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RESEARCH ARTICLE

Cancer Establishments Unintentionally Block the Solution of Cancer

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Abstract

The objective of this article is to correct the mistakes unintentionally made by cancer establishments to block the solution of cancer. Cancer therapy had a bad start to rely on toxic chemicals to kill cancer cells (CCs). Perpetual proliferation of CCs was the most outstanding feature of cancer. Naturally, killing of CCs was a choice of cancer therapy and the tumor shrinkage became a standard diagnosis of the success of cancer therapy, which were made at a time when cancer was not yet completely known. Cytotoxic chemotherapy and radiotherapy were the choice of cancer establishments when President Nixon declared War on Cancer as a Presidential Project during 1971-1976, which was not successful. Despite the failure to win the war on cancer, cytotoxic chemotherapy and radiotherapy still dominated cancer therapies, simply because cancer establishments could not find drugs that could kill CCs and to cause the shrinkage of tumor better than the failed cytotoxic agents. The consequence is as expected that cancer mortality keeps on escalating.

To successfully solve cancer, it is essential to establish a valid concept of cancer. Cancer evolving due to wound unhealing was a valid concept of cancer introduced by Virchow in 1858. This valid concept was apparently forgotten by the recent authorities to direct cancer therapies in violation of this valid concept unintentionally to stir up cancer as a giant killer of cancer patients. The valid approach of cancer therapy is to heal the unhealed wounds. The cancer establishments unintentionally put up a rule of tumor shrinkage to block this valid approach of cancer therapy. The same rule also blocks their mission to win the world on cancer. Health profession is an authoritarian profession. When the mistake is made at the very top, the mistake carries on to damage the reputation of health profession as a profession unable to solve cancer and to hurt cancer patients to result in huge casualty. Cancer is actually a disease not very difficult to solve, if the solution is done correctly. Wound healing comes naturally without having to put up any effort, because the nature creates chemo-surveillance and immuno-surveillance to heal wounds perfectly. But if these protection mechanisms break down to result in wounds unhealing, it can lead to disastrous consequences such as cancer and cardiovascular diseases, the two giant killers of humans. Perfection of wound healing following the guidance of Virchow is the correct solution of cancer. Cancer establishments put up a rule of tumor shrinkage unintentionally to block the solution of cancer based on completion of wound healing, which must be remove to achieve cancer therapy.

Keywords: Cancer Therapies, Cytotoxic Therapy, Chemo-Surveillance, Differentiation Therapy, Wound Healing.

1. Introduction

Cancer therapy had a bad start to rely on toxic chemicals to kill CCs. Cytotoxic chemotherapy is a tragic byproduct of World War II. During the war, toxic sulfur mustard gas bombs were used. Victims of toxic gas all displayed depletion of leukocytes in their blood specimens, which inspired oncologists to employ toxic chemicals to kill leukemia cells. Indeed,

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toxic chemicals were very effective to kill leukemia cells to relief symptom. Cytotoxic chemotherapy thus became a standard cancer therapy, and the disappearance of tumor became a standard diagnosis for the evaluation of the success of cancer therapy. Cytotoxic cancer therapy was the therapy employed when President Nixon declared War on Cancer during 1971-1976, which was not successful [1]. If a cancer therapy is drilled as a Presidential Project to receive unlimited support of national resources but fails to achieve its goal to put cancer away, it is only fair to conclude that this particular therapy is not good for cancer therapy and should be removed. Obviously, cancer establishments were made up by leaders of various approaches. The failure of cytotoxic therapies to win the war on cancer dealt a severe blow to the leaders of cytotoxic therapies to yield the dominance to other approaches. Gene therapy was the first choice during 1976-1996, anti-angiogenesis therapy was the second choice during 1996-2016 and immunotherapy was the third choice during 2016-2036 [2]. They did not produce cancer drugs to replace failed cytotoxic agents and kept using failed cytotoxic agents for cancer therapy. The consequence is as expected that cancer mortality keeps on escalating to reach 10 million around the world in 2019 and with an expected annual increment of 5% according to the statistics of National Cancer Institute, and to reach 0.61 million in the USA in 2024 and with an expected annual increment of 0.2% according to the statistics of American Cancer Society [3]. The ever-escalation of cancer mortality is an indication of the failure of cancer therapies focusing on the killing of CCs.

Cancer stem cells (CSCs) became known in 1997 [4]. The discovery of CSCs unraveled CSCs as the cells to initiate tumor growth and the cells to cause the most fatal effects of cancer [5-9]. CSCs and CCs became competing battle fields of cancer therapy. CSCs are the far more critical battle field to decide the outcome of cancer therapy [10-13]. Our studies of abnormal methylation enzymes [14-16], chemo-surveillance [17-19], wound healing [20-24] and CDA formulations [3, 25-31] are closely related to the issue of CSCs, thus, we are in a unique position to offer the solution of CSCs to save cancer patients [3, 24, 32-39].

