telomerase changes the kinetic properties of MEs and the regulatory role of MEs greatly in favor of promoting cell growth. K_m values of telomerase associated MAT^{LT}-$SAHH^{LT}$ isozyme pair are 7-fold high than the normal MAT^{L}-$SAHH^{L}$ isozyme pair. The higher K_m values suggest that MEs in telomerase expressing cells are far more stable and active, and the pool sizes of S-adenosylmethionine (AdoMet), S-adenosylhomocysteine (AdoHcy) and Hcy are much larger, since the study of Prudova et al. indicated that AdoMet could protect protein against protease digestion [25], and the study of Chiva et al. indicated that when HL-60 cells were induced to undergo terminal differentiation, the pool sizes of AdoMet and AdoHcy shrank greatly. Therefore, larger pool sizes of AdoMet, AdoHcy and Hcy are required to promote the growth of cells expressing telomerase. Consequently, abnormal MEs are at the center of growth regulation, the bullseye of fatal diseases evolving due to wound unhealing [27, 28]. Cancer is basically a problem of growth regulation going awry. Abnormal MEs and chromosomal abnormalities to activate oncogenes or to inactivate suppressor genes are the most critical factors to mesh up growth regulation, abnormal MEs to block differentiation and chromosomal abnormalities to speed up cell replication. Studies of chromosomal abnormalities received the most attention, including

many Novel prizes, which, however, did not yield any drug to benefit cancer patients, despite a great effort was put in during 1976-1996 to develop gene therapy. It was indeed very difficult to correct chromosomal abnormalities. Good thing that the development of gene therapy was not successful. If it was successful, we would be trapped in a very difficult approach of cancer therapy. Actually, it is not feasible to develop gene therapy. One gene therapy if successful, there may soon pop up another chromosomal abnormality to negate the previous effort. It is going to be endless struggle trying to put out chromosomal abnormalities. Solution of abnormal MEs is a better choice. After all, oncogenes and suppressor genes are cell cycle regulatory genes. These genes have important roles to play when cell is in cell cycle replicating. But if replicating cell is induced to undergo terminal differentiation, these genes have no roles to play. So, the solution of abnormal MEs can also put to rest the problems of chromosomal abnormalities. Solution of abnormal MEs does not require difficult technology. Solution of chromosomal abnormalities does require difficult technologies the cancer establishments could not achieve. They wasted 20 years to learn the difficulty of gene therapy. Solution of abnormal MEs offers the most intelligent approach to put away fatal diseases evolving due to wound unhealing.

Evidently, wound healing is a very important health issue, so that the nature put up chemo-surveillance and immuno-surveillance to ensure perfection of wound healing to avoid disastrous consequences of wound unhealing that can be fatal, chemo-surveillance to heal wounds due to toxic chemicals or physical means and immuno-surveillance to heal wounds due to infectious agents. DIs and DHIs are hydrophobic metabolites. Data presented in Table 1 are quantitative data of peptides in the plasma and urine. Peptides share chemical-physical properties similar to DIs and DHIs. Therefore, peptides can be used as surrogate molecules to represent DIs and DHIs. As a matter of fact, acidic peptides are major DIs of Antineoplaston preparations Burzynski purified from urine for cancer therapy [29-30]. Peptide analyses presented in Table 1 clearly show chemo-surveillance was selectively destroyed in cancer patients, which was another important experimental datum we produced to support the validity of Virchow's concept of cancer evolving due to wound unhealing. Because of the collapse of chemo-surveillance, cancer becomes established and the progress of cancer further causes chemo-surveillance to deteriorate. Toxic chemotherapeutic agents creating wounds also contribute to the deterioration of chemo-surveillance. CDA level of 2.5 may be a threshold of responsiveness. Above this threshold, patients are responsive to cytotoxic cancer therapies, because chemo-surveillance can be restored to subdue the surviving cancer stem cells (CSCs) which are not responding to cytotoxic cancer therapy. CSCs are protected by drug resistance and anti-apoptosis mechanisms to resist cytotoxic cancer therapies [31-37]. CDA formulations are the only drugs to deal with CSCs [38-41]. Of course, cancer establishments knew the importance of CSCs to the success of cancer therapy. Approximately 19 years ago, the pharmaceutical giant GSK put up an outrageous 1.4 billion, the most expensive investment on a cancer drug, to develop monoclonal antibodies against CSCs invented by the scientists of Stanford University, which was not successful, because killing of CSCs was not an option to deal with CSCs. It was very strange that the topics of monoclonal antibodies against CSCs totally disappeared as if these topics never existed. The cancer establishments made big noise on the possibility of wiping out CSCs to put cancer away. When they failed, they became silent. Now they are making big noises on immunotherapy to put away cancer with a climax of Novel prize in 2025. Immuno-surveillance is importantly related to the issue of cancer. The core problem of cancer is growth regulation. Immunology has nothing to do with growth regulation. The discovery of programmed death antigen to mark pathological cells to be eliminated by immunological mechanism was a remarkable scientific achievement deserving Nobel prize. But the elimination of cancer cells (CCs) expressing programmed death antigen cannot solve cancer. Cytotoxic agents are very effective to eliminate CCs. The inability to eliminate CSCs and the contribution to the damage to chemo-surveillance are the reasons to cause the failure of cytotoxic cancer therapies. Immunotherapy has the same problem to show ineffectiveness against CSCs and to contribute to the damage of chemo-surveillance. CSCs are PSCs without ten-eleven translocator-1 (TET-1) enzyme. The cell feature, antigenicity and cell mission of CSCs are exactly the same as those of PSCs. PSCs are normal embryonic stem cells which are tolerant to natural immune mechanisms. CSCs are also tolerant to natural immune mechanisms. The advantage of immunotherapy over cytotoxic therapies is the selectivity of immunotherapy to target CCs expressing programmed death antigen to spare unipotent stem cells (UPCs) which do not express programmed death

