Wound Healing Metabolites to Heal Cancer and unhealed wounds

Abstract

Cytotoxic agents were the choice of cancer enemyto combat cancer when President declared War on Cancer in 1971. After the failure to win the war on cancer during the 5 years of intensive presidential support, it was concluded that cytotoxic agents were unable to win the war on cancer. The emphasis of cancer research was then shifted from cytotoxic agents to DNA research, and gene and targeted therapiesduring the period of 1976 – 1995. Entire human genomes were sequenced which was a phenomenal achievement. The achievement, however, helped very little on cancer therapy. Studies of aberrant DNA methylationsbecame a fashion, which, however, failed to grasp the critical issue of abnormalmethylation enzymesto let the solution of cancer to slip away. Gene therapy was too difficult and too expensive to yield acceptable cancer drugs. Many excellent targeted drugs were discovered, which were good differentiation helperand inducer to promote terminal differentiationof cancer cells. These excellent cancer drugs could not replace cytotoxic agents because they were unable to cause the tumor to disappear.These excellent targeted cancer drugs were primarily used for the therapy of hematological cancers. The emphasis was then shifted to anti-angiogenesis studies during 1995-2015, which did not produce good cancer drugs, and now to the immunotherapy,whichhas produced promising drugs for lung cancer.Immunotherapy has the potential to replace cytotoxic agents.Immunotherapy, however, appears to have the same problems as cytotoxic agents to cause damage to chemo-surveillance but show ineffectiveness against cancer stem cells, which were primarily responsible for the failure of cytotoxic agents to win the war on cancer. Such deleterious effects can be remedied by the employment of cell differentiation agent formulations.

Wound healing metabolites are the nature's creation of chemo-surveillanceto ensure perfection of wound healing to avoid cancer evolution.Cancer arises due to the collapse of chemo-surveillance, thus, wound healing metabolites are the right medicines to heal cancer. These drugs may also be applicable for the therapy of diseases arising due to the collapse of chemo-surveillance such as dementia and tissue fibrosis.

Key words: abnormal methylation enzymes; cachexia; cancer stem cells; cell differentiation agents; differentiation inducers; differentiation helper inducers; progenitor stem cells; terminal differentiation; wound healing; dementia; fibrosis.

Introduction

Cytotoxic chemotherapy of cancer was a tragic byproduct of World War II. Sulfur mustard gas bombs were used during the war. Victims died of poisonous gas all displayed deficiency of lymphocytes, which inspiredoncologists to employ toxic chemicals to treat leukemia patients. Oncologists were apparently satisfied with theselective toxicity of cytotoxic agents toward leukemiacells. Cytotoxic agents quickly became the standard therapeutic agents not only forleukemia, butalso for solid tumors. Disappearance of leukemia cells and tumor became the standard criterion for the evaluation of therapeutic efficacy. When President declared"War on Cancer" in 1971, cytotoxic agents were the choice of cancer enemyto combat cancer. Cancer establishments, however, failed the challenge to win the war on cancer during thefive years of intensive presidential support. If a treatmentmodality has been drilled through as a presidential project and failed to achieve the goal to win the war on cancer, it was fair to conclude that this treatment modality was unable to win the war on cancer.Apparently, cancer establishments agreedon this conclusion to shift the emphasis of cancer research from cytotoxic agentsto DNA research, and gene andtargeted therapies. Entire human genomes were sequenced, whichwas a phenomenal achievement. The achievement, however, helped very little on cancer therapy.Studies of DNA methylation became afashion around1985,disclosing a lot of aberrant DNA methylations of cancer cells. Studies of tRNA methylationwerealso a fashion around 1966 finding a lot of aberrant tRNA methylations. Cancer establishments werebrilliant to identify the important issues of cancer, but unfortunately failed to grasp the most criticalissue of abnormal methylation enzymes (MEs)to letthe solution ofcancer to slip away around1966 and 1985.

