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Establishing a Valid Concept of Cancer to Confront Cancer Successfully

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ABSTRACT

The objective of this article is to establish a valid concept of cancer in order to pursue a right approach of cancer therapy. Cancer is a complex disease involving multiple contributing causes. Elucidation of all contributing causes is important to establish a valid concept of cancer to confront cancer successfully, Cancer therapies in the past have been based on piecemeal displays of cancer symptoms, resulting in a horrible record of 10 million annual mortality worldwide. A more effective cancer therapy based on the valid concept of cancer is definitely needed to turn around the ever escalation of cancer mortality. The valid concept of cancer evolving due to wound unhealing was introduced by Virchow in 1858, which was unfortunately ignored by the cancer establishments. Evidently wound healing is an important issue of health, so that the nature creates chemo- and immuno-surveillance for the perfection of wound healing. The collapse of chemo-surveillance is closely related to wound unhealing, forcing progenitor stem cells (PSCs) to evolve into cancer stem cells (CSCs), and then to progress to faster growing cancer cells (CCs). The appearance of CSCs is critically linked to wound unhealing, and the appearance of CCs is also attributable to wound unhealing. Therefore, healing wound is a valid concept to confront cancer successfully.

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Introduction

Cancer is an old and feared disease, because treatments in practice are excruciating and ineffective. Cancer therapy had a bad start to rely on toxic chemicals to kill CCs which was developed at a time we did not have complete knowledge of cancer. Cytotoxic chemotherapy was 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 use toxic chemicals to treat leukemia patients. Toxic chemicals are indeed very effective to eliminate leukemia cells. Thus, cytotoxic chemotherapy became a standard care of cancer and the reduction of tumor became a requirement as cancer drugs. Both are wrong. CCs are not very critical because these cells are not that fatal in comparison to CSCs which are not known at that time [1-5]. The use of toxic chemicals is particularly bad, which can kill CCs, but also can kill cancer patients [4,6-10]. Cytotoxic agents and radiation were the major drugs employed during the War on Cancer declared by President Nixon during 1971-1976, which was not successful [11]. If a cancer drug is drilled through as a presidential project to receive unlimited support from national resources, but fails to achieve its goal, it is only fair to conclude that this drug is not good for cancer therapy and should be removed. Apparently, cancer establishments agreed to this conclusion and started to search alternatives to cytotoxic agents and radiation [12]. They wasted 20 years, 1976-1996, to learn the difficulty of gene therapy, which was obviously a top choice to replace chemotherapy and radiotherapy. Gene therapy is a right choice. Chromosomal abnormalities are a pivotal issue to mess up growth regulation, which is the most important issue of cancer. Many scientists in this field received Nobel prizes, the highest honors of scientific excellency. They gave up, because it was really very difficult to achieve gene therapy. They wasted another 20 years, 1996-2016, unsuccessfully to develop anti-angiogenesis therapy, their second choice. The successful anti-angiogenesis therapy ended up causing the death of patients due to internal bleeding. That echoed the failure of chemotherapy. The successful chemotherapy to reach complete remission ended up causing the death of cancer patients due to adverse effects or recurrence. Now, they are engaged to the third choice of immunotherapy during 2016-2036. It is too early to make a definitive conclusion. It does not look promising, because cancer is basically a problem of growth regulation going awry. Immunology has nothing to do with growth regulation. Meanwhile, they keep on using failed cancer drugs to result in ever-escalation of cancer mortality. That is inexcusable.

CSCs became known in 1997 [13]. The discovery of CSCs unraveled a very important issue of cancer to reveal CSCs as the cells to initiate tumor growth and to contribute to the most fatal effects of cancer [14-19]. Thus, elimination of CSCs is essential to the success of cancer therapy [5, 20, 21]. Our studies of abnormal MEs [22-24]; chemo-surveillance [25-27]; wound healing [28-32]; and cell differentiation agent (CDA) formulations [22-37] are closely related to the issue of CSCs. Thus, we are in a unique position to offer the solution to CSCs to put cancer away.