2. Cancer Establishments Unintentionally Block the Solution of Cancer and Discussion

2.1 Establishing a Valid Concept of Cancer to Confront Cancer Successfully

Cancer is a feared disease, because the cytotoxic therapies are excruciating and ineffective. Patients in the terminal moment are often very painful to scream day and night. When they are no longer screaming, they are dead. It is really very miserable to die from cancer. Cancer should be solved at all cost for the sake of eliminating miserable suffering of cancer patients. Cytotoxic cancer therapies dominate cancer therapy in the past including the War on Cancer during 1971-1976. Apparently, cytotoxic approach is incorrect for cancer therapy [41]. To confront cancer successfully, it is necessary to establish a valid concept of cancer [42]. Cancer evolving due to wound unhealing was a concept of cancer introduced by the Germany pathologist Virchow in 1858 [43]. Virchow was a respected pioneer on cancer. His advice may be too ancient to remain in the memory of recent cancer authorities. His concept of cancer evolving due to wound unhealing was brought up by Dvorak recently in 1986 in the privileged N Engl J Med [43] that should attract the attention of recent cancer authorities. Apparently, cancer establishments prefer the approach of killing CCs in opposition to Virchow's advice. Creation of wound and completion of wound are mutually antagonistic. Only one is the correct approach. Creation of wound dominates cancer therapies in the past. It failed the Presidential Project of War on Cancer during 1971-1976 [1], that was a decisive failure of the cytotoxic approach of cancer therapy. Obviously, cancer establishments are made up by leaders of different approaches. Leaders of cytotoxic approach constitute the major faction. The failure of the war on cancer forced them to yield the dominance to other factions. Leaders of gene therapy took over during 1976-1996, but wasted 20 years to learn the difficulty of gene therapy. The therapeutic endpoint of gene therapy is terminal differentiation which is not a favored approach of cancer establishments. The discoveries of oncogenes and suppressor genes were, however, major cancer accomplishments at that time, which also received many Nobel prizes. Scientific achievements may not be translated into benefits to help cancer patients. The leaders of anti-angiogenesis took over during 1996-2016. They also wasted 20 years to develop anti-angiogenesis therapy. The successful therapy ended up causing the death of patients due to internal bleeding, which echoed the failure of cytotoxic cancer therapies. The cytotoxic therapy may be successful, but the patients often succumb to adverse effects or recurrence. Now the leaders of immunotherapy took over during 2016-2036. Cancer establishments must have run out of choices to put the hope on immunotherapy. Cancer is basically a problem of

growth regulation going awry. Immunology has nothing to do with growth regulation. The discovery of programmed death antigen of pathological cells was an outstanding scientific achievement. Three scientists of immunotherapy were awarded Nobel prizes this year. Immunotherapy is a better version of cytotoxic cancer therapies to spare adverse effects on normal stem cells. But it has the same problem of cytotoxic cancer therapies to show ineffectiveness against CSCs and to contribute to the damage of chemo-surveillance which are the reasons to cause the failure of cytotoxic cancer therapies. CSCs are progenitor stem cells (PSCs) minus ten-eleven trasnslocator-1 (TET-1). Cell feature, antigenicity and cell mission of CSCs are exactly the same as PSCs which are tolerable to natural immune mechanisms. So, CSCs are not recognized as pathological cells by immune mechanisms even though CSCs actually contribute the most fatal effects of cancer. Immunological response tend to trigger the production of tumor necrosis factor (TNF) which is very damaging to chemo-surveillance. TNF is a cytokine produced in response to immunological response, which is very toxic to contribute to the cell killing of immunological response. TNF is also named cachectin after its notorious effect to cause cachexia symptoms. A manifestation of cachexia symptoms is the excessive urinary excretion of low molecular weight metabolites. Wound healing metabolites are among low molecular weight metabolites lost resulting in the collapse of chemo-surveillance. The collapse of chemo-surveillance is the reason wound cannot be healed to cause the evolution PSCs to become CSCs. Immunotherapy can improve the quality of life of cancer patients, but not much on cancer mortality. It is half way through on the development of immunotherapy, cancer mortality is still on the trend of escalation.

Our studies of carcinogenesis, chemo-surveillance and the mechanism of wound healing strongly support the validity of Virchow's concept of cancer evolving due to wound unhealing. Shortly after the application of hepatocarcinogens to rats, we noticed the appearance of numerous tiny hyperplastic nodules which displayed abnormal methylation enzymes (MEs) [45]. These tiny hyperplastic nodules must represent the proliferation of PSCs in the process of wound healing. Most of these tiny hyperplastic nodules disappeared shortly afterward, indicating the completion of wound healing. Only a few large size carcinomas appeared later from unhealed tiny hyperplastic nodules. If Antineoplaston A10 was administered after the application of hepatocarcinogen aflatoxin B_1, the appearance of hepatocarcinomas could be effectively prevented as shown in Fig. 1, which is reproduced from the reference [46].

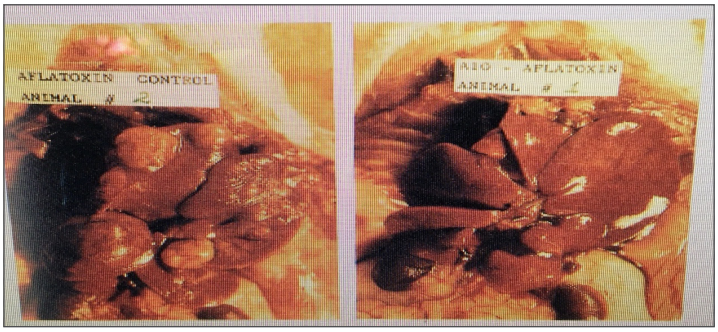


Figure 1. *Effective prevention of hepatocarcinogenesis by Antineoplaston A10.*

The figure on the left is the control liver receiving aflatoxin B1 only, and the figure on the right is the liver receiving aflatoxin B1 followed by the administration of Antineoplaston A10, namely phenylacetylglutamine.