Emphasis on DNA research during 1976-1995 did not produce cancer drugs that could replace cytotoxic agents. Gene therapy was a fascinating field. But the technology was simply too difficult and too expensive to yield acceptable drugs. Studies of targeted therapies on inhibitors of growth factors and signaltransductions did produce many excellent cancer drugs. These inhibitors were good differentiation helper inducers (DHIs).[1] The therapeutic endpoint of DHIs was the terminal differentiation ofcancer cells (CCs)which was unable to cause the shrinkage of tumor.These excellent cancer drugs were mostly used in the therapy of hematological cancers.The criterion of tumor disappearance prevented the discovery of good cancer drugs not based on cell killing.
Since DNA research did not produce cancer drugs that could Causecomplete shrinkage of tumor,the emphasis was then shifted to anti-angiogenesis during 1995-2015, only found anti-angiogenesis agents caused more deaths due to bleeding than cytotoxic agents due to toxicityand ineffectiveness against cancer stem cells (CSCs). After the failure of anti-angiogenesis attempt, theattentionwas then shifted to immunotherapy, which did produce encouraging drugs on the therapy of lung cancer. We don't know if it can replace cytotoxic therapy. It is definitely more selective than cytotoxic agents to take out CCs. But Ithas the same problemsas cytotoxic agents to cause damage to chemo-surveillance and may not be

effective against CSCs. CSCs are Progenitor Stem Cells (PSCs) minus TET-1.[2] The antigenicity of CSCs should be the
same as PSCs, whichis tolerable to the human immune system. Still immunotherapy has the advantage not to harm normal stem cells. The deleterious effects to cause the damage to chemo-surveillance and to show ineffectiveness against CSCs can be remedied by the application of cell differentiation agent (CDA) formulations.[3]

Our studies strongly suggested that cancer arose as a consequence of wound not healing properly.[3] The concept of cancer as a non-healing wound was first introduced by a great German scientist Virchow in 19th century.[4] It was again brought up by Harold and Dvorak in 1986.[5]We provided the most important details on this subject that included abnormal MEs to block differentiation;[6-8] differentiation inducers (DIs) and DHIs as wound healing metabolites and also as the active players of chemo-surveillance;[9-11] hypomethylation of nucleic acids as the most critical mechanism to accomplish terminal differentiation of PSCs;[12] the evolutionofCSCs from progenitor stem cells (PSCs) due to the collapse of chemo-surveillance
;[9] the mechanism of wound healingand the impact of wound on the evolution of cancer .[3, 13-15] Since cancer iscaused by a wound not healing properly, wound healing metabolites must be the most appropriate medicines for cancer therapy.[16, 17]

Commentaries and Discussions

Wound Healing and the Evolution of Cancer

Wound healing and the evolution of cancer are closely related to involve PSCs as the critical common elements. Wound healing is a process to involve the breakdown of membrane bound phosphatidyl inositol to release arachidonic acid (AA) for the synthesis of prostaglandins (PGs) ,[18] which are responsible for the initial stage of wound to promote the proliferation of PSCs. The final stage of wound healing is carried out by the wound healing metabolites, DIs and DHIs, to promote the terminal differentiation of PSCs. DIs and DHIs are the important constituents of chemo-surveillance.[9-11] Healthy persons are able to maintain a steady level of DIs and DHIs to direct efficient terminal differentiation of PSCs to heal the wound. So wound healing comes naturally to healthy persons without having to put up any effort. Sutures and antibiotics are subsidiary of wound healing to speed up and to prevent infection.Butif DIs and DHIs are not sufficient due to pathological conditions, then the wound healing process will be affected to allow PSCs toevolve into CSCs. It takes only a single hit to silence TET-1 enzyme to convert PSCs to CSCs, which is very easy for PSCs to accomplishbecause these cells have abnormally active MEslike CCs.[6-8] Chemo-surveillance is the nature's creation to prevent that fromhappening.The protection of the functionality of chemo-surveillance is very important to ward off cancer. Wound also triggers immunological response to produce cytokines. Tumor necrosis factor (TNF) among such cytokines is bad for wound healing. TNF is also named cachectin afterits effect to induce cachexia symptom. TNF is toxic to proliferating cells to induce apoptosis,

normal stem cells andCCs included. It is also active to inducehyperpermeability of blood vessel [19, 20] to causeexcessive excretion of low molecularweight metabolites. Wound healing metabolites are among such low molecular weight metabolites excreted. The consequence is the loss of ability to heal the wound, thus allowing PSCs to evolve into CSCs, and then to progress to faster growing CCs by the activation of oncogenes and/or the inactivation of suppressor genes.