Establishing a Valid Concept of Cancer to Confront Cancer Successfully

Establishing a Valid Concept of Cancer

Establishing a valid concept of cancer is extremely important to the solution of cancer. Thus far, we have been directed by cancer establishments to fight cancer based on piecemeal displays of cancer symptoms, which were not successful [11]. Perpetual proliferation of CCs was the most outstanding symptom of cancer. But it was not the most critical issue of cancer. We were directed to kill CCs to stop perpetual proliferation of CCs. The result was cancer mortality kept on escalating. We have to explore what causes CCs to proliferate perpetually. Elimination of the causes is far more effective than the elimination of the symptoms to stop the perpetual proliferation of CCs. It is the wisdom of oriental medicine that stresses the importance of drugs that can prevent the disease from taking place and the drugs to target the cause of disease [38]. Oriental medicine regards the drugs that can prevent the diseases from taking place as the best drugs, and the drugs to target the causes of the disease as the next to the best. Western medicine appears to like the drugs that can put out symptoms to produce immediate effects, which are the drugs not valued highly by the oriental medicine.

Cancer evolves due to wound unhealing. The concept of cancer evolving due to wound unhealing was introduced by the great German pathologist Virchow in 1858 [39]. Virchow was a very well respected pioneer on cancer. But his concept of cancer evolving due to wound unhealing was not accepted by the cancer establishment. Had his concept of cancer evolving due to wound unhealing accepted by the cancer establishment, chemotherapy would not come into practice. Chemotherapy creating wound definitely violates his concept. Virchow's concept of cancer evolving due to wound unhealing was brought up once 128 years later by Dvorak [40]. Again, it was ignored by the cancer establishments. Cancer establishments have a tendency to ignore very critical concept they don't like to result in the failure to solve the important problems. They ignored the very important concept of Virchow to let caner becoming a difficult disease to torment human being for 167 years. Now it becomes a giant killer of advanced cancer patients to claim 10 million casualties annually worldwide. Burzynski unknowingly pursued cancer therapy during 1976-1990 following the Virchow's guidance of wound healing employing wound healing metabolites purified from urine he named Antineoplastons to produce impressive results, which was unfortunately blocked by the cancer establishments [41]. We knew the practice of Burzynski targeting abnormal MEs to achieve wound healing was an excellent approach of cancer therapy [10]. We went to China to develop CDA-2 which was disallowed in the USA, and proved that CDA-2 was an excellent cancer drug and the best drug to solve CSCs [34,42]. Cancer is after all not that difficult to solve if the solution follows the valid concept. Cancer evolving due to wound unhealing is a valid concept. We have produced two experimental data to support the validity of this concept. One datum was the selective destruction of chemo-surveillance in cancer patients as shown in Table 1, which is reproduced from the reference [25].

Table 1: Chemo-Surveillance Selectively Destroyed in Cancer Patients

Plasma/Urine Peptide Ratio	CDA Levels	Patient Number	% 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

Chemo-surveillance was a terminology we created to describe an observation that healthy people could 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. DIs are metabolites that can eliminate the tumor factor telomerase from abnormal MEs [24] and DHIs are metabolites active as the inhibitors of MEs that can strongly potentiate the activity of DIs. DIs and DHIs are hydrophobic metabolites produced by the degradative products of dead erythrocytes [41] and organs involved in steroid hormone metabolism. Peptides share physical chemical properties similar to DIs and DHIs. Therefore, peptides can be used as surrogate molecules to represent the level of DIs and DHIs in the plasma and the urine. Quantitative determination of peptides presented in Table 1 clearly shows CDA levels are selectively destroyed in cancer patients.

DIs and DHIs are critically involved in wound healing. Wound triggers biological and immunological responses [43]. The biological response involves the release of arachidonic acid (AA) from membrane bound phosphatidylinositol for the synthesis of prostaglandin E2 (PGE2) to orchestrate wound healing process. PGE2 causes edema in the wound area to promote the proliferation of PSCs during the initial phase of wound. PSCs are the most primitive stem cells to initiate the development of organ or tissue during the embryonic stage of fetal development. A small number of these cells, usually less than 2% of the organ or tissue mass, is reserved for the expansion or repair of organ or tissue. The final phase of healing is carried out by chemo-surveillance [28]. Therefore, the functionality of chemo-surveillance dictates the success of wound healing [26]. The functionality of chemo-surveillance can be influenced by immunological response triggering the production of tumor necrosis factor (TNF). 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 due to blood vessel hyperpermeability created by TNF [44,45]. DIs and DHIs are among low molecular weight metabolites excreted, resulting in the collapse of chemo-surveillance to cause wound unhealing and the initiation of cancer evolution. The immunological response of wound is bad for wound healing. It is the balance of biological response and the immunological response triggered by the wound to decide the outcome of wound healing. If biological response prevails wound is healed. If immunological response prevails wound cannot be healed to result in the clinical symptoms such as tissue fibrosis, organ failure, dementia or cancer. Acute wounds

usually favor wound healing and chronic wounds often results in wounds unhealing to produce clinical symptoms.