Antineoplaston A10 Is phenylacetylglutamine which is biologically inactive chemical. But it can antagonize TNF to prevent the loss of wound healing metabolites [17]. By keeping the functioning of chemo-surveillance intact, Antineoplaston A10 can effectively prevent carcinogenesis induced by potent carcinogen. The interpretation of Fig. 1 is clear and simple that Virchow's concept of cancer evolving due to wound unhealing is correct. Wound even created by potent carcinogen if healed perfectly will not give rise to cancer.

Chemo-surveillance was a terminology we created to describe an observation that healthy people were able to maintain a steady level of metabolites active as differentiation inducers (DIs) and differentiation helper inducers (DHIs), whereas cancer patients tended to show deficiency of such metabolites as shown in Table 1, which is reproduced from the reference [17]. DIs are metabolites capable of eliminating telomerase from abnormal MEs. DHIs are inhibitors of MEs capable of potentiating the activity of DIs.

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 – 0.4 (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

Obviously, wound healing is an important health issue, so that the nature creates chemo-surveillance to ensure perfection of wound healing. Wound healing requires the proliferation and the terminal differentiation of PSCs [20]. PSCs are the primitive stem cells to initiate the development of organ or tissue during embryonic stage of fetal development. A small percentage of these cells, usually less than 2% of the organ or tissue mass, are preserved in the organ or tissue for future expansion or repair. PSCs express telomerase. MEs of cells expressing telomerase are abnormal due to association with telomerase, which changes the kinetic properties of MEs and the regulation greatly in favor of cell growth. The exceptional growth promoted by abnormal MEs is needed for the normal development of the fetus and wound healing. The operation of abnormal MEs in embryonic stem cells expressing telomerase is well guarded by safety mechanisms, Chemo-surveillance being the last defense mechanism. When this defense mechanism is destroyed, the cancer symptom shows up as presented in Table 1. Table 1 shows quantitative analyses of plasma and urinary peptides. Peptides share physical-chemical properties similar to DIs and DHIs. As a matter of fact, acidic peptides are major DIs of Antineoplaston preparations purified from urine [47, 48]. Therefore, peptides can be used as surrogate molecules to represent DIs and DHIs. If the patients undergoing Antineoplaston therapy and responded well, CDA levels could be restored back to the normal level, whereas unresponders continued to show progressive decline of CDA levels [17, 49]. Our studies of chemo-surveillance also provide experimental data to support the validity of Virchow's concept of cancer evolving due to wound unhealing.

2.2 The Logic of Wound Unhealing to Cancer and Other Diseases

Wound healing comes naturally. So, nobody cares to know how wound is healed. Take surgical wound for example, suture and antibiotic application are subsidiary measures to speed up the heal and to prevent infection. Actually, wound healing is a very important health issue, so that the nature creates chemo-surveillance and immuno-surveillance to ensure the perfection of wound healing to avoid disastrous consequences of wound unhealing, chemo-surveillance to heal wounds from toxic chemicals or physical means, and immuno-surveillance to heal wounds from infectious agents. In the case of wound healing, chemo-surveillance and immuno-surveillance act synergistically to heal wound. Wound 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 [50-52]. Although AA and PGs are active DIs [28, 29], the induction of terminal differentiation of PSCs at the initial stage of wound is not the primary objective of PGs. Rather, the localized inflammation caused by PGs [51] is the primary objective for the increase of membrane permeability to facilitate the extravasation of regulatory factors for the proliferation of PSCs in order to produce enough PSCs to heal wound. Normally, DIs and DHIs function as a brake to inhibit the proliferation of PSCs. This brake must be released in order for PSCs to proliferate. The production of PGs serves the purpose to release the brake. PGs are unstable molecules [51]. Their biological half lives are measured by seconds and minutes [50]. Thus, the biological effects of PGs must be brief and localized. PGs are produced to orchestrate the process of wound healing. The production of PGs is for the promotion of the proliferation of PSCs, whereas the terminal differentiation of PSCs to produce functional cells is achieved by chemo-surveillance. The end products of PGs may then to participate in the critical mechanism of wound healing to induce terminal differentiation of PSCs [20].

Immunological response triggered by wound is bad for wound healing, because immunological response tends to trigger the production of TNF to damage chemo-surveillance. Thus, immuno-surveillance can

be antagonistic to chemo-surveillance. 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 disastrous consequences of wound unhealing. In general, acute wound favors wound healing, whereas chronic wound tends to result in wound unhealing. Wound if unhealed because of the collapse of chemo-surveillance, there is no mechanism to rectify the collapse of chemo-surveillance. Instead, PSCs are forced to proliferate. 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 convert PSCs into CSCs [53, 54]. This is an easy task for PSCs to accomplish, since these cells are equipped with exceptionally active MEs. The evolution of CSCs still cannot heal the wound, because the problem of wound unhealing is the collapse of chemo-surveillance. CSCs are then forced to progress to faster growing CCs by chromosomal abnormalities of translocations to activate oncogenes or deletions to inactivate suppressor genes. These are the areas of remarkable cancer achievements. Unfortunately, these exceptional scientific accomplishments did not produce cancer drugs to benefit cancer patients. The correction of chromosomal abnormalities is very difficult.