Chemo-surveillance

Chemo-surveillance was a term we created to describe anatural defense mechanism against cancer.[9] Now, we modify it as a term to ensure perfection of wound healing as the primary objective and the defense of cancer as the secondary consequence.[10, 11]Whatever comes naturallyisthe nature's creation to benefit human beings.The prime example is the photosynthesis that turnsCO_2 into O_2. Immuno-surveillance is another example that is well accepted. Chemo-surveillancewe brought up was completely ignoredbecause the active elements DIs and DHIswere non-toxic unacceptable to the concept of destruction of cancer with toxic agents.We used peptides as the surrogate molecules of wound healing metabolites to carry out studies of chemo-surveillance.The plasma and urinary peptide analyses of cancer patients as shown in the following Table1clearly shows that cancer patientsexcreteexcessive amounts of peptides resulting in the decrease ofplasma/urine ratios. Peptide analysis was conducted aspreviously described[9] by purification of peptides through C18 cartridge, and then ran peptide analysis by HPLCresolution and Ninhydrin reaction.The unit of plasma peptides was nmole/ml, and the unit of urinary peptides was nmole/mg creatinine.

Table 1. Plasma/urine peptide ratios of cancer patients

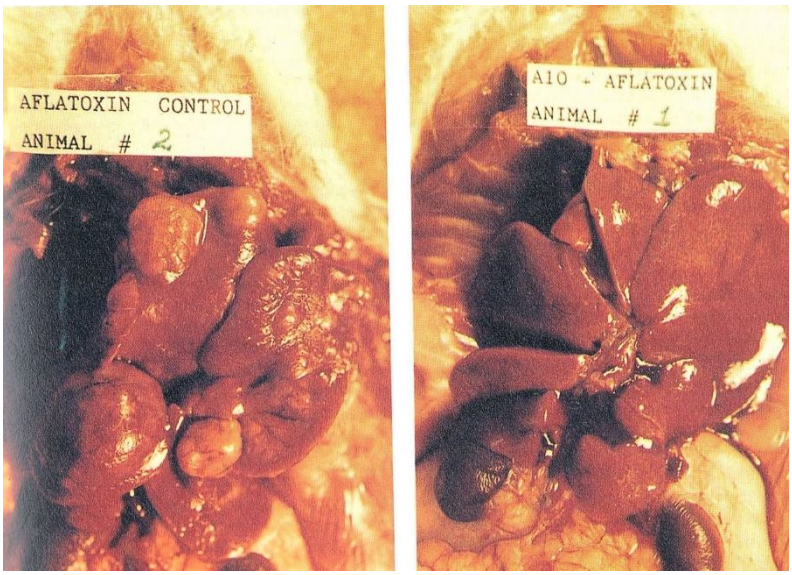
Plasma/UrineCDA RatiosScoresPatients	Number of Patients	% Distribution
0.8-0.83 (normal)	5	2
0.6-0.8	4	7
1.8		
6.5		