The second datum we produced to support the Virchow's concept of cancer evolving due to wound unhealing is presented in figure 1, which is reproduced from our studies of prevention of aflatoxin B1 induced hepatocarcinogenesis by Antineoplaston A10, namely phenylacetyl-glutamine [46]. Phenylacetylglutamine can effectively antagonize TNF to protect the functionality of chemo-surveillance [25,41]. By the protection of the functionality of chemo-surveillance, cancer can be effectively prevented even under the challenge with a potent carcinogen. The validity of Virchow's concept of cancer evolving due to wound unhealing is strongly supported by our experimental data shown in Table 1 and Figure 1.

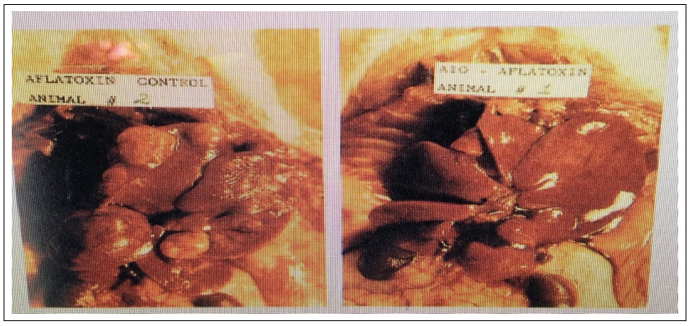

Figure 1: Effective Protection of Aflatoxin B1 Induced Hepatocarcinogenesis by Phenylacetylglutamine (Antineoplaston A10)

Wound unhealing under most circumstances is attributable to the collapse of chemo-surveillance. The nature does not have a mechanism to rectify the collapse of chemo-surveillance which is always operating at the maximum capacity. Instead, the natural response is to force PSCs to replicate. The capacity of PSCs proliferation is limited by contact inhibition. PSCs are then forced to evolve into CSCs in order to escape the limitation of contact inhibition. It takes a single hit to silence ten-eleven translocator-1 enzyme (TET-1), which is an enzyme responsible for lineage transitions, to convert PSCs to become CSCs, which is an easy task for PSCs to accomplish since these cells are equipped with exceptionally active abnormal MEs. The proliferation of CSCs still cannot heal the wound, because the problem is the collapse of chemo-surveillance. CSCs are then forced to progress to faster replicating CCs by translocations or deletions of chromosome to activate oncogenes or to inactivate suppressor genes eventually pushing CSCs to become full blown CCs. The appearance of CSCs in the primary tumor is critically linked to wound unhealing. Therefore, induction of terminal differentiation by destabilization of abnormal MEs is the only option to solve the issue of CSCs, which is also a key mechanism to achieve wound healing [47].

Destabilization of Abnormal MEs as the only Option for the Solution of CSCs to Achieve
Life-long Survival of Cancer Patients

Evolution of cancer proceeds from PSCs due to wound unhealing to become CSCs, and then from CSCs to progress to CCs still due to wound unhealing. The occurrence of myelodysplastic syndromes (MDSs) and acute myeloid leukemia fits this developmental model. MDSs often start with a display of an immunological disorder or wound which prompts the local production of inflammatory cytokines [48]. Among such cytokines, TNF is the critical factor related to the development of MDSs since antibody to TNF can prevent the progression of MDSs [49]. TNF causes excessive apoptosis of bone marrow stem cells, thus severely affecting the ability of the patient to produce hematopoietic cells such as erythrocytes, platelets or neutrophils. TNF is also responsible for the collapse of chemo-surveillance as above described. As a consequence, chemo-surveillance normally operating in healthy people to keep PSCs in check becomes dysfunctional, allowing PSCs to evolve into CSCs in order to replenish unipotent stem cells wiped out by TNF. The propagating pathological cells of MDSs have been identified as human CSCs [50]. MDSs are diseases attributable entirely to CSCs. Inactivation of abnormal MEs is the only drugs effective for the therapy of MDSs. Vidaza, Decitabine and CDA-2 are the three drugs approved by the Chines FDA for the therapy of MDSs. CDA-2 is a preparation of urinary wound healing metabolites we produced [33,34]. Vidaza and Decitabine are also approved by the US FDA for the therapy of MDSs. Professor Ma, the Director of the Harbine Institute of Hematology and Oncology, was instrumental in carrying out clinical trials of all three MDSs drugs. According to his assessments based on two cycles of treatment protocols each 14 days, he has found that 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 [42].