antigen. Cancer patients can be spared of excruciating toxic adverse effects of cytotoxic agents. Immunotherapy currently in the development during 2016-2036 is not likely to win the war on cancer. It is half way through, the cancer mortality remains in the trend of escalation at a rate of 0.2% annually [3]. There is no reason for immunotherapy to be successful. The critical issue to the success of cancer therapy is the elimination of CSCs. Cancer establishments have no solution of CSCs. The alliance of Virchow and Liau et al. has the intelligent solution of CSCs via CDA formulations [38-41]. Cancer patients if responding will to Antineoplaston therapy, which could induce both CSCs and CCs to undergo terminal differentiation, CDA levels would gradually increase to the level of healthy people [42]. Cancer patients if not responding well to Antineoplaston therapy, CDA levels would continue to decline. Not all cancer patients responded well to Antineoplaston therapy. The responders were the majority. Cancer cells are known to express a high level of degradative enzymes to salvage substrates for macromolecular syntheses to support faster growth. DIs and DHIs are natural metabolites which may be degraded in faster growing cancer cells to lose activities. Antineoplaston therapy achieved a remarkable therapeutic success during 1976-1990, unfortunately it was blocked by cancer establishments because it was not toxic to cause the tumor to shrink. That was the most grave mistake of cancer establishments [43]. The same rule they put up to block the acceptance of Antineoplastons also block their mission to win the war on cancer, because induction of TD is the only option to solve the issue of CSCs [38-41]. Solution of CSCs is an absolute necessity to the success of cancer therapy. It is incredible that the cancer establishments put up a rule to defeat themselves. MDSs are a classic model to elucidate the evolution of cancer due to wound unhealing. MDSs often start with a display of immunological disorder to trigger the production of inflammatory cytokines [13]. TNF among cytokines produced is the critical factor related to the development of MDSs [12, 14, 15]. It causes excessive apoptosis of bone marrow stem cells, thus severely affecting the production of hematopoietic cells such as erythrocytes, platelets or neutrophils. TNF is also responsible for the collapse of chemo-surveillance as above described to force the evolution of CSCs from PSCs to escape contact inhibition which is a safety mechanism to limit the extent of proliferation of PSCs. It takes a single hit to silence TET-1 enzyme to convert PSCs to become CSCs, allowing CSCs to propagate beyond the space limit. The propagating pathological cells of MDSs have been identified as human CSCs [44]. So, MDSs are diseases attributable entirely to CSCs. Induction of TD is the only option to solve CSCs [38-41]. Vidaza, Decitabine and CDA-2 were the three drugs approved by the Chinese FDA for the therapy of MDSs. CDA-2 was a preparation of wound healing metabolites purified from urine we produced [45]. Vidaza and Decitabine were also approved by the US FDA for the therapy of MDSs. Professor Ma, the Director of the Harbin Institute of Hematology and Oncology, was instrumental in carrying out clinical trials of all three MDSs drugs in China. According to his assessments based on two cycles of treatment protocols, each 14 days, CDA-2 had a noticeably better therapeutic efficacy based on cytological evaluation, and a markedly better therapeutic efficacy based on hematological improvement evaluation, namely becoming independent of blood transfusion to stay healthy as shown in Fig. 2, which is reproduced from the reference [46]. Fig. 2 is a very valuable datum produced by Professor Ma to support the validity of cancer evolving due to wound unhealing. Therapy of MDSs requires the conversion of pathological cells to become functional cells. Induction of TD of pathological cells is the only option. CDA-2 achieves the therapy by targeting on the tumor factor telomerase of abnormal MEs [17, 45], whereas Vidaza and Decitabine achieve the therapy by the covalent bond formation between MT and 5-azacytosine incorporated into DNA [47]. CDA-2 is without adverse effects, whereas Vidaza and Decitabine are proven carcinogens [48, 49], and very toxic to DNA [50-52]. CDA-2 is clearly the drug of choice for the therapy of MDSs. We have predicted that the winner of the contest to eradicate CSCs won the contest of cancer therapies. We were the clear winner. But our winner's status was stripped by the cancer establishments who put up the rule of tumor shrinkage as a condition of cancer drugs. CDA-2 can turn CSCs to become functional cells as the therapy of MDSs demonstrated. It can also turn solid hepatocarcinoma into well organized structure very much like normal hepatic histology as shown in Fig 3, which is reproduced from the reference [53]. Requirement of the disappearance of tumor as a cancer drug is incorrect. CSCs are critically linked to wound unhealing. Induction of TD is the only option for the solution of CSCs. CCs are not critically linked to wound unhealing. But induction of TD can also be an option to put away CCs. Terminally differentiated CCs are unable to proliferate. If the residual tumor is

a concern, it can be safely removed by surgery without the feared possibility of the dissemination of metastasis.In summary, Virchow introduced a valid concept of cancer evolving due to wound unhealing. He did not produce experimental data to advance his outstanding concept. The experimental data we produced as shown in Fig. 1-3 and Table 1, strongly support the validity of his concept of cancer evolving due to wound unhealing. Thus, Virchow and Liau et al. are in an alliance to promote the perfection of wound healing as an intelligent solution of cancer.