Wound if not healed can lead to cancer as above described. It can also lead to other illnesses. Wounds if not healed can be the causes of tissue fibrosis, and organ failure [55, 56]. White lung is the tissue fibrosis caused by COVID-19 infection, which is fatal [57]. Liver cirrhosis caused by hepatitis B and C, although not fatal, can lead to fatal hepatoma. Dementia and neurological abnormalities are caused by toxic proteins produced by the body as a consequence of immunological responses. Cardiovascular diseases may also be caused by wound unhealing like cancer. Aberrant DNA methylation has been implicated in the cause of atherosclerosis, heart failure and cardiac arrhythmias [58]. The study of Yang el al. indicated that heart development and cardiomyocytes were very sensitive to the inhibitor of DNA methylation [59]. Vital reds is a food supplement produced by the famed cardiologist Steven Gundry, which contains polyphenols as the major ingredients. Polyphenols are excellent DHIs [27, 60], The efficacy of vital reds to open up the blocked blood vessels may be attributable to wound healing just like wound healing metabolites to cure cancer. Therefore, perfection of wound healing is good for the elimination of two giant killers of humans, cancer and cardiovascular diseases.

2.3 Abnormal MEs as the Most Critical Issue of Cancer

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 important factors to mesh up growth regulation, abnormal MEs to block differentiation and chromosomal abnormalities to speed up replication. Chromosomal abnormalities received the most attention, but produced very little benefits to help cancer patients. Aberrant tRNA methylation caught the attention of cancer establishments during a few years around 1966, and aberrant DNA methylation caught the attention of cancer establishments during a few years around 1985. But the focus of attention was on methylated tRNA and methylated DNA to miss the critical issue of abnormal MEs. Had they focused the attention on abnormal MEs like we did, cancer was solved in 1966 or 1985. Had they followed the advice of Virchow, cancer was solved in 1885. Cancer establishments are able to identify the important issues of cancer, but tend to miss the most critical point.

MEs play an essential role on the regulation of cell growth, differentiation and apoptosis by virtue of the fact that DNA MEs control the expression of tissue specific genes [61], and rRNA MEs control the production of ribosome [62], which in turn dictates the commitment of the cell to enter cell cycle [63]. If the enhanced production of ribosome is locked in place, it becomes the driving force of carcinogenesis [64]. MEs are a ternary enzyme complex consisting of adenosylmethionine transferase (MAT)-methyltransferase (MT)-S-adenosylhomocysteine hydrolase [65], which plays a pivotal role on the regulation of cell growth, differentiation and apoptosis as shown in Chart 1. Regulation of cell growth is a very important biological regulation. Enzymes involved in important biological regulation are often subjected to delicate biological regulation. Allosteric regulation is the most pervasive biological regulation. Because of the important role on growth regulation, MEs are subjected to double allosteric regulations, one on the individual enzymes and one on the enzyme complex [66]. On individual enzymes,

MEs of steroid hormone target tissues are under the regulation MEs of steroid hormone. SAHH is a steroid hormone receptor. Steroid hormone promotes

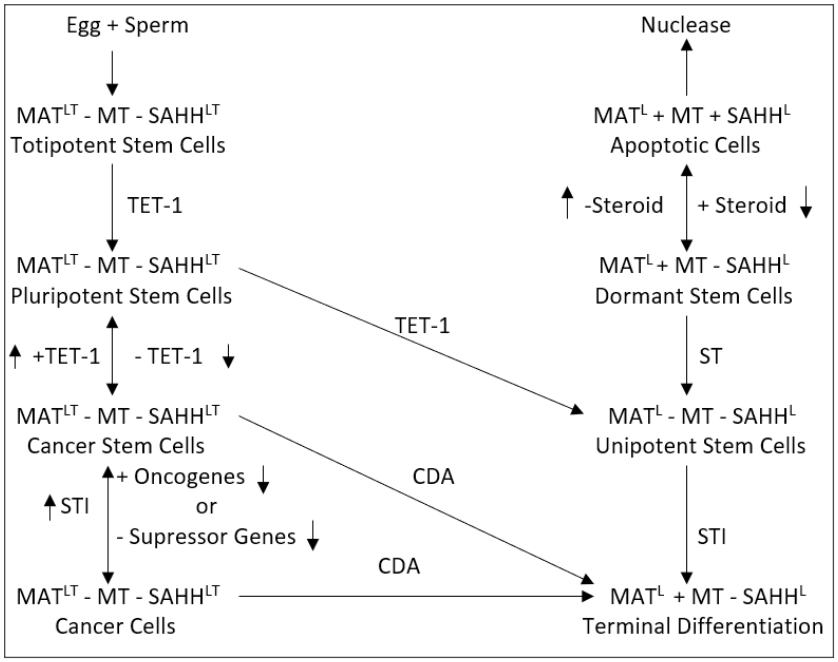


Chart 1. *Regulation of Cell Growth by MEs*

MATL and SAHHL are low Km isozyme pair of normal MEs, and MATLT and SAHHLT are telomerase associated isozyme pair. TET-1 is the enzyme to carry out lineage transitions. ST is signal transduction and STI is inhibitor of signal transduction. CDA is cell differentiation agent to induce terminal differentiation of cells expressing abnormal MEs.