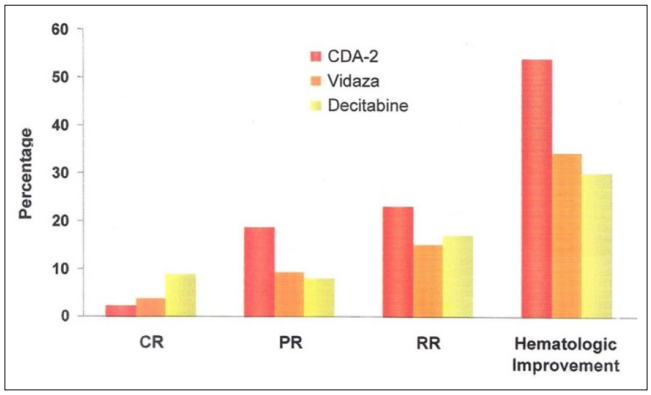

Figure 2: CDA-2 as the Best Drug for the Therapy of MDSs

Therapy of MDSs requires the conversion of pathological CSCs to become functional erythrocytes, platelets or neutrophils. Thus, induction of terminal differentiation is the only option for the therapy of MDSs. CDA-2 achieves therapy of MDSs by destabilization of abnormal MEs, which is a selective pharmacological action to target the tumor factor telomerase of abnormal MEs through wound healing metabolites [22-24], whereas Vidaza and Decitabine remove methyltransferase (MT) by covalent bond formation between MT and 5-azacytosine incorporated into DNA [51], which is non-selective on cancer cells. CDA-2 is devoid of adverse effects, whereas Vidaza and Decitabine are proven carcinogens [52,53] and very toxic to DNA [54-56]. Clearly, CDA-2 is the drug of choice for the therapy of MDSs with superior therapeutic efficacy and devoid of adverse effects. We are the clear winner on the contest to win the eradication of CSCs to also win the contest of cancer therapies [20]. Our winning status was denied by the cancer establishments who put up shrinkage of tumor as a requirement of cancer drugs. That requirement is actually a grave mistake of cancer establishments to account for the failure of developing effective cancer drugs [5,57]. They set up a rule to defeat their own mission to win the war on cancer.

A comparison of cancer therapies currently in practice on the important cancer parameters such as CSCs, CCs, unipotent stem

cells (USCs), chemo-surveillance, immuno-surveillance, tumor shrinkage and life-long survival is summarized in Table 2.

Table 2: A Comparison of Cancer Therapies on CSCs, CCs, USCs, Chemo-Surveillance, Immuno- Surveillance, Tumor Shrinkage and Life-Long Survival

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

Effects on CSCs: + means able to induce terminal differentiation and – means unable to induce terminal differentiation; on CCs: A means induction of terminal differentiation and B means cell killing; on USCs: + means can damage and – means no affect; on chemo-surveillance: + means can improve and – means can damage; on immuno-surveillance: 0 means no effect, - means can damage and + means can improve; on Tumor Shrinkage: - means cannot cause tumor shrinkage and + means can cause tumor shrinkage; on Life-long Survival: + means patient can survive until natural death and – means patient' death is attributable to cancer or its treatments, + Early means life-long survival for early stage cancer patients and – Late means late stage cancer patients are most likely to die from cancer or its treatments.