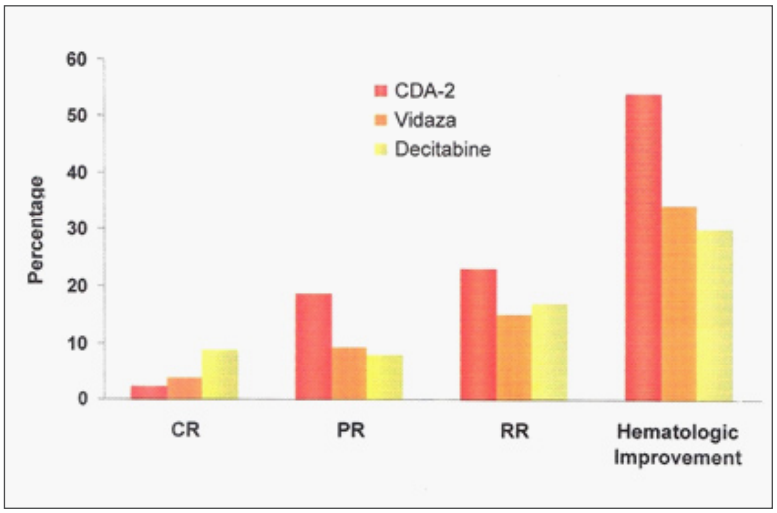
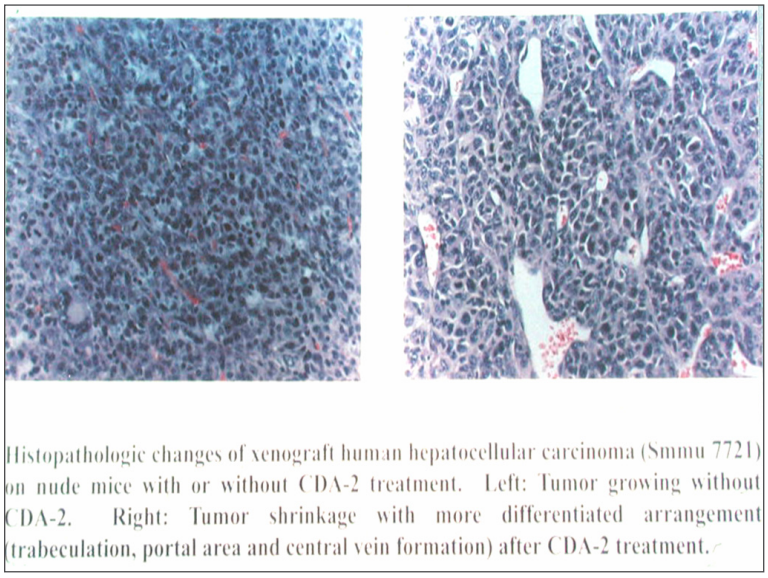


Figure 2.*CDA-2 as the Best Drug for the Therapy of MDSs*



Histopathologic changes of xenograft human hepatocellular carcinoma (Smmu 7721) on nude mice with or without CDA-2 treatment. Left: Tumor growing without CDA-2. Right: Tumor shrinkage with more differentiated arrangement (trabeculation, portal area and central vein formation) after CDA-2 treatment.

Figure 3. *Histological Chages of Solid Hepatoma Smmu 77721 Induced by CDA-2*

2.2 On the Mechanism of Wound Healing

Wound healing comes naturally. It is a very simple matter unable to attract attention. But if wound is not healed, it can lead to disastrous consequences. Cancer is an example as above described. We should pay more attention to wound healing. Wound healing requires the proliferation and the TD of PSCs [19]. Wound usually triggers biological and immunological responses. The biological response involves the release of arachidonic acid (AA) from membrane bound phosphatidylinositol through phospholipase A2 for the synthesis of prostaglandins (PGs) by cyclooxygenases and PG synthases [54, 55]. Although AA and PGs are active DIs [56, 57], the induction of TD of PSCs at the initial stage of wound is not the primary objective of PGs. Rather, the localized inflammation caused by PGs [54] 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 that is the primary objective of PGs to orchestrate the healing process. Chemo-surveillance mediated through DIs and DHIs normally functions as a brake to prevent the buildup of cells with abnormal MEs such as PSCs. The brake provided by DIs and DHIs must be released for PSCs to proliferate to produce enough cells to heal the wound. PGs are metabolically

unstable [54]. Their biological effects are most likely brief and confined to the wound area. Thus, the promotion of the proliferation of PSCs is the primary objective of PGs on wound healing, whereas the induction of TD of PSCs at the final stage of wound healing is accomplished by chemo-surveillance. The stable end products of PGs may participate in the final stage of wound healing, which are also active as DIs, although not as active as PGs [56].

The immunological response triggered by wound is not good for wound healing. Immunological response tends to trigger the infiltration of leukocytes to produce cytokines, which are toxic proteins to assist immunotherapy. These toxic proteins create wounds to aggravate the already bad situation of wound unhealing. TNF among cytokines is particularly bad for wound healing as above described. It appears that immunological response can act antagonistically to chemo-surveillance on wound healing. It is the balance of biological response and immunological response to dictate the outcome of wound healing. If biological response prevails, wound is healed. If immunological response prevails, wound cannot be healed to result in the display of clinical symptoms. If the symptom is a fatal symptom like the white lung of COVID-19 infection or heart attack of CVDs, fatality is the endpoint. If the symptom is not a fatal symptom like the wound created by carcinogens, there is a great possibility that unhealed wound will be forced to evolve into cancer. Wound unhealing in most instances is due to the collapse of chemo-surveillance caused by pathological buildup of TNF. Chemo-surveillance is always operating at the maximum capacity. There is no mechanism to replenish chemo-surveillance when it is destroyed. So, the pressure will buildup to force the proliferation of PSCs. The proliferation of PSCs is limited by contact inhibition. PSCs are then forced to evolve into CSCs to escape contact inhibition. It takes a single hit to silence TET-1 enzyme to achieve the conversion [58, 59]. This is a very easy task for PSCs to accomplish, since these cells are equipped with exceptionally active MEs. This is the initial process of oncogenesis as demonstrated in the diseases of MDSs above described. The proliferation of CSCs still cannot heal the wound, because the problem is the collapse of chemo-surveillance to induce TD of PSCs and CSCs, not the insufficiency of stem cells. CSCs are then forced to progress to faster proliferating cancer cells (CCs) by chromosomal abnormalities to activate oncogenes by translocations or to inactivate suppressor genes by deletions. Thus, the concept of cancer evolving due to wound unhealing introduced by Virchow is a valid concept. Evidently, the proliferation of PSCs to replace damaged cells is an important aspect of wound healing. PSCs are the stem cells most well protected like CSCs [31-37]. Wound unhealing due to the shortage of PSCs can only happen when these cells are prematurely induced to undergo TD. Kidney failure obviously is a case of damage to the glomerulus resulting in the accumulation of wound healing metabolites to cause premature TD of PSCs in an attempt to repair the damage. The situation is like the entry of thalidomide to cause malformation of limb. Placenta must function as a barrier to limit the entry of maternal wound healing metabolites into fetal blood circulation to interfere fetal development. Wound healing metabolites are hydrophobic that cannot pass through plascenta. But thalidomide is hydrophilic which is allowed to pass through placenta barrier to inhibit MEs to cause premature TD of PSCs to result in malformation of body parts. Malformation of limb is non-lethal. If malformation affects important organs such as brain or heart, the malformation may cause still birth. The solution of wound unhealing of kidney failure must be handled differently to focus on the promotion of the proliferation of PSCs. Brain is a compartment protected by blood brain barrier. Brain compartment is enriched in hydrophobic metabolites similar to the situation of kidney failure with too much wound healing metabolites to induce premature TD of PSCs. Dementia is a case of neurological cells damaged by beta-amyloid and tau proteins. Premature induction of TD of PSCs during wound healing may also be the reason unable to heal the wound to lead to Alzheimer's disease. Majority of wound unhealing is caused by the collapse of chemo-surveillance that can be cured by CDA formulations.