the formation of MEs to become stable and functional ternary enzyme complex to engage in the promotion of cell growth. In the absence of steroid hormone, MEs dissociate into inactive MAT^L + $MT\text{-}SAHH^L$ to become dormant state or to undergo terminal differentiation. In the extreme depletion of steroid hormone, MT-SAHH dimer also dissociates into monomeric enzymes. MT in the monomeric state has a tendency to be modified by proteolytic enzymes to become nuclease, which can create damage to promote apoptosis. In telomerase expressing cells, MEs are allosterically regulated by telomerase. The association of MEs with telomerase change kinetic properties of MAT-SAHH isozyme pair and the regulation of cell growth greatly in favor of cell growth. K_m values of telomerase associated MAT-SAHH isozyme pair are 7-fold higher than K_m values of normal isozyme pair. The increased K_m values implicate that cells with abnormal MEs have pool sizes of S-adenosylmethione (AdoMet) and S-adenosylhomocysteine (AdoHcy) 7-fold higher than cells with normal MEs, which are important to promote exceptional growth of cells with abnormal MEs. The study of Prudova et al. indicated that AdoMet could stabilize protein against protease digestion [67]. Therefore, MEs with a larger pool size of AdoMet are far more stable to promote cell growth. The study of Chiba et al. indicated that when cancer cells (HL-60) were induced to undergo terminal differentiation, pool sizes of AdoMet and AdoHcy shrank greatly [68]. So, larger pool sizes of AdoMet and AdoHcy are essential to promote the growth of cells with abnormal MEs. It appears that the seed of cancer is sown at the very beginning of life, namely the fertilization of the egg with a sperm to activate totipotent stem cell which expresses telomerase. The expression of telomerase spreads through pluripotent stem cells during the embryonic development of the fetus, but secedes when pluripotent stem cells undergoing lineage transitions to reach unipotent stem cells. Exceptional growth promoted by abnormal MEs is a normal biological process during the embryonic stage of fetal development. A disruption of the operation of abnormal MEs can have deleterious effects. The disruption of abnormal MEs by thalidomide during fetal development results in the malformation of body parts, noticeably limbs. The entry of maternal DIs and DHIs may also produce deleterious effects on the development of the fetus, which does not happen. The nature has a delicate ways to prevent mishaps from happening. Placenta must play a barrier to limit hydrophobic DIs and DHIs from getting into fetal blood circulation. Thalidomide is hydrophilic to be stopped by placenta. So, abnormal MEs are established at the very beginning of life, which are passed on to PSCs, and then to CSCs when wound healing is incomplete. Contact inhibition and TET-1 enzyme play important roles to prevent the evolution of PSCs to become CSCs. The silencing of TET-1 enzyme destroys the protection mechanism to prevent the evolution of PSCs to become CSCs. The evolution

of PSCs to become CSCs is the critical first step of cancer evolution, which if effectively prevented from happening, cancer can be stopped. Figure 1, Table 1 and Chart 1 are the testimonies to these effects. Virchow was right to give the advise that cancer evolving due to wound unhealing. Consequently, the most important priority of cancer therapy is to restore chemo-surveillance to arrest the progression of carcinogenesis [65]. Since abnormal MEs are the origin of cancer to start from the very beginning of life and shared by all human cancers [15], we consider abnormal MEs as the bullseye of cancer target [66]. In other words, abnormal MEs are the most important target for cancer therapy. Indeed, abnormal MEs are the most important target, much more important than chromosomal abnormalities which received enormous attention but yielded very little benefits to help cancer patients. Afterall, oncogenes and suppressor genes are cell cycle regulatory genes. These genes have important roles to play when cells are in cell cycle replicating. But, if the replicating cells exit cell cycle to undergo terminal differentiation, these genes have no role to play. Thus, solution of abnormal MEs to push replicating cancer cells to undergo terminal differentiation can also solve chromosomal abnormalities, which are very difficult to solve. Actually, the solution of chromosomal abnormalities is not feasible. A chromosomal abnormality may be solved, there may soon pop up another chromosomal abnormality to negate the previous effort. Cancer establishments wasted 20 years, between 1976-1996, on the development of gene therapy. If they were successful in the development of gene therapy, they may waste many more years to pursue endless gene therapies. Cytotoxic cancer therapy can also put to rest abnormal MEs and chromosomal abnormalities. That has been tried, but failed.