It is our belief that only cancer drugs able to eradicate CSCs can achieve life-long survivors of cancer patients [1-3,8,20]. Examination of all cancer drugs in practice as summarized in Table 2 shows that CDA, Vidaza and Decitabine are the only three cancer drugs able to achieve the induction of terminal differentiation of CSCs to offer life-long survival of cancer patients. But the adverse effects of Vidaza and Decitabine on USCs may not allow life-long survival. That leaves CDA as the solo cancer drug to achieve the solution of CSCs to save cancer patients for life-long. Chemotherapy, radiotherapy, immuno-therapy and targeted therapy all rely on the restoration of chemo-surveillance to subdue surviving CSCs. So, only the early stage cancer patients whose chemo-surveillance have not yet fatally damaged can benefit from these therapies. Early stage cancer patients may include CDA levels above 2.5, stage I & II patients without metastasis, Gleason score below 7 and CSCs count below 1% in the primary site. Although targeted therapy cannot induce CSCs to undergo terminal differentiation. Targeted therapy does not cause the damage of chemo-surveillance, therefore, cancer patients can benefit from targeted cancer therapy to achieve life-long survival. It is clear that cancer drugs that can heal wounds are much better than those that create wounds to save cancer patients. Tumor shrinkage is a bad diagnosis on cancer therapy [57].

Abnormal MEs as the Most Critical Issue of Cancer

Perpetual proliferation is the most outstanding symptom of cancer, which is caused by the failure to heal wound. Perpetual proliferation is basically a problem of growth regulation going awry. Methylation enzymes becoming abnormal and chromosomal abnormalities to activate oncogenes or to inactivate suppressor genes are two issues most critically related to mess up the growth regulation. We believe that MEs becoming abnormal is an issue more important than gene abnormalities, because MEs play a pivotal role on the regulation of cell growth and differentiation by virtue of the fact that DNA methylation controls the expression of tissue specific genes [58] and 2'-O-ribose methylation of pre-rRNA controls the production of ribosome [59], which in turn functions as a master check point to initiate cell cycle. If enhanced production of ribosome is locked in place, it becomes a driving force to promote carcinogenesis [60,61].

The role of MEs is a critical role to initiate cell cycle to promote cell growth, whereas the role of gene abnormalities is to produce factors to enhance the activity of MEs to promote cell growth. MEs play a major role and chromosomal abnormalities play an assistant role. The relationship is like CSCs and CCs. CSCs are a major critical battle field and CCs are a very big but not so essential battle field. Cancer establishments always make a bad judgement to pay attention on less important issues. They focused attention on chromosomal abnormalities on the regulation of cell growth and devoted 20 years, 1976-1996, on the development of gene therapy to fail the advancement on cancer therapy. They also focused attention on the killing of CCs from 1971 up to now to fail to win the war on cancer. The more critical issues are abnormal MEs [10] and CSCs [5] which dictate the success of cancer therapy. Abnormal MEs and CSCs are the same issue, because destabilization of abnormal MEs is the only option for the solution of CSCs [11,33,47,63].

MEs are a ternary enzyme complex consisting of methionine adenosyltransferase (MAT)-Methyltransferase (MT)-S-adenosylhomocysteine hydrolase (SAHH). Enzymes playing important biological roles are often subjected to delicate biological regulation. Allostertic regulation is the most pervasive biological regulation. MEs are exceptionally subjected to double allosteric regulations, one on the individual enzymes and the other one on the enzyme complex [64]. On the individual enzymes, SAHH is the receptor of steroid hormone to respond to steroid hormone regulation of MEs [65]. On the enzyme complex, MEs are regulated by telomerase and chemo-surveillance. As shown in Chart 1, there are two systems of regulation of MEs. In cells which do not express telomerase, MEs are regulated by steroid hormones or related regulators and in cells expressing telomerase, telomerase becomes the allosteric regulator of MEs. The association of MEs with telomerase changes the kinetic properties of MAT-SAHH isozyme pair and the regulation greatly in favor of cell growth. K_m values of telomerase associated MATsurLT-SAHHsurLT isozyme pair are 7-fold higher than K_m values of normal isozyme pair MATsurL-SAHHsurL.