2.3 Fatal Diseases Evolving due to Wound Unhealing

Wound unhealing can cause fatal diseases, but is always neglected by the health authorities. White lung of COVID-19 infection is caused by the buildup of PSCs unable to undergo TD because of the collapse of chemo-surveillance during the earlier stage of viral infection producing too much TNF [60]. White lung is a fatal symptom of COVID-19 infection. If this symptom can be effectively controlled, COVID-19 may not be so fearful. CDA-formulations are the right solution of white lung. Tissue fibrosis symptoms are like the white lung of COVID-19 infection due to the buildup of PSCs unable to undergo TD because of the collapse of chemo-surveillance [61, 62]. CDA formulations are the best drugs to target the cause of

diseases. It is the wisdom of oriental medicine to stress the importance of drugs that can prevent the diseases from taking place as the best drugs, and the drugs to target the cause of the diseases as the next to the best drugs [16]. Wound unhealing is the cause of fibrosis symptoms. CDA formulations are the right drugs to target the cause of diseases evolving due to wound unhealing. CVDs, the top killer of humans, are also caused by wound unhealing [63]. CVDs are caused by the damages to the artery's inner lining that trigger the buildup of PSCs to heal the damages. Aberrant DNA methylation detected in atherosclerotic aortic samples [64-66] and elevated Hcy associated with patients of CVDs [65] are an indication of metabolism of cells with abnormal MEs. Inability of PSCs to undergo TD triggers infiltration of leukocytes and the deposit of light density lipoproteins to create the buildup of plagues to display symptom of hypertension, which is the most outstanding symptom of CVDs. Treatments of CVDs are primarily focused on the reduction of hypertension. Drugs targeting symptoms to produce immediate effects are the favorite of western medicine, which are not as effective as CDA formulations to target on the cause of wound unhealing. Vital reds is a food supplement produced by the famed cardiologist Steven Gundry [67], which contain polyphenols as the major active ingredients. Vital red is effective to clear plagues of CVDs. Polyphenols are active DHIs. The effectiveness of Vital reds to clear blocked blood vessel is very likely due to the perfection of wound healing to remove the primary cause of wound unhealing. Drugs to target on the cause are always better than drugs to target on symptoms [16].

Wound unhealing in the cases of kidney failure or dementia is quite different. Kidney failure results in the accumulation of wound healing metabolites to induce premature TD of PSCs to fail wound healing. The enrichment of wound healing metabolites in the brain compartment may also cause premature TD of PSCs in the process of wound healing to fail wound healing. So, the cause of wound unhealing must be established to offer solution. In the case of kidney failure, CDA formulations will do more harm. The intelligent solution of kidney failure is to promote the proliferation of PSCs by PGs or growth factors such as erythropoietin to produce enough PSCs to heal the wound. The solution of dementia may need the same consideration. Brain compartment is different from other body compartments. It is protected by blood brain barrier. It is enriched with wound healing metabolites. Malignant brain tumors are enriched with CSCs to counter elevated level of wound healing metabolites [68-70]. CSCs count of glioma are all above 3% [70], whereas CSCs count of other primary tumors are below 2%. According to Thon et al., tumors with CSCs count less than 1% are responsive to cytotoxic cancer therapy, whereas tumors with CSCs count above 3% are unresponsive to cytotoxic cancer therapy [70]. No wonder that cytotoxic cancer therapies are unable to put cancer away. Toxic agents kill sensitive CCs to raise the percentage of CSCs which are not responsive to cytotoxic agents [31-37]. When CSCs reach the threshold above 3%, that tumor become unresponsive to further treatments like malignant brain tumors. Cytotoxic cancer therapies including immunotherapy can save a quarter of cancer patients in the early stage, but can cause the deaths of three quarters of cancer patients in the advanced state. Perfection of wound healing is the only option to put away PSCs, which is an issue exactly the same as CSCs. Therefore, perfection of wound healing and the solution of CSCs are the utmost important issue of health profession, which has been neglected by the health authorities.

2.4 Development of CDA Formulations as the Only Intelligent Solution to Win the War on Cancer, on CVDs and on a Series of Fatal Diseases Evolving due to Wound Unhealing

We have carried out extensive studies of natural and non-natural DIs and DHIs for the manufacture of CDA formulations [16, 18, 29, 30, 38-41, 45, 56, 57, 63, 71-73]. Active DIs and DHIs are presented in Table 2 and 3, which are summarized from references above listed.