0.4-0.6	3	18	16.7
0.2 -0.4	2	38	35.2
0.1 - 0.2	1	24	22.2
0.02- 0.1	0	19	17.6

Plasma/urine peptide ratios correspond very well to the severity of cancer patients. Antineoplastonsare urinary wound healing metabolites purified by C18 reverse phase chromatography as the purification of peptides above described.If cancer patients responded well to the therapy with antineoplastons, their plasma/urine peptide ratios would increase and eventually reached the level of healthy persons.[21] The therapy with antineoplaston A10, the code name for phenylacetylglutamine, produced similar results.[9]The favorable responses to antineoplaston A10 were limited to patients withCDA scores of 3 and above.Antineoplaston A10 was inactive as DI nor as DHI. It did not have inhibitory effect on HL-60 cellseven at a very high concentration of 100 mM, but it had remarkable effect to prevent hepatocarcinogenesis induced by potent hepatocarcinogen aflatoxin B_1(AFB_1) as shown in Figure 1, which was reproduced from our published paper.[22]Male Fisher rats, 26 each group, were fed control diet or diet with 1% A10.AFB_1dosing was started 8 days after feeding with A10 diet. $AFB_1$was administered by gavage at the dose of 25 μg/day, 5 days weekly for 8 consecutive weeks. The experiment wasterminated at 66 weeks from the first dosing of AFB_1.Animal #1 was the rat fed A10 showingliver without neoplastic lesion. Animal #2 was the rat fed diet without A10 showing numerousneoplastic lesions. So, by keeping the functionality of chemo-surveillance intact, wound healing metabolites, namely CDA components, could effectivelyprevent hepatocarcinogenesis induced by AFB_1.

Figure1. Protective effect of antineoplaston A10 on hepatocarcinogenesis

Induced by aflatoxin B_1



Our studies clearly indicate that chemo-surveillance is a very effective mechanism to ensure perfection of wound healing. If a wound can be efficiently healed, then cancer evolution can be avoided.[9-11]The protection of the functionality of chemo-surveillance is very important for efficient wound healing. PGs produced in response to wound is helpful to the maintenance of chemo-surveillance and wound healing. On the contrary,TNF produced in response to wound is bad for wound healingdue to it effect to induce cachexia symptom. This bad effect can be effectively antagonized by phenylacetylglutamine.

Myelodysplastic syndrome (MDS) is a classic disease to illustrate the evolution of cancer due to wound not healing properly. MDS often starts with a display of an immunological disorde,[23]which prompts the production of inflammatory cytokines. Among such cytokines, TNF is the critical factor related to the development of MDS, because antibody of TNF could effectivelyreverse the progression of the disease at the early stage.[24] The propagating cells of MDS have been identified as a rare form of human CSCs.[25]Therefore, MDS is at a stage of CSCs evolved from PSCs. During our studies of chemical hepatocarcinogenesis, we were able to detect abnormal MEsin the preneoplastic hyperplastic nodules, which might represent the proliferation of PSCs.[26]Therefore, the genesis of cancer must proceed from PSCs to CSCs, and then progress to CCs.

Abnormal Methylation Enzymes as the Bullseye of Cancer Target

Had the cancer establishments focused the attention on abnormal MEs during the fashionable studies of aberrant tRNA methylations around1966 and aberrant DNA methylationsaround 1985, cancer might have been solved. In 1966, before the declaration of War on Cancer, and in 1985 after the declaration of War on Cancer that failed. Cancer establishments missed the critical issue of abnormal MEs to win the war on cancer.[27]