Cells expressing telomerase are very precious stem cells. Hence, these cells are protected by drug resistance and anti-apoptosis mechanisms [5-9]. These cells express ABCG2 multidrug resistance gene to exclude toxic chemicals from getting into the cells. These cells also express aldehyde dehydrogenase and methylguanine methyltransferase (MGMT), a DNA repair gene, to detoxify toxic chemicals and to repair DNA damages to prevent apoptosis induced by toxic chemicals and DNA damages. These cells also express CXCR4 chemokine receptor to migrate to the wound area producing peptides as chemokines. All primitive embryonic stem cells are very precious and well protected. These are also the cells very tough to kill. That is why cancer therapies based on cell killing have little successful records. Besides, killing is not an option to solve the issue of CSCs, which are critically linked to wound unhealing as above described. Of course, cancer establishments knew the importance of CSCs, which became known in 1997 [4]. Approximately 18 years ago, the pharmaceutical giant GSK put up an outrageous 1.4 billion to develop monoclonal antibodies against CSCs invented by the scientists of Stanford University to develop therapy against CSCs, which was apparently not successful, because there was no announcement of the success of developing drug against CSCs, neither any follow up as if it has never happened. Yes, the cancer establishments tried to solve CSCs, but failed. This was also a very significant failure of cancer establishments.

The discovery of CSCs was a great achievement [4]. It put CSCs as the most important battle field to achieve cancer therapy [10, 12, 13, 30, 60]. Myelodysplastic syndromes (MDSs) offer a test case on the solution of CSCs. They are also a solid case to illustrate the validity of Virchow's concept of cancer evolution. MDSs often start with a display of immunological disorder [71], which prompts the local production of inflammatory cytokines. Among such cytokines, TNF is the critical factor related to the development of MDSs, since the antibody against TNF was effective to halt the progression of MDSs [72]. TNF causes excessive apoptosis of bone marrow stem cells, thus severely affect the ability of the patient to produce hematopoietic cells such as erythrocytes, platelets or neutrophils. TNF also causes damage to chemo-surveillance as above described. As a consequence, chemo-surveillance normally operating in healthy people to direct terminal differentiation of PSCs becomes dysfunctional, allowing PSCs to evolve into CSCs to propagate beyond the limit of space allowed for the propagation of PSCs. The propagating pathological cells of MDSs patients have been identified as human cancer stem cells [73]. Thus, MDSs are diseases attributable entirely to CSCs. Solution of MDSs requires the induction of terminal differentiation of PSCs and CSCs to become functional erythrocytes, platelets or neutrophils. Killing of pathological cells is not an option, as killing of pathological cells cannot produce functional erythrocytes, platelets or neutrophils. Thus far, Vidaza, Decitabine and CDA-2 are the three drugs approved by the Chinese FDA for the therapy of MDSs in China. Vidaza and Decitabine are also approved by the US FDA for MDSs therapy. Professor Ma, the Director of the Institute of Harbin

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 noticeable better therapeutic efficacy based on cytological evaluation, although slower to reach complete remission, and a markedly better therapeutic efficacy based on hematological improvement evaluation, meaning becoming independent on blood transfusion to stay alive, as shown in Fig. 2, which is reproduced from the reference [74].

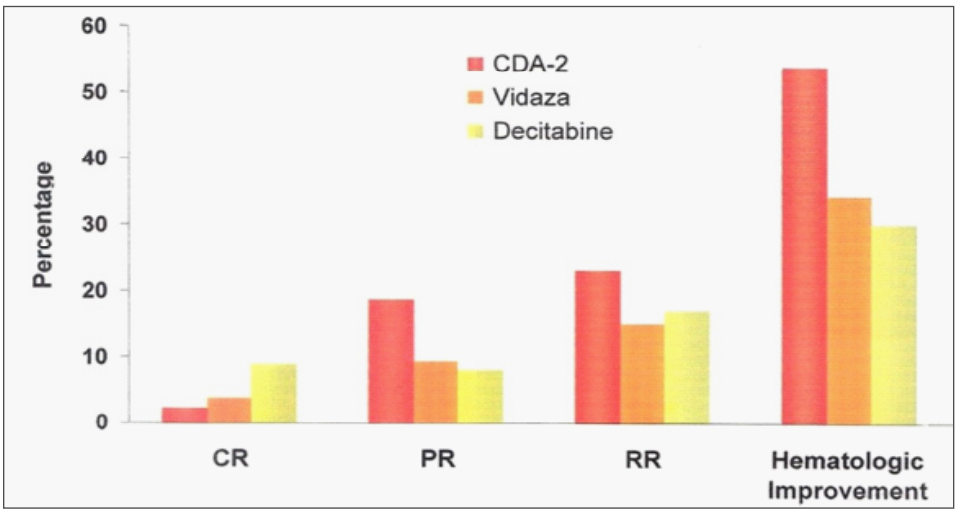


Figure 2. *CDA-2 as the Best Drug for the Therapy of MDSs*

Induction of terminal differentiation of CSCs is the only option to solve MDSs. CDA-2 achieves induction of terminal differentiation by targeting on the tumor factor telomerase of abnormal MEs [16], whereas Vidaza and Decitabine inactivate MT by the covalent bond formation between MT and 5-aza-cytosine incorporated into DNA of cancer cells [75]. CDA-2 is without adverse effects, whereas Vidaza and Decitabine are proven carcinogens [76, 77], and very toxic to DNA [59, 78, 79]. Obviously, CDA-2 is the best drug among the three for the therapy of MDSs.