Table 2. *Active DIs*

DIs	ED25 (μM)	ED50 (μM)	ED75 (μM)
ATRA	0.18	0.36	0.75
PGJ2	7.9	13.8	20.5
PGE2	20.6	32.0	40.5
DicycloPGE2	21.0	43.5	-
AA	21.0	42.0	-
BIBR1532	32.3	43.7	55.1
Boldine	60.1	78.8	94.2

$ED_{25,}$ ED_{50} and ED_{75} of DIs and reductive index 0.5 ($RI_{0.5}$) of DHIs are included to facilitate manufacturing of CDA formulations. $RI_{0.5}$ of DHI is equivalent to ED_{25} of DI, which can be determine through procedure previously reported [70]. DIs and DHIs can be excellent cancer drugs. ATRA, a DI, is the standard care of acute promyelocytic leukemia [74] and gleebec, a DHI, is the standard care of chromic myeloid leukemia [75]. It has to demonstrate an excellent therapeutic efficacy to be designate as a standard care. ATRA requires the expression of the receptor of ATRA, namely RAR, to achieve the therapeutic efficacy. RAR is a repressor of the gene coding for oligoisoadenylate synthetase. The association of RAR with ATRA activates oligoisoadenylate synthetase gene to produce oligoisoadenylate synthetase. The product of this enzyme, oligoisoadenylate, is the active DI to destabilize abnormal MEs [76]. ATRA is actually an indirect DI. Oligoisoadenylate has to be synthesized inside the cell to function. The triphosphate structure prevents it to be taking in from ouside by the cell. The rest of DIs in Table 2 are direct DIs. PGs are approved drugs for the delivery and BIBR1532 and boldine are approved cancer drugs as telomerase inhibitors. Telomerase is a recognized oncogenic protein. The association with MEs to make MEs abnormal is the most important reason for telomerase to become an oncogenic protein, that was our finding not generally recognized. CDA formulations achieve cancer therapy by antagonizing two important oncogenic proteins, telomerase and TNF.

Table 3. *Active DHIs*

SAHH Inhibitors	RI0.5 (μM)	Signal Transduction Inhibitors (STIs)	RI0.5 (μM)
Pyrivinium Pamoate	0.012	Sutent	0.28
Vitamin D3	0.61	Berberine	1.62
Dexamethasone	0.75	Vorient	10.1
Beta-Sitosterol	1.72	Gleevec	11.9
Dihydroepiandrosterone	1.79	Selenite	19.7
Prenisolone	2.22		
Hydrocortisone	4.59	Polyphenols	RI0.5 (μM)
Pregnenolone	7.16		
		Tannic Acid	0.37
MT Inhibitors	RI0.5 (μM)	EGCG	0.62
		Resveratrol	1.16
Uroerythrin	1.9	Curcumin	1.24
Hycanthone	2.1	Kuromanin	1.43
Riboflavin	2.9	Coumestrol	1.95
		Genisteine	2.19
MAT Inhibitor	RI0.5 (μM)	Pyrogallol	3.18
		Silibinine	3.80
Indol Acetic Acid	220	Caffeic Acid	3.87
Phenylacetylvaline	500	Ferulic Acid	7.41
Phenylbutyric Acid	970	Ellagoc Acid	4.45
Phenylacetylleucine	780	Gallic Acid	5.35
Butyric Acid	850	Phloroglucinol	38.82

As shown in Table 3, inhibitors of SAHH and MT are better DHIs than inhibitors of MAT. The stability of three MEs is proportional to the enzyme mass [20]. SAHH is the smallest of the three, and is the most unstable enzyme that requires steroid hormone to assume a stable configuration for the formation of MT-SAHH dimer to become stable. MAT has a mass similar to the MT-SAHH dimer, which is the most stable enzyme of the three. The association with telomerase in abnormal MEs further increases its stability. Therefore, it requires very large amounts of inhibitors to function as DHIs. Inhibitors of SAHH and MTs are better DHIs. Although pregnenolone is not the most active DHI, we consider it as a very valuable DHI. It is the master substrate of all biologically active steroids. It is also a single steroid to have profound

influence on the development of cancer. According to Morley, the production of pregnenolone is bell shape in relation to ages with a peak daily production of around 50 mg at the ages of 20-25 [77]. The youngest and the oldest people produce the lease amounts of pregnenolone, and these are the two age groups most vulnerable to develop cancer. It is our top choice to make CDA-PSC, CSC.

DIs are more important than DHIs for the induction of TD. But DIs alone cannot achieve differentiation to reach completion, because elimination of telomerase from abnormal MEs tends to cause the dissociation of MEs into individual enzymes. MT as a monomer has a tendency to be modified by protease to become nuclease, which can create damage to disrupt differentiation process. The damage can be repaired to cause recurrence. The therapy of acute promyelocytic leukemia with ATRA was excellent, reaching above 90% complete remission, but most patients recurred within one year [74]. The inclusion of SAHH or MT inhibitors can keep MT-SAHH dimer intact to prevent modification of MT to become nuclease to disrupt differentiation process. It is a good idea to include both DI and DHI to make CDA formulations.

The finding of STIs as excellent DHIs is expected, since STs always lead to the production of factors to enhance the activity of MEs. STIs are tyrosine kinase inhibitors, but the inhibition of the activity of MEs is the consequence. STIs and inhibitors of MEs become synonyms. The finding of polyphenols as excellent DHIs is a surprise. Epigallocatechin-3-gallet (EGCG) has been found as a good STI to inhibit MT [78, 79]. It is possible that all polyphenols act via inhibition of tyrosine kinase to result in the inhibition of MEs like EGCG. Vital reds is a food supplement containing polyphenols as the major active ingredients which is produced by the famed cardiologist Steven Gundry [67]. Vital reds is effective to clear blocked blood vessel to cure CVDs. Gundry is a famous cardiologist. He found an intelligent solution of CVDs in alliance with our promotion of perfection of wound healing to put away fatal diseases evolving due to wound unhealing. Polyphenols are generally considered as health foods. The finding of polyphenols as excellent DHIs enhances the credibility of polyphenols as health foods.