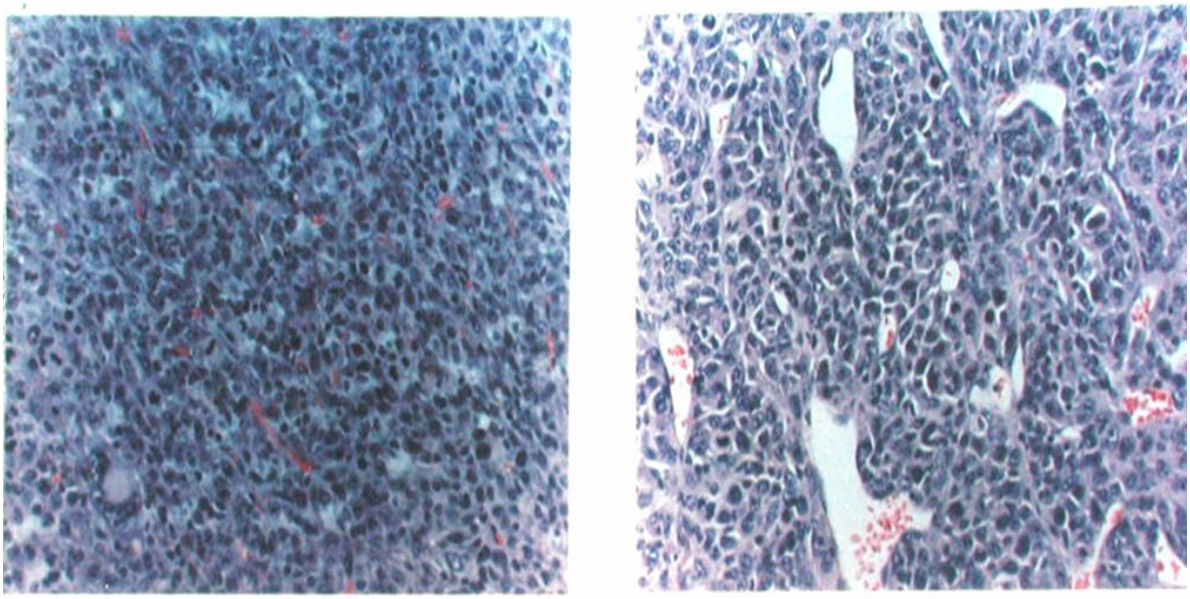
MEs play a critical role on the regulation of cell replication, differentiation and apoptosisby virtue of the fact that DNA MEs control the expression of tissuespecific genes[28], and pre-rRNA MEs control the production of ribosome[29], which in turndictates the commitment of cells to initiate replication[30].If enhanced production of ribosome is locked in place, it becomes a factor to drive carcinogenesis.[31]Biological methylation ismediated by a ternary enzyme complex consisting of methionine adenosyltransferase (MAT)-methyltransferase (MT)-S-adenosylhomocysteine hydrolase (SAHH).[32, 33] MEs must be in the ternary enzyme complex to become stable and functional. SAHH is the most unstable enzyme of the three MEs which requires a stabilizing factor to protect its stability. Steroid hormones are the stabilizing factors of SAHH of the steroid hormone target tissues. Other tissues may require factors similar to steroid hormones to protect the stability of SAHH. These stabilizing factors of SAHH are often the important factors for the regulation of MEs to influence cellular functions.

MEs become associated with telomerase in cell expressing telomerase. The association with telomerase changes kinetic properties and the regulatory functions of MEs. The $K_m$values of the telomerase associated MAT-SAHH isozyme pair are 7-fold higher than the K_m values of the normal isozyme pair. The increased $K_m$values offer greater stability of the abnormal MEs associated with telomerase.It has been shown by Prudova et al.[34] that the binding of S-adenosylmethionine (AdoMet) greatly increased the stability of protein against protease digestion.The increased K_m values expand pool sizes of AdoMet and S-adenosylhomocysteine (Ado-Hcy). A bigger pool size of AdoMet and AdoHcy is obviously required to maintain malignant growth. It was shown by Chiba et al.[35] that the induction of terminal differentiation of HL-60 cells resulted in great shrinkage of the pool size of AdoMet andAdoHcy. These studies support our findings that abnormal MEs play an important role to promote malignant growth. Since abnormal MEs play such an important role to promote malignant growth, destabilization of abnormalMEs by DIs and DHIs is an effective strategy to combat cancer.[33, 36] DIs are chemicalscapable of eliminating telomerase from abnormal MEs, and DHIs are inhibitors of MEs which can greatly potentiate the activity of DIs. DIs and DHIs are actually wound healing metabolites of the nature's creation toplay the role of chemo-surveillance.The strategy of destabilization of abnormal MEsis a perfect cancer therapy that restores the functionalityof chemo-surveillance topromote terminal differentiation of both CCs and CSCs. By promoting terminal differentiation of both CCs and CSCs, wound healing metabolites can also put to rest gene abnormalities that contribute to malignant growth. Oncogenes and suppressor genes are cell cycle regulatory genes. They have important role to play when cells are in cell cycle replicating. But if replicating cells exit cell cycle to undergo terminal differentiation, they have no role to play.So, induction of terminal differentiation is an easy way to solve gene abnormalities which are otherwise very difficult to solve.Wound healing metabolites have a unique advantage no other cancer drugs can compete. They are able to take out PSCs and CSCs protected by drug resistance and anti-apoptosis mechanisms.[36] Repair is the biological mission of these cells. Wound healing metabolites are the partner to their biological mission. Therefore, wound healing metabolites can easily access these cells to promote terminal differentiation of PSCs and CSCs to accomplish healing role.A complete remission achieved by wound healing metabolites is worth life time, whereas recurrence is a common happening to other therapies.