We were the clear winner of the contest for the solution of CSCs [10]. Our winner's status was denied by the cancer establishments, who set up a rule of tumor shrinkage as a condition of cancer drugs. The therapeutic endpoint of CDA-2 is the terminal differentiation of CCs, which cannot make tumor to disappear. Evidently, induction of terminal differentiation of CSCs is the only option to the solution of CSCs [10, 11, 26, 37, 41, 60]. By blocking the approval of CDA-2, cancer establishments also block their mission to win the war on cancer. They became the culprits to damage the reputation of health profession as a profession unable to achieve a Presidential Project and to hurt cancer patients causing 10 million casualties annually around the world. Putting up drugs to cause the death of patients in legal term is malpractice. Cancer establishments direct the entire health profession to perform malpractice. They must remove cytotoxic agents to reduce their responsibility of malpractice.

Drugs such as CDA-2 purified from urine may not be acceptable by the western medicine which requires the listing of ingredients. Oriental medicine is therapeutical efficacy oriented medicine, while chemical composition can be largely unknown [38]. CDA-2 is acceptable in China, but not in USA. We knew the active components of CDA-2. We have carried out extensive studies of CDA-2 [25, 26, 30, 32, 47]. It consists membrane fragments containing phosphatidylinositol designated as PP-0 as the major DIs, AA or dicycloPGs in liposome complexes with pregnenolong designated as OA-0.79 as the minor DIs. Pregnenolone and steroid metabolites and uroerythrin are the major DHIs. Phenylacetylglutamine is a major chemical constituent of CDA-2. Although inactive as DI or DHI, it has important therapeutic role to restore chemo-surveillance by antagonizing TNF. Therefore, we can pattern after CDA-2 to make CDA formulations acceptable to western medicine.

2.4 CDA Formulations as the Only Cancer Drugs to Achieve Life-long Survival

Effects pf cancer therapies on the important parameters such as CSCs, CCs, unipotent stem cells (UPSs), chemo-surveillance, immuno-surveillance, tumor shrinkage and life-long survival are listed in Table 2 for comparison. Gene therapy and anti-angiogenesis are not included.

Table 2. *Comparison of Cancer Therapies on CSCs, CCs, USCs, Chemo-surveillance, Immuno- Surveillance, Tumor Shrinkage and Life-long Survival*

Cancer Therpies	CSCs	CCs	Chemo-surveillance	Immuno-surveillance	Tumor Shrinkage	Life-long Survival
Cytotoxic Therapies :						
Chemo	-	A	+	-	+	+ Early - Late
Radio	-	A	+	-	+	+ Early - Late
Immuno	-	A	-	-	+	+ Early - Late
Differretiation Therapies:						
CDA	+	B	-	0	-	+
Vidaza & Decitabine	+	B	+	-	-	+ Early - Late
Targeted	-	B	-	0	-	+

Effects on CSCs: - means cannot induce terminal differentiation of CSCs and + means can induce terminal differentiation of CSCs; on CCs: A means killing of CCs and B means induction of terminal differentiation; on USCs: + means can cause damage to USCs and – means cannot cause damage to USCs; on chemo-surveillance: – mean negative effects and + means positive effects; on immuno-surveillance: - means negative effects, + means positive effects and 0 means no effect; on tumor shrinkage: + means can cause tumor shrinkage and – means cannot cause tumor shrinkage; on life-long survival: + means patient' death is not related to cancer or its treatments, + Late means early stage cancer patient' death is not related to cancer or its treatments, - means cancer patient's death is caused by cancer or its treatments, and – Late means late stage cancer patient's death is caused by cancer or its treatments.

because to these therapies have been rejected by cancer establishments. Elimination of CSCs is essential to the success of cancer therapies [10, 11, 26, 37, 41, 60]. Cytotoxic therapies cannot affect these cells because these express drug resistance genes and anti-apoptosis mechanisms. Only early stage cancer patients can benefit from cytotoxic therapies, relying on the restoration of chemo-surveillance to subdue surviving CSCs. The success of cytotoxic therapies is actually attributable to chemo-surveillance provided by the nature which has not been damaged beyond restoration. The early stage cancer patients include CDA levels above 2.5, cancer stages in I and II without evidence of metastasis, Gleason scores below 7, and CSCs count of the tumor below 1%. According to Thou et al., CSCs counts of astrocytomas are less than 1% which are responsive to cytotoxic therapies, whereas CSCs counts of glioblastomas are above 3% which are unresponsive to cytotoxic therapies [80]. Consequently, cytotoxic therapies are not a good choice, which kill CCs to promote the proliferation of CSCs to rise above 3% to become unresponsive to cancer therapies [41, 81]. The rule of tumor shrinkage they set up for the evaluation of cancer therapy is really damaging to the success of cancer therapy, which must be removed along with the removal of DNA interacting cancer drugs. CDA formulations and targeted therapies are the best to offer life-long survivor of cancer patients. These drugs cannot cause tumor to shrink. Tumor residue is made up by terminally differentiated cells unable to proliferate, thus harmless. If it is too much of a concern, it can be removed by surgery without having to worry on cancer dissemination.