The manufacture of CDA formulations can be the following formulas to reach plasma concentrations as ED_{25} of a DI + $3xRI_{0.5}$ of a DHI, or ED_{50} of a DI + $2xRI_{0.5}$ of a DHI, or ED_{75} of a DI + $RI_{0.5}$ of a DHI [38]. We recommend to make two sets of CDA formulations: one set CDA-CSC, PSC consisting of AA + pregnenolone to access to PSCs and CSCs, and another set CDA-CC consisting of BIBR1532 + pyrivinium pamoate to resist enzymatic degradation of natural active ingredients by faster growing cancer cells. The application of phenylacetylglutamine is also recommended to antagonize TNF, which can be administered independently as a capsule preparation and monitored independently through quantitative assay of plasma and urinary peptides as described in Table 1 [9, 42]. The therapeutic endpoint of phenylacetylglutamine can be the recovery of CDA to reach the healthy level of 5.0 of the Table 1. The therapeutic endpoint of cancer can be the drop of carcino-embryonic antigens to the acceptable values. The therapeutic endpoint of CVSs can be the drop of blood pressure to normal value. Therapeutic endpoint of other fatal diseases can be the disappearance of clinical symptoms.

2.5 Promotion of the Alliance of Virchow-Liau et al. as the Only Intelligent Solution to Win the War on Cancer, on CVDs and on a Series of Fatal Diseases Evolving due to Wound unhealing.

Health profession is a dumb profession unable to solve simple problems evolving due to wound unhealing. Health profession is dominated by powerful inept bosses who are not only unable to solve problems, but also to block the solution. This is a political issue which must be resolved by political means. Since the solution of top killing diseases is an important issue of national interest. Congressional hearing is appropriate to investigate why health profession cannot put out simple diseases such as cancer, CVDs and many other diseases evolving due to wound unhealing. The alliance of Virchow-Liau et al. has intelligent solutions to put out diseases evolving due to wound unhealing. Our intelligent solutions are blocked by the inept authorities of health profession. Political leaders must step in to resolve this impasse.

3. Conclusion

Wound unhealing contribute to major killing of humans. Perfection of wound healing is the intelligent solution of diseases evolving due to wound unhealing. Cancer authorities insist on the creation of wounds to solve cancer, exactly the opposition to the advice of Virchow-Liau et al. alliance and CVDs authorities focus on the secondary symptom of hypertension to miss the more critical primary cause of wound unhealing. The alliance of Virchow-Liau et al. has intelligent solution to win the war on cancer, on CVDs

and a series of fatal diseases evolving due to wound unhealing. Our intelligent solutions were blocked by the inept health authorities. Since the solution of top killing diseases is an important issue of national interest, a congressional healing to discuss the issue is appropriate to provide a political solution.

Consent and Ethical Approval

It is not applicable.

Acknowledgements

We appreciate very much the support of studies on abnormal MEs by Professor Robert B. Hurlbert of University of Texas MD Anderson Cancer Center and Professor George C Y. Chiou of Texas A & M University Medical Center, the support of studies on DIs, DHIs and chemo-surveillance by Dr. Stanislaw R. Burzynski of Burzynski Research Institute of Stafford, TX, the support of clinical development of CDA-2 by Mr. Ringo M L. Chang of Everlife Pharmaceutical Company of Hefei, Anhui, China, and the support of the development of CDA formulations by Professor John P. Fruehauf of Chao's Family Comprehensive Cancer Center of University of California Irvine Medical Center.

Competing Interests

Authors have declared that no competing interests exist.

Funding

No funding.

4. References

1 Liau MC, Fruehauf JP. It has been half a century since President Nixon declared war on cancer: Destabilization of abnormal methylation enzymes has the blessing of the nature to win the war on cancer. Adv Complement Alt Med. 2020; 6(1): 638-639.

2 Liau MC, Fruehauf JP. Winning formulas to fulfill cancer moonshot. Intl J Res Oncol. 2022; 1(1): 1-5.

3 Google search. Cancer mortalities-American Cancer Society.

4 Virchow R. Die Cellular Pathologie in Ihrer Begrundung auf Physiologische und Pathologische Gewebelehve. Hirschwald. 1858; 16: 440.

5 Dvorak HF. Tumors: Wounds that do not heal. N Engl J Med. 1986; 315(26): 1650-1659.

6 Liau MC, Lin GW, Hurlbert RB. Partial purification and characterization of tumor and liver S-adenosylmethionine synthetases. Cancer Res. 1977; 37(2): 427-435.

7 Liau MC, Chang CF, Becker FF. Alteration of S-adenosylmethionine synthetases during chemical hepatocarcinogenesis and in resulting carcinomas. Cancer Res. 1979; 39(6): 2013-2019.

8 Kamparath BN, Liau MC, Burzynski B, Burzynski SR. Protective effect of Antineoplaston A10 in hepatocarcinogenesis induced by aflatoxin B_1. Intl J Tiss React. 1990; 12(Suppl.): 43-50.

9 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.

10 Itkin T, Rafii S. Leukemia cells "gas up" leaky bone marrow blood vessels. Cancer Cell. 2017; 32(3): 276-278.

11 Passaro d, Di Tullo A, Abarrategi A, Rousault-Pierre K, Foster K, Artiza-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.

12 Niture S, Dong X, Arthur E, Chimet U, Niture SS, Zheng W, Kumar D. Oncogenic role of tumor necrosis factor alpha-induced protein 8 (TNFA1A8). Cells. 2019; 8(1): 9. https://Doi.org/10.3390/Cells80.10009.

13 Williamson PJ, Druger AR, Reynolds PJ, Hamlin TJ, Oscier DG. Establishing the incidence of myelodysplastic syndromes. Br J Haemato. 1994; 87(4): 743-745.

14 Boula a, Vougarelis M, Glamouli S, Katrinakis G, Psyllaki M, Pontikoglou S, 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.

15 Stirewalt DL, Mhyre AJ, Marcondes M, et al. Tumor necrosis factor-induced gene expression in human marrow stroma: due to pathophysiology of MDS? Br J Haemato. 2008; 140(4): 444-453.

16 Liau MC, Craig CL, Baker LL. CDA formulations as superb and excellent cancer drugs to save cancer patients. J Cancer Reds Rev Rep. 2025; 7(1): 1-9. DOI:doi.org/10.47363/JCRR/2025(8)209.