CDA-2 as a PerfectCancer Drug

CDA-2 is a preparation of wound healing metabolites purified by reverse phase chromatography using XAD-16 as the adsorbant and ethanol as the organic solvent.[38]The active components include AA as the major DI, and pregnenolone and uroerythrin as the major DHIs.[2, 38]Phenylacetylglutamine is a major chemical component as an anti-cachexia agent. The therapeutic endpoint is the induction of terminal differentiationas shown in Figure 2. It could greatly improve the quality of life of patients undergoing cytotoxic chemotherapy, but could not cause the tumor to shrink. It was approved by the Chinese FDA for cancer therapy as a supplement to chemotherapy in 2004.[39]CSCs was not an issue when the clinical trial of CDA-2 was conducted. The effect of CDA-2 on CSCs was not evaluated.The ability of CDA-2 to take out CSCs, and to restore the functionality of chemo-surveillance was a great improvement to cytotoxic chemotherapy.

Figure 2. Effectiveness of CDA-2 on the induction of terminal differentiation ofhuman Smmn7722hepatocellular carcinoma xenografted into nude mice

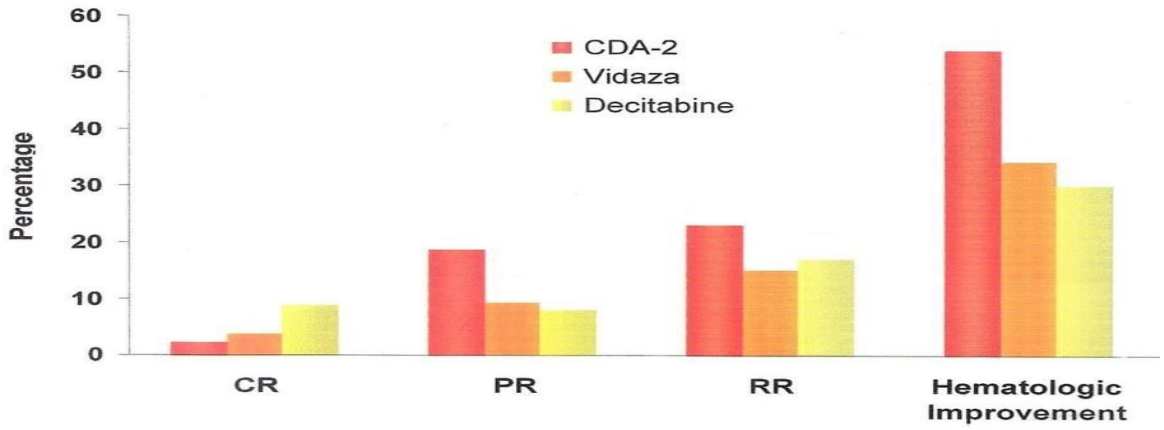


Control CDA-2 treated

Actually, CDA-2 is best for the therapy of MDS, a disease attributable entirely to CSCs. The therapy requires the differentiation of pathological CSCs to become functional cells.The clinical trial of CDA-2 on MDS was conducted during 2004 to 2007 when Ming C. Liau was in chargeof clinical development of CDA-2 for the Ever Life Pharmaceutical Companywhich manufactured CDA-2. Dr. Jun Ma, the Director of Harbin Institute of Hematology and Oncologywho was then the chairman of Chinese Society of Clinical Oncology, carried out clinical trial of CDA-2 on 117

MDS patients.Based ontwo cycles of treatments, each 14 days, the therapeutic efficacy of CDA-2 in comparison to Vidaza and Decitabine as shown in Figure 3was slightly better based on cytological evaluation, and markedly better based on hematological improvement evaluation, namely becoming independence on blood transfusion. Better yet, CDA-2was totally devoid of serious adverse effects, whereas Vidaza and Decitabine were proven carcinogens[40, 41] andvery toxic to DNA.[42-44]CDA-2 is definitely a better drug than Vidaza and Decitabine for thetherapy of MDS. CDA-2 was approved for the therapy of MDS by the Chinese FDA in 2017.[36]