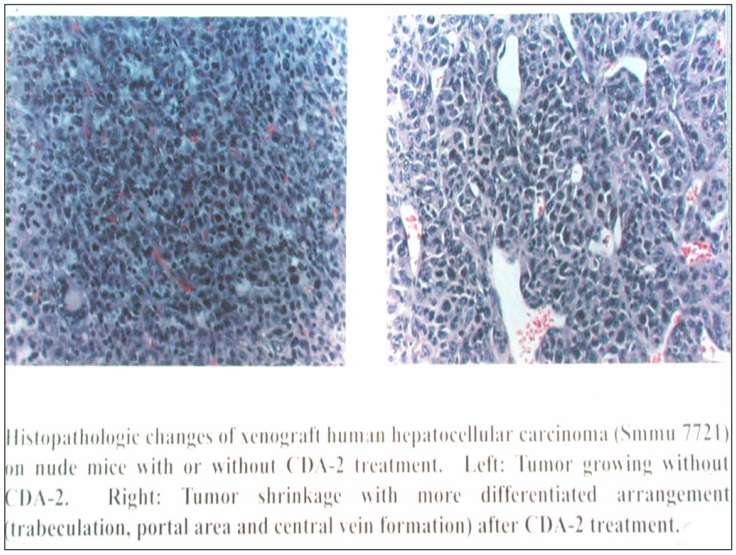
2.5 Strategies to Promote CDA Formulations

Virchow was extremely talented to comprehend the logic of wound unhealing to cancer at a time neither cancer nor wound healing was completely known [43]. Dvorak was also very talented to appreciate the logic of wound unhealing to cancer [44]. We were also extremely talented to decode the logic of wound unhealing to cancer by the discoveries of abnormal MEs [14-16], chemo-surveillance [17-19], and the mechanism of wound healing [20-24]. Hence, Virchow, Dvorak and Liau et al. are in an alliance to promote the valid concept of cancer evolving due to wound unhealing. The nature creates chemo-surveillance and immuno-surveillance. for the perfection of wound healing to avoid disastrous consequences of wound unhealing. Our alliance includes the creator of the nature. Humans can make mistakes. But the creator of the nature is always right. We are a minor alliance, but we are the right alliance to solve cancer. Although cancer establishments are not right to direct cancer therapies, they are very powerful to resist correct solution of cancer. We must develop winning strategies to challenge their blockade of CDA formulations, the

right drugs for cancer therapy. They are the bosses. We cannot get into head collision to solve the issue. We may win the arguments, but we are certainly to lose the lifeline. They control our lifeline. We have to avoid head on collision. Our strategies may include seeking approval of political leaders suffering from advanced cancer such as King Chares of England and President Biden of USA, approval of hematological oncologists, surgical oncologists and oncologists in attendance of metastatic, unresponsive and recurrent cancer patients.

King Chares's cancer was metastatic cancer. His chemo-surveillance must have been severely damaged for metastatic cancer to show up. President Biden's cancer was in advance state with Gleason score of 9 and bone metastasis. Their cancers are beyond the help of cytotoxic cancer therapies. CDA formulations are the only help they can count on. We are calling for their influence to push for the approval of CDA formulations that can help themselves and many other cancer patients in the similar desperate situation.

Tumor shrinkage is not an issue of hematological oncologists. The endpoint of hematological cance is the disappearance of cancer cells. The disappearance can be the death of cancer cells or terminal differentiation which displays morphology distinctly different from undifferentiated cancer cells. There is no arguments between out approach to push for terminal differentiation and hematological oncologists to push for the disappearance of cancer cells. Terminally differentiated cells display morphology distinctly different from undifferentiated cancer cells as shown in Fig. 3, which is reproduced from the reference [30]. Our approach of cancer therapy and the approach of hematological oncologists are the same to seek the disappearance of cancer cells. Radiological images can only reveal tumor size, but not morphological detail. Hematological oncologists may like CDA formulations better, since CDA formulations do not cause excruciating sufferings.



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. *Inductikon of Histological Modification of Hapatoma by CDA-2*

Tumor shrinkage is also not an issue to surgical oncologists. They take the tumor out. Dissemination of metastasis is their concern. Metastasis is the making of CSCs [6], and CDA formulations are the best drugs to control CSCs [10, 11, 27, 37, 41, 60]. We have published an article to call for the unification of surgeons and cancer patients to push for approval of CDA formulations to make surgery a top choice of cancer therapy [82].

CSCs are the dominant issue of metastatic, non-responsive and recurrent cancers. There are no drugs for the care of CSCs. These patients are often adviced to undergo hospice care. These patients can be saved by CDA formulations. But the damages created by cytotoxic agents are often irreversible. It is not only the problem of CSCs, although CSCs are a dominant factor. We also published an article to recommend the acceptance of CDA formulations for the rescue of metastatic, unresponsive and recurrent cancer patients [39]. The damages done by cytotoxic agents may not be rescuable.

3. Conclusion

Tumor shrinkage was a rule set up by cancer establishments to evaluate cytotoxic therapies which were apparently incorrect for cancer therapy. Cancer is caused by wound unhealing, thus forcing PSCs to evolve into CSCs and then to progress to faster growing CCs. Elimination of CSCs is essential to the success of cancer therapy. CSCs are critically linked

to wound unhealing, therefore, perfection of wound healing is the only option to deal with CSCs. CDA formulations are the best drugs for the solution of CSCs, which were blocked by cancer establishments because these drugs could not make tumor to disappear. The blockade of CDA formulations was a grave mistake of cancer establishments, which also blocked their mission to win the war on cancer. This mistake must be rectified to achieve cancer therapy.

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The authors declare no conflicts of interests.

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