17 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.

18 Liau MC, Liau CP, Burzynski SR. Potentiation of induced terminal differentiation by phenylacetic acid and related chemicals. Intl J Exptl Clin Chemother. 1992; 5(1): 9-17.

19 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.

20 Liau MC, Chang CF, Saunder GF, Tsai YH. S-Adenosylhomocysteine hydrolases as the primary target enzymes in androgen regulation of methylation complexes. Arch Biochem Biophys. 1981; 208(1): 262-272.

21 Racanelli AC, Turner FB, Xie LY, Taylor SM, Moran RG. A mouse gene that coordinate epigenetic controls and transcriptional interference to achieve tissue specific expression. Mol Cell Biol. 2008; 28(2): 836-848.

22 Liau MC, Hunt ME, Hurlbert RB. Role of ribosomal RNA methylases in the regulation of ribosome production. Biochemistry. 1976; 15(14): 3158-3164.

23 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.

24 Liau MC, Craig CL, Baker LL. Exceptional allosteric regulation of methylation enzymes. In: Sarydin Su (ed), Novel Research Aspects in Medicine and Medical Research. 2023; Vol 4: 39-56.

25 Prudova A, Bauman Z, Braun A, Vitvitsky V, Lu SC, Banerjee R. S-Adenosylmethionine stabilizes cystathionine beta-synthase and modulates redox capacity. Pro Natl Acad Sci USA. 2006; 103(17): 6489-6494.

26 Chiba P, Wallner C, Kaizer E. S-adenosylmethionine metabolism in HL-60 cells: Effect of cell cycle and differentiation. Biochim Biophys Acta. 1988; 971(1): 38-45.

27 Liau MC, Baker LL. Abnormal methylation enzymes as the bullseye of targeted cancer therapies. Novel Res Sci. 2021; 7(4): 1-3.

28 Liau MC, Craig CL, Baker LL. Abnormal methylation enzymes as the most critical issue of cancer. Intl Res J Oncol. 2023; 6(2): 168-172.

29 Liau MC, Burzynski SR. Differentiation inducing components of Antineoplaston A5. Adv Exptl Clin Chemother. 1988; 88/6: 9-25.

30 Liau MC, Burzynski SR. Separation of active anticancer components of Antienoplaston A2, A3 and A5. Intl J Tiss React. 1992; 12(Suppl.): 1-18.

31 Zhou S, Schuetz JD, Bunting KD, Colapietro AM. The ABC transporter Bcrp/ABCG2 is expressed in a wide variety of stem cells and is a molecular determinant of the side-population phenotype. Nat Med. 2001; 7(9): 1028-1034.

32 Zhang M, Atkinson RL, Rosen JM. Selective targeting of radiation resistant tumor initiating cells. Proc Natl Acad Sci USA. 2010; 107(8): 3522-3527.

33 Moitra K, Lou H, Dean M. Multidrug efflux pumps and cancer stem cells: Insight into therapy resistance and therapeutic development. Clin Pharmacol Ther. 2011; 89(4): 491-502.

34 Frame FM, Maitland NJ. Cancer stem cells, model of study and implication of therapy resistance mechanisms. Adv Exp Med Biol. 2011; 720(2): 105-118.

35 Kim YJ, Siegler EL, Siriwon N, Wenig P. Therapeutic strategies for targeting cancer stem cells. J Cancer Metasts Treat. 2016; 2: 233-242.

36 Bartato L, Bocchetti M, Di Biase A, Regad T. Cancer stem cells and targeting strategies. Cells. 2019; 8: 926. Https://doi.org/10.3390/cells8080926.

37 Aromini B, Masciale V, Grisendi G, Bertrolini F, Maur M, Guaitoli G, et al. Disecting tumor growth: The role of cancer stem cells in drug resistance and recurrence. Cancers. 2022; 14: 976. Https://doi.org/10.3390/cancers14040976.

38 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 J. 2019; 4(1): 1-15.

39 Liau MC, Craig CL, Baker LL. Development of good cancer drugs effective against cancer stem cells. Intl Res J Oncol. 2023; 6(2): 238-247.

40 Liau MC, Craig CL, Baker LL. Destabilization of abnormal methylation enzymes as the only viable option for the elimination of cancer stem cells to save cancer patients. Intl Res J Oncol. 2024; 7(1): 142-152.

41 Liau MC, Craig CL, Baker LL. Decoding cancer stem cells: A game change in oncology therapeutics. Arch Oncol Cancer Ther. 2025; 5(1): 24-33.

42 Liau MC, Szopa M, Burzynski B, Burzynski SR. Quantitative assay of plasma and urinary peptides as an aid for the evaluation of cancer patients undergoing Antineoplaston therapy. Drug Exptl Clin Res. 1987; 13(Suppl. 1); 61-70.

43 Liau MC, Craig CL, Baker LL. Tumor shrinkage can be a promising diagnosis toward remission or can also be an ominous diagnosis toward fatality. J Cancer Res Rev Rep. 2024; 6(6): 1-8.

44 Woll PS, Kjallquist LJ, Chowdhury O, Doolittle H. Wedge DC, Thongjuea S, et al. Myelodysplastic syndromes are propagated by rare and distinct human cancer stem cells in vivo. Cancer Cell. 2014; 25(6): 794-808.

45 Liau MC. Pharmaceutical composition inducing cancer cell differentiation and the use for treatment and prevention of cancer thereof. US Patent. 2007; 7232578.B2.

46 Ma J. Differentiation therapy of malignant tumor and leukemia. In: Treaties of Chinese Society of Clinical Oncology on the Education of Clinical Oncology. 2007; pp 480-486.

47 Santi DV, Norment A, Garret CE. Covalent bond formation between DNA-cytosine methyltransferase of DNA containing 5-azacytosine. Proc Natl Acad Sci USA. 1984; 81(22): 6993-6997.

48 Prassana P, Shack S, Wilson VL, Samid D. Phenylacetate in chemoprevention of 5-aza-2'-deoxycytidine-induced carcinogenesis. Clin Cancer Res. 1995; 1(18): 865-871.