Figure 3. Effectiveness of CDA-2 for the therapy of MDS in comparison to Vidaza and Decitabine



Cancer is caused by multiple factors including the breakdown of chemo-surveillance due to TNF[9, 23],evolution of CSCs from PSCs due to the failure of wound healing,abnormal MEs to block differentiation and activation of oncogenes and/or inactivation of suppressorgenes. Phenylacetylglutamineof CDA-2can antagonize TNF. DI and DHIs can take care of differentiation blockade of both CCs and CSCs. By promotion of terminal differentiation, CDA-2 can also put to rest gene abnormalities. Therefore, CDA-2 is a perfect cancer drugs to eliminate all important factors contributing to the development of cancer.

DIs and DHIs for the Design of CDA Formulations

We have discovered many effective DIs and DHIs for the design of CDA formulations, which are listed in Table 2 and 3. DIs are listed as ED_{25}, ED_{50} and ED_{75}, and DHIs are listed as reductive $index_{0.5}$, which is an expression of potency. The dosage of a DHIto achieve a reductive $index_{0.5}$ is equivalent to the dosage of a DI to achieve ED_{25}. These data have been previously published.[1, 37, 38, 45-47]

Table 2. Effective DIs We Have Studied, Most of Which were Our Discoveries

DIs	ED_{25}	ED_{50}	ED_{75}
Phorbal ester, nM	0.17	0.26	0.38
Retinoic acid, μM	0.18	0.36	0.75
PGI2, μM	7.9	13.8	20.5
16, 16-dimethylPGE2, μM	10.8	17.3	30.1
PGE2, μM	20.6	32.0	46.5
BicycloPGE2, μM	21.0	43.5	-
AA, μM	24.0	46.8	-
BIBR1532, μM	32.3	43.7	55.1
Boldine, μM	60.1	78.3	94.2

Phorbal ester and retinoic acid were well known DIs discovered by others. AA and PG derivatives were wound healing metabolites, and BIBR1532 and boldine were telomerase inhibitors.

Table 3-1. Inhibitors of MEs as DHIs

SAHH Inhibitors	$RI_{0.5}$, μM	MT Inhibitors	$RI_{0.5}$, μM

Pyrvinium pamoate	0.012	Ethidium bromide	1.10
Vitamin D3	0.61	Uroerythrin	1.75
Dexamethasone	0.75	Hycanthone	2.10
Testosterone	1.55	Riboflavin	2.30
Gugulsterone	1.59		
Beta-Sitosterol	1.72		
Dehydroepiandrosterone	1.79	MAT Inhibitors	$RI_{0.5}$, μM
Dihydrotestosterone	2.10		
Prenisolone	2.22		
Estradiol	2.45	Indol acetic acid	220
Progesterone	3.55	Phenylacetylvaline	500
Hydrocortisone	4.59	Phenylacetylleucine	780
Pregnenolone	7.17	Phenylacetylisoleucine	800
Pregnenolone sulfate	7.35	Butyric acid	850
Phenylbutyric acid	970		

All DHIs were our discovery. The potency of DHI $RI_{0.5}$ was determined as previously described.[45] The dosage of DHI to achieve $RI_{0.5}$ is equivalent to DI of ED_{25}.

Table 3-2. Inhibitors of Signal Transductions and Growth Factors as DHIs

Signal Transduction Inhibitors	$RI_{0.5}$, μM	Growth Inhibitors	$RI_{0.5}$, μM
Sutent	0.28	Arsenic acid	0.28
Berberine	1.62	Cobalt chloride	0.62
Vorient	10.1	Selenite	19.7
Gleevec	11.9		
Metformin	44.9		