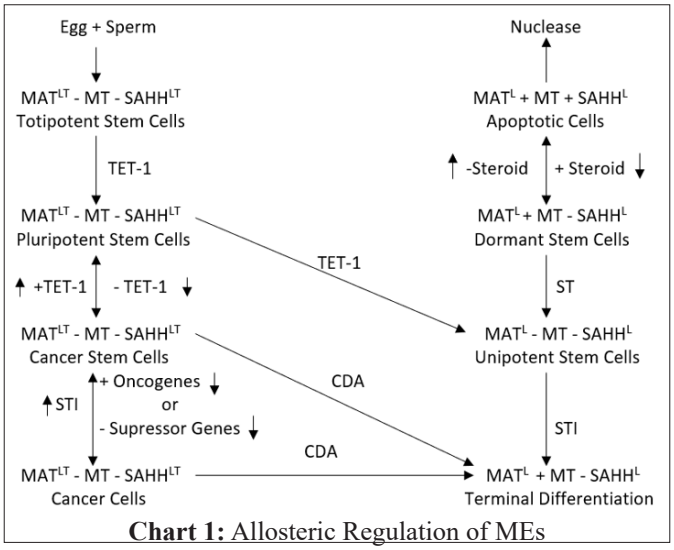

Chart 1: Allosteric Regulation of MEs

The higher K_m values of MAT^{LT}-SAHH^{LT} are an indication that cells expressing telomerase have larger pool sizes of S-adenosylmethionine (AdoMet) and S-adenosylhomocysteine (AdoHcy), which are needed for the promotion of the exceptional growth of cells expressing telomerase, as the study of Prudova et al. showed that AdoMet could protect protein against protease digestion [66], and the study of Chiva et al. showed that when HL-60 cells were induced to undergo terminal differentiation, the pool sizes of AdoMet and AdoHcy shrank greatly. Obviously, the larger pool sizes of AdoMet and AdoHcy are needed to promote the growth of cells expressing telomerase that include embryonic pluripotent stem cells and cells derived from pluripotent embryonic stem cells such as PSCs, CSCs and CCs. 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 the totipotent stem cell which expresses telomerase. The expression of telomerase spreads through pluripotent stem cells, but secedes when pluripotent stem cells undergoing lineage transitions to reach unipotent stem cells. Evidently, abnormal MEs are essential for the development of the fetus. Interruption of abnormal MEs by thalidomide results in malformation, noticeably limbs. Placenta must play an important role as a barrier to limit the entrance of maternal DIs and DHIs to interfere with fetal development. Abnormal MEs do not seem to cause problems of embryonic cells, because these cells are guarded by safety mechanisms such as contact inhibition, TET-1 enzyme and chemo-surveillance. If such safety mechanisms become dysfunctional, then clinical symptoms arise. TET-1 enzyme is responsible for lineage transition. This enzyme is specifically inactivated in cancer cells [68,69]. It appears that the silencing of TET-1 is a very important mechanism of carcinogenesis to eliminate the protection mechanism on abnormal MEs. We have to learn the detail of cancer evolution to effectively confront cancer. The valid concept of cancer is that CSCs evolve from PSCs due to the collapse of chemo-surveillance to escape contact inhibition, and then to progress to faster growing CCs. The progression to faster growing CCs is also caused by wound unhealing, but the proliferation of CCs is not critically linked to wound unhealing. The elimination of CCs by induction of terminal differentiation is right indication of cancer therapy, whereas the elimination of CCs by cell killing to create wound is contra-indication of cancer therapy very hard to achieve the goal of cancer therapy. It is very important to establish a right concept of cancer to confront cancer successfully.

Development of CDA Formulations

As shown in Table 2, CDA formulations are the only drugs for the solution of CSCs to achieve life-long survival of cancer patients. We have carried out extensive studies of natural and non-natural DIs and DHIs for the manufacture of CDA formulations [1-10]. The development of CDA formulations is blocked by the cancer establishments because these drugs cannot make tumor to shrink, which is an enormously difficult problem we have to overcome.

Conclusion

To successfully win the war on cancer, it is very important to establish a valid concept of cancer. Cancer evolving due to wound unhealing was a valid concept of cancer introduced by Virchow in 1858. Cancer establishments pursue cancer therapies opposite to the advice of Virchow to result in cancer becoming a giant killer of cancer patients, claiming 10 million casualties annually worldwide. We must get to the very fundamental to establish a valid concept of cancer to confront cancer successfully.

The valid concept of cancer is cancer evolving due to wound unhealing because of the collapse of chemo-surveillance which is a safety mechanism created by the nature for the perfection of wound healing to avoid cancer. Wound unhealing forces PSCs to evolve into CSCs which are the most critical battle field of cancer, although only a very tiny battle field. CDA formulations are the only option for the solution of CSCs, which are the only cancer drugs able to achieve life-long survivor of cancer patients.

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Competing Interests

Authors have declared no competing interests exist.

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