49 Gaudet F, Hodgson JG, Eden A, Jackson-Grusby, Dausman J, Gray JW, et al. Induction of tumor in mice by genomic hypomethylation. Science. 2003; 300(5618): 489-492.

50 Palii SS, van Emburgh BO, Sankpal UT, Brown KD, Robertson KD. DNA methylation inhibitor 5-aza-2'-deoxycytidine induces reversible DNA damage that is distinctly influenced by DNA-methyltransferase 1 and 3B. Mol Cell Biol. 2008; 28(2): 752-771.

51 Kiezietepe T, Hideshima T, Catley L, Raje N, Yasui H, Shiraishi 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.

52 Yang Q, Wu F, Wang F, Cai Y, Ahang Y, Sun Q, et al. Impact of DNA methyltransferase inhibitor 5-azacytidine on cardiac development of zebrafish in vivo and cardiomyocyte proliferation, apoptosis, and the homeostasis of gene expression in vitro. J Cell Biochem. 2019 ; 120(10) : 17459-17471.

53 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. ISBN: 978-620-2-66889-7.

54 Hwa J, Martin K. Chapter 18: The eicosanoids: prostaglandins, thromboxanes and related compounds. In: Kazung BG (ed), Basic and Clinical Pharmacology (14th ed) New York, NY: McGraw-Hill Education.

55 Ho ATV, Palla AR, Blake WR, Yual ND, Wang YX, 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): 6675-6684.

56 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.

57 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 Pharcol Toxicol Res. 2021; 4(1): 7-10.

58 Kudo Y, Tateishi K, Yamamota K, Yamamota S, Asaoka Y, Ijichi H, et al. Loss of 5-hydroxy-methycytosine is accompanied with malignant cellular transformation. Cancer Sci. 012; 103(4): 670-676.

59 Ficz GM, Gibben JG. Loss of 5-hydroxymethylcytosine in cancer: Cause or consequence? Genomics. 2014; 104(5): 352-357.

60 Liau MC, Baker L L. The impact of COVID-19 pandemic on cancer patients. Intl Res J Oncol. 2022; 6(4): 13-17.

61 Wynn TA. Cellular and molecular mechanisms of fibrosis. J Pathol. 2008; 214: 199-210.

62 Rybinski B, Cukieman E. The wound healing, chronic fibrosis, and cancer progression triad. Physiol Genomics. 2014; 46(7): 223-244.

63 Liau MC, Craig CL, Baker LL. CDA formulations to remove cancer and cardiovascular diseases as the top killers of humans. Arch Oncol Cancer Ther. 2025; 5(2): 20-32.

64 Zaina S, Heyn H, Carmona FJ, Varol N, Savols S, Condom E. DNA methylation map of human atherosclerosis. Circ Cardiovasc Genet. 2014; 7: 692-700.

65 Illi B, Ciarapica R, Capogrossi MC. Chromatin methylation and cardiovascular aging. J Mol Cell Cardiol. 2015; Https://dx.doi.org/10.1016/j.yomcc.2015.02.011.

66 Shama P, Kumar J, Garg G, Kumar A, Patowary A, Karthikeyan G, et al. Detection of altered global DNA methylation in coronary artery disease patients DNA. Cell Biol. 2008;27: 357-365.

67 Gundry S. Vital reds. Google search on Steven Gundry-Vital reds.

68 Mongeri-Sacca M, Dimrino S, Der Maria R. Biological and clinical implication of cancer stem cells in primary brain tumors. Front Oncol. 2013; 3: 6.

69 Liu YC, Lee IC, Chen PYT. Biomimetic brain tumor niche regulates glioblastoma cells toward a cancer stem cell phenotype. J Neurooncol. 2018; 137(3): 511-522.

70 Thon N, Damianoff K, Hegermann J, Gram S, Crebs B, et al. Presence of pluripotent CD133+ cells correlates with malignancy of glioma. Mol Cell Neurosci. 2010; 43: 51-59.

71 Liau MC, Huang LJ, Lee DH, Chen SC, Kuo SC. Development of differentiation helper inducers for the differentiation therapy of cancer. Chin Pharm J. 1998; 50 (5): 289-303.

72 Liau MC, Liau CP. Methyltransferase inhibitors as excellent differentiation helper inducers for differentiation therapy of cancer. Bull Chin Cancer.2002; 11: 166-168.

73 Liau MC, Kim JH, Fruehauf JP. Potentiation of ATRA activity in HL-60 cells by targeting methylation enzymes. J Pharmacol Pharmaceu Pharmacovigi. 2019; 3: 009.

74 Huang M, Ye Y, Chen S, Chai JR Wang ZY. Use of all trans-retinoic acid in the treatment of acute promyelocytic leukemia. Blood. 1988; 72: 567-572.

75 Le Cjuture P, Mologni L, Cleria L, Marchesi E, Buchdunger A, Giardini R, et al. In vivo eradication of human BCR/ABL-positive cells with an ABL kinase inhibitor. J Natl Cancer Inst. 1980; 91: 163-168.

76 Bourgead MF, Beasancon F. Induction of 2',5'-oligoadenylate synthetase by retinoic acid in two transformed human cell lines. Cancer Res. 1984; 44; 5355-5360.

77 Morley JE. Hormone, aging and endocrines in the elderly. In: P. Felig & L. A. Frohman (eds), Endocrinology and Metabolism, 4th ed, McGrow-Hill Inc., Medical Publishing Division, pp. 1455-1482.

78 Fang MZ, Wang Pk Ai H, Hou Z, Sun Y, et al. Tea polyphenol-epigallocatechin-3-gallate inhibits DNA methyltransferase and reactivates methylation silenced genes in cancer cell lines. Cancer Res. 2003; 63(22): 7563-7570.

79 Supia G, Jogodic M, Magic Z. Epigenetics: A new link between nutrition and cancer. Nutrition and Cancer. 2013; 65(6): 781-792.