Table 3-3. Polyphenols as DHIs

Polyphenols	$RI_{0.5}$, μM	Polyphenols	$RI_{0.5}$, μM

Tannic acid	0.37	Pyrogallol	3.18
Epigallocatechin gallet	0.62	Silibinin	3.30
Resveratrol	1.16	Caffeic acid	3.87
Curcumin	1.24	Ellagic acid	4.45
Kuromanin1.43Gallic acid	5.35		
Coumestrol	1.95	Ferulic acid	7.41
Genisteine	2.16	Phloroglucinol	38.8
Pterostilbene 2.19			

From the active DIs and DHIs listed in Tale 2 and Table 3-1 through 3-3, it is easy to design CDA formulations to accomplish the induction of terminal differentiation to reach 100%. DIs alonecannot reach 100%, so ED_{75} is about the maximal dosage of DIs, and if supplemented with DHI of $RI_{0.5}$ could achieve the induction of terminal differentiation to reach 100%. Those dosages arein the amounts per liter of blood.A normal person has 5 liters of blood. We have to multiply the amounts by a factor of 5 to provide enough medicines to reach 100%terminal differentiation of cancer cells.Three times a day of the maximum dosages to achieve 100% induction of terminal differentiation of cancer cellsshould provide good therapy of cancer.

The employment of wound healing metabolites for cancer therapy offers a unique advantage to eliminate CSCs, which is very important for the completion of cancer therapy. We were aware that the winner of the contest to eliminate CSCs won the contest of cancer therapies.[48]In consideration of designing CDA formulations for specific cancer, we have to pay attentionto specific problem confronting that particular cancer. For example, brain cancerhas the problemof blood brain barrier, melanoma has the problem of hypoxia, and pancreatic
cancer has the problem of collagen envelope.So, there are issues not related to cancer to contributeto cancer problems.

Therapeutic endpoint of CDA formulations is the induction of terminal differentiation. The evaluation of therapeutic efficacy must be set differently from the disappearance of tumor set for cytotoxic agents.Disappearance of cancer markers or circulating CCs and CSCs may be the valid endpoints for the evaluation of CDA formulations on cancer therapy. The elevation of CDA score to the 5 of healthy persons as listed in Table 1 may be helpful for the evaluation of therapeutic efficacy ofCDA formulations.

Apparently, wound healing metabolites are the right drugs for the therapy of cancer which is the most feared disease arising due to the collapse of chemo-surveillance. Untreatable diseases arising due to the collapse of chemo-surveillance may include dementia[49] and tissue

fibrosis.[50,51]Dementia is a progressive and untreatable disease. Lung fibrosis is the most damaging symptom contributing to the death of Covid-19 infection.Studies of wound healing metabolites on unhealed wounds may be helpful to save such fatal diseases.

Conclusions

Health professionals have the obligation to solve health problems contributing to death. Covid-19 is now the major concern. The solution of Covid-19 should be the first priority. Cancer was recognizedby President as the main concernof healthto declare "War on Cancer" in 1971. At that time, cytotoxic agents were the choiceof cancer establishments to solve the most outstanding feature ofcancer which was the perpetual cell replication.Cytotoxic agents, however, failed to win the war on cancerwithin the five years of apresidential project. Cancer establishments realized thatcytotoxic agents could not win the war on cancer, thus, shifted the emphasis of cancer research from cytotoxic agents to DNA research, and gene and targeted therapies. Many excellent targeted agents were discovered which, however,could not compete withcytotoxic agents to cause the tumor to disappear, so the search turned to anti-angiogenesis, which also failed to producecancer drugs to replace cytotoxic agents. The currentemphasis was ontheimmunotherapy, which has produced promising drugs for lung cancer.Immunotherapy, however, appears to have the same problems as the cytotoxic agents to cause the damage to chemo-surveillance and to show ineffectiveness against CSCs. These deleterious effects can be remedied by the employment of CDA formulations.

Wound healing metabolites are the nature's creation to ensure perfection of wound healing to avoid the evolution of PSCs to become CSCs.Cancer arises due to the collapse of chemo-surveillance, thus, wound healing metabolites are the most appropriate medicines to heal cancer. Wound healing metabolites may also be the most appropriate medicines for the therapy of untreatable diseases arising due to the collapse of chemo-surveillance such as dementia and tissue fibrosis